

PHYSIOLOGY

Lung Volume Abnormalities and its Correlation to Spirometric and Demographic Variables in Adult Asthma

VIPUL V. JAIN, MBBS, MD, FCCP,¹ BELAYNEH ABEJIE MD,² MUHAMMAD H. BASHIR MD,² TIM TYNER MS,²
AND JOSEPH VEMPILLY, MBBS, MD, MRCP, FCCP^{1,*}

¹Division of Pulmonary & Critical Care, Department of Medicine UCSF-Fresno, Fresno, CA 93701, USA.

²Division of Internal Medicine, Department of Medicine UCSF-Fresno, Fresno, CA 93701, USA.

Background. Presence of airflow obstruction in asthma has been based on a fixed FEV₁ (forced expiratory volume at 1 second)/FVC (forced vital capacity) ratio abnormality. The accuracy of FEV₁/FVC ratio in diagnosing airflow obstruction remains controversial. Lung volume abnormalities have been observed in severe asthma. We utilized simultaneously measured spirometry and lung volume to determine the utility of residual volume (RV)/total lung capacity (TLC) ratio in diagnosing airflow obstruction and to identify predictors of abnormal RV in asthmatic subjects. **Methods.** Data from physician-diagnosed asthmatics referred for lung function tests were collected retrospectively. Patient demographics and lung function data were analyzed using general linear modeling. **Results.** Of the 321 subjects, 221 were female (69%). The ethnicity was Caucasian in 157 (49%), Hispanic in 131 (41%), and African-American in 33 (10%). The percentage of subjects with FEV₁/FVC ratio <70%, FEV₁-predicted <80%, and FEF_{25–75%} <65% were 25%, 25%, and 38%, respectively. Fifty-two and fifty-seven percent of the patients had abnormal residual volume and abnormal RV/TLC ratio, respectively. A significant bronchodilator response was observed in 32% of the patients. A positive correlation was observed between RV to age ($r = 0.4$) and height ($r = 0.3$). A negative correlation was observed between RV to FEF_{25–75%} ($r = 0.5$) and body weight ($r = 0.07$). There was no significant correlation between FEV₁ reversibility and residual volume ($r = 0.1$). RV correlated significantly better with FEF_{25–75%} ($r^2 = 0.25$) than FEV₁ ($r^2 = 0.16$). **Conclusion.** A significant proportion of asthmatic patients have elevated residual volume and abnormal RV/TLC ratio in the presence of normal FEV₁/FVC ratio and absence of significant bronchodilator response. The clinical significance of these findings in asthma needs further prospective study.

Keywords asthma, FEV₁/FVC ratio, residual volume, RV/TLC ratio

BACKGROUND

Asthma is characterized by airway inflammation that is thought to cause bronchospasm manifesting as airflow obstruction on pulmonary function tests (PFTs). The accuracy of simple spirometry in diagnosing airflow obstruction based on fixed ratios has been questioned (1). However, airflow obstruction in patients with asthma continues to be defined based on a fixed FEV₁ (Forced expiratory volume in first second)/FVC (Forced vital capacity) ratio (using a ratio of 70% to 75% or less), or a post-bronchodilator improvement of at least 12% and 200 ml in FEV₁ or FVC (2, 3). Concerns regarding over- or under-diagnosis of airflow obstruction in the extremes of age have led to recent recommendations by both ATS and ERS for the use of LLN (lower fifth percentile of a reference population) in place of a fixed FEV₁/FVC ratio (4). However, the LLN was reported in a recent evidence-based review to actually underestimate airflow obstruction, at least in patients with COPD (5).

Previous studies have documented a lack of correlation between asthma symptoms and spirometry indices (6, 7). Furthermore, spirometric criteria alone have been shown to be inadequate in the diagnosis of obstructive ventilatory defect in asthma (8, 9). As an example, only a small percentage of subjects meeting the spirometric inclusion

criteria for asthma drug trials is indicative of this dilemma (10). In addition, these established criteria might overlook the underlying pathology in the small airways encountered in mild and severe asthmatics (11, 12). Interestingly, fatal asthma has been associated with only mild abnormalities in FEV₁ and FEV₁/FVC ratio (13). Clearly, there remains a need for improvement in the current diagnostic tools used to detect airflow obstruction in asthma.

Lung volume abnormalities have been documented in adult asthmatics in as early as the 1970's (14–16). Lung volume measurements have been reported to be useful in children for assessing the severity of asthma symptoms (17, 18). Recently, hyperinflation was reported to be associated with severe exacerbation of asthma in children in the presence of unchanged forced expiratory flows (19, 20). However, current guidelines do not recommend the assessment of lung volumes for characterization of airflow obstruction in asthma. Although long associated, lung volumes have not been utilized for its discriminatory capacity in adult asthmatics to characterize airflow obstruction (21). Therefore, we examined the utility of lung volume measurements in the characterization of airflow obstruction using a cohort of physician-diagnosed adult asthmatics.

METHODS

Patient Selection: Patients with established physician-diagnosed asthma who underwent complete lung function

*Corresponding author: J. Joseph Vempilly MBBS, MD, MRCP, FCCP, Associate Professor of Medicine, Division of Pulmonary & Critical Care, UCSF-Fresno, Fresno, CA 93701, USA. E-mail: jjoseph@fresno.ucsf.edu

testing including spirometry, lung volumes, and diffusion capacity for carbon mono-oxide (DLCO) analyses between the periods of 2005 to 2010 were selected. Inclusion criteria included: age > 17 years, history of physician-diagnosed asthma, and DLCO >70%. Subjects without DLCO measurements and/or bronchodilator response assessments were excluded. A total of 321 subjects with an established diagnosis of asthma that had undergone spirometry and lung volume measurements simultaneously were found to be eligible for the study. The conduct of this study was approved by IRB # 2010023.

Lung Function Studies: Spirometry, lung volume measurements, DLCO measurement, and reversibility were done using the standard accepted 2005 ATS/ERS guidelines. Lung volume measurement was performed using body plethysmography (Medical Graphics Corporation, St. Paul, Minnesota, USA). Devices were calibrated as per ATS recommendations. For this study, an abnormal residual volume (RV) and total lung capacity (TLC) were defined as a value exceeding 100% of the predicted value. An abnormal RV/TLC ratio was defined as a ratio >35.

Statistical Analyses: General Linear Modeling was used for predicting significant factors and covariates for residual volume. Covariates with significant co-linearity (FEV_1 , FEF25–75, and Peak expiratory flow) were excluded from the model. The model was run with peak flow, FEV_1 , and FEF25–75% values separately. The best model fit included FEF25–75% as a covariate. Residual analysis showed no significant lack of fit of the model. Interactions were checked between fixed factors before assessing the main effect. Correlation between continuous variables was checked using the Spearman correlation coefficient. The relationship between FEV_1 and lung volumes was plotted using locally weighted scatter plot curves (LOWESS) to minimize the effect of extreme values on the trend line. $P < .05$ was considered statistically significant.

RESULTS

As shown in Table 1, among the 321 study subjects, 49% were Caucasians, 41% Hispanics, and 10% African-Americans; women constituted 69% of the study subjects. The total number of smokers was 166 (51%), of which 65% were women. The prevalence of smoking was significantly higher among Caucasians (55%) compared to Hispanics (34%) and African-Americans (11%) ($p = .03$).

Figure 1 shows the percentage of abnormal tests in the study subjects. Abnormal FEV_1/FVC ratio (<75%) was observed in 25%, FEV_1 predicted (<80%) in 25%, and FEF25–75% predicted (<65%) in 38% of the subjects. By contrast, the percentage of patients with abnormal residual volume and abnormal RV/TLC ratio were 52% and 57%, respectively, more than double the number of subjects with

TABLE 1.—Base-line characteristics of study subjects.

Variable	Mean	Std. deviation
Age	47.91	13.63
Height	164.03	9.57
Weight	89.93	27.23
BMI	33.49	9.83
Smoking pack year	9.5	13.3
FEV_1 actual	2.54	0.84
FEV_1 % predicted	84.89	20.11
FEV_1 reversibility%	6.5	8.6
FEV_1/FVC ratio	76.20	10.19
FEF25–75 actual	2.33	1.14
FEF25–75 % predicted	78.02	34.21
Expiration time (sec)	8.45	2.17
RV actual	1.90	0.66
RV % predicted	107.97	33.95
TLC actual	5.24	1.19
TLC % predicted	96.40	13.88
RV/TLC ratio	36.50	9.90

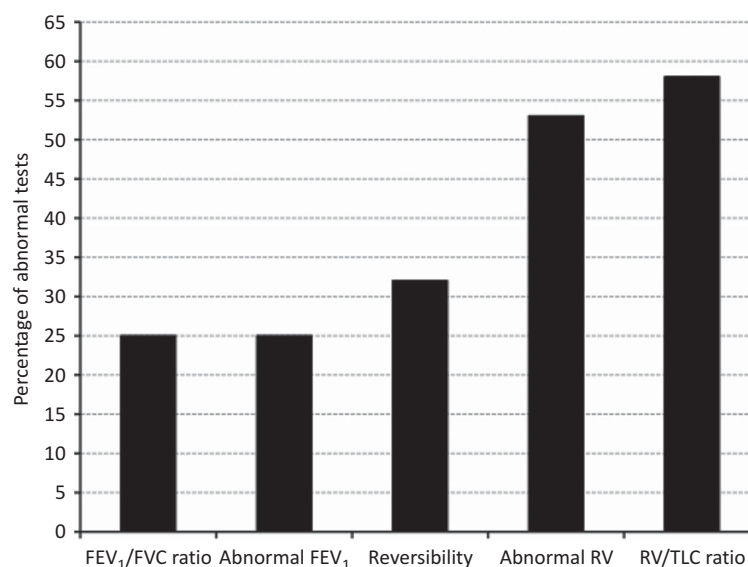


FIGURE 1.—Shows the percentage of abnormal indices observed in our study subjects. While spirometry abnormality was observed in about 25%, lung volume abnormality was present in more than 50% of the study subjects.

abnormal FEV_1/FVC . Only 32% had bronchodilator response, which was defined as improvement in FEV_1 of at least 12% and an absolute increase of 200 ml or more.

Relationship Between $FEV_1\%$, FEV_1/FVC Ratio, and Corresponding Lung Volumes

Figure 2 shows the relationship between $FEV_1\%$ predicted values and % predicted Lung volumes in study subjects. There was a sharp increase in RV, when the FEV_1 value was 90% of the predicted normal. The TLC

values decreased linearly until the FEV_1 values were below 90% and thereafter, there was a tendency for TLC to increase with declining FEV_1 values. Also, the FVC declined linearly with FEV_1 values, resulting in the FEV_1/FVC ratio to remain well above the 70% cutoff value until the FEV_1 had dropped below 65%. However, the RV/TLC ratio was observed to increase well above 35 when the $FEV_1\%$ predicted values declined below 90%. Figure 3 shows the relationship between FEV_1 and FEF25–75% to RV. The strength of correlation was better for FEF25–75% with RV

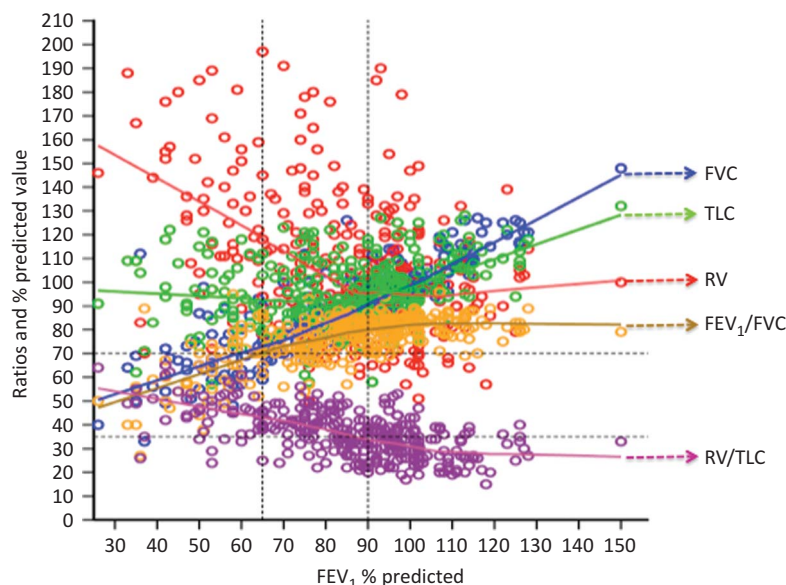


FIGURE 2.—Shows the relationship between $FEV_1\%$ predicted on X-axis and % predicted values of other PFT variables on Y-axis. The trend lines were plotted using the LOWESS equation. The horizontal hatched line represents the 70% and 35% cutoff value. The vertical hatched lines were drawn at inflection points for FEV_1/FVC ratio and RV/TLC ratio.

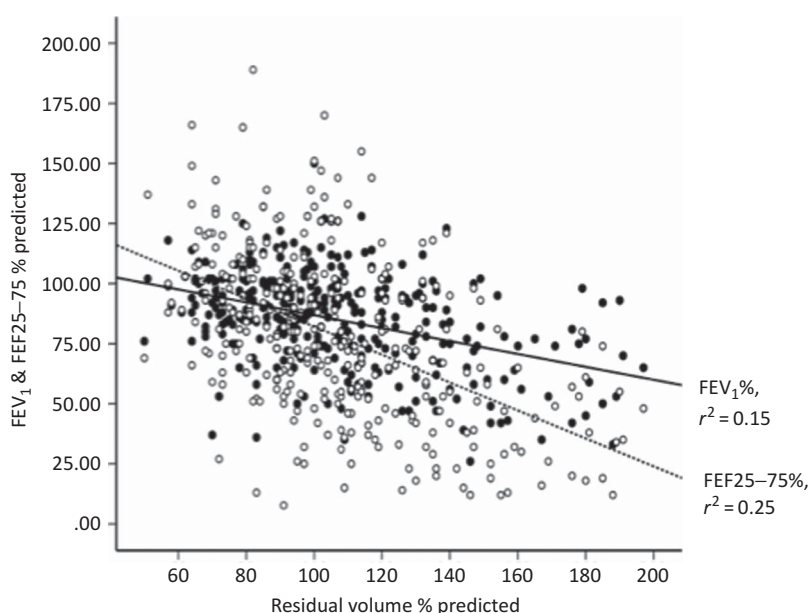


FIGURE 3.—Open circles represent FEV_1 value and closed circles depict FEF25–75% values. There was a significant correlation between FEV_1 and FEF25–75% values to RV (all $p < .01$). However, the strength of correlation was better for FEF25–75% ($r^2 = 0.25$) than FEV_1 ($r^2 = 0.16$), indicating small airway dysfunction as a major contributor to increased residual volume.

TABLE 2.—Significant predictors of residual volume in study subjects.

Parameter	B	Std. error	p value	95% CI		Partial eta squared
				Lower bound	Upper bound	
Intercept	−1.187	0.656	.071	−2.479	0.104	0.011
Female	−0.281	0.092	.003	−0.463	−0.100	0.029
African-American	−0.514	0.146	.000	−0.801	−0.228	0.039
Smoking (Pack year)	0.008	0.002	.000	0.004	0.012	0.053
Age	0.011	0.002	.000	0.007	0.015	0.078
Height	0.021	0.004	.000	0.014	0.029	0.095
Weight	−0.003	0.001	.001	−0.005	−0.001	0.036
FEF25–75	−0.226	0.027	.000	−0.280	−0.173	0.183
FEV ₁ reversibility	0.004	0.003	.195	−0.002	0.011	0.005
Gender × ethnicity	0.001	0.111	.993	−0.217	0.219	0.000

TABLE 3.—Significant predictors of residual volume in smokers and non-smokers.

Smoking status	Source	Type III sum of squares	Mean square	Sig.	Partial eta squared
No	Corrected model	25.262 ^a	2.526	0.000	0.389
	Intercept	0.242	0.242	0.346	0.006
	Age	1.891	1.891	0.009	0.045
	Height	2.396	2.396	0.003	0.057
	Weight	1.898	1.898	0.009	0.046
	FEF25–75%	4.485	4.485	0.000	0.102
	FEV ₁ reversibility	0.420	0.420	0.214	0.010
	Sex	0.548	0.548	0.156	0.014
	Ethnicity	2.058	1.029	0.024	0.049
	Sex * Ethnicity	0.698	0.349	0.278	0.017
	Corrected model	37.424 ^b	3.742	0.000	0.524
Yes	Intercept	0.355	0.355	0.205	0.010
	Age	1.707	1.707	0.006	0.048
	Height	3.247	3.247	0.000	0.087
	Weight	1.081	1.081	0.028	0.031
	FEF25–75%	10.019	10.019	0.000	0.228
	FEV ₁ reversibility	0.121	0.121	0.458	0.004
	Sex	0.706	0.706	0.075	0.020
	Ethnicity	2.678	1.339	0.003	0.073
	Sex * ethnicity	0.284	0.142	0.525	0.008

($r^2 = 0.25$) than FEV₁ with RV ($r^2 = 0.16$), indicating small airway dysfunction as a major contributor to increased residual volume.

Table 2 shows the predictors of abnormal residual volume in our study subjects. A significant positive correlation was observed between age, height, and pack year of smoking with residual volume (all $p < .01$). The body weight was associated with a significant negative correlation with RV. More importantly, there was no significant correlation between bronchodilator response and residual volume ($p = .2$). A separate GLM model regression analysis demonstrated similar results in smokers and non-smokers (Table 3).

DISCUSSION

Although still debated, the spirometric criteria have been used for decades to diagnose airflow obstruction in the form of FEV₁/FVC ratios as well as FEV₁ reversibility (3). In our study subjects with asthma, the data suggest that a fixed FEV₁/FVC ratio <70% was observed in only 25%

of the patients. This observation was consistent with a prior finding by Cockcroft et al., who reported that less than 10% of the subjects attending a tertiary clinic met the typical spirometric inclusion criteria for asthma trials (10). Conversely, only about 55% of the patients who did meet the ATS criteria for bronchodilator reversibility were thought to have clinical criteria consistent with asthma (9). However, the prevalence of abnormal RV and RV/TLC was over 50% in our study subjects. The reason for the poor performance of FEV₁/FVC ratio to diagnose obstructive ventilatory defect may be explained by the fact that as the FEV₁ value declined, FVC value also declined linearly and proportionately, thus maintaining the FEV₁/FVC ratio well above 70% until the FEV₁ dropped below 65% of the predicted normal (Figure 2). Furthermore, the increased prevalence of abnormal RV/TLC ratio in our subjects was primarily due to a disproportionate increase in RV with declining FEV₁ resulting in abnormal RV/TLC ratio. This trend for rising RV/TLC ratio was observed when the FEV₁ values were well above the normal standard of 80% of the predicted values.

Air trapping from increased residual volume has been reported to be associated with mild and severe asthma (22, 23). Airflow limitation has been shown to increase hyperinflation in subjects with asthma (24). Broncho-dilatation has been shown to improve FEV₁, especially after deep breathing in subjects with asthma (25). Furthermore, Brown and associates have shown that there was a three-fold increase in the RV compared to a relative reduction in FVC with increasing smooth muscle tone in adult subjects with asthma (26). Therefore, our observation of a large increase in RV and a modest increase in TLC with declining FEV₁ is in agreement with observations by Brown and associates.

Previously reported prevalence of significant FEV₁ reversibility in asthmatics has varied widely from 4% to 40% (27, 28). We observed significant reversibility in only 32% of our subjects, which falls within this range. It is possible that the low prevalence of significant FEV₁ reversibility in these studies is due to the unrecognized presence of coexistent COPD phenotype. Interestingly, we also observed a lack of correlation between FEV₁ reversibility and residual volume in our study subjects. This finding may suggest that FEV₁ reversibility is closely associated with airway smooth muscle response to beta-2 agonist, just as abnormal FEV₁/FVC ratio reflects the function of the larger airways (26). Consistent with this explanation, we found a stronger significant correlation of residual volume with FEF_{25–75%} than with FEV₁ (Figure 3). This may suggest that while not a gold standard, FEF_{25–75%} may be a better index of small airway closure (29). Additionally, the findings of Gelb and associates that abnormal elevation of lung volumes in asymptomatic subjects with asthma resulting from possible loss of elastic recoil may further strengthen our conclusions (30, 31). To further address airway closure, we investigated mid-flows in our cohort of asthma patients as a surrogate of small airway obstruction. Using a cutoff of <65% for the mid-flows, we identified an additional 13% of individuals with asthma compared to a fixed FEV₁/FVC ratio <70%; thus reaffirming the traditional consensus of declined mid-flows as an early indicator for obstructive airway disease (32).

Finally, our observation of high prevalence of abnormal RV and RV/TLC ratio lends support to the concept described by Gibbons et al. who suggested that the focus of asthma might be misdirected on airway narrowing rather than airway closure and gas trapping (33). Indeed, the mechanisms of airflow obstruction are relatively poorly understood in terms of its site and the relative contribution of small airways to airflow limitation. Airflow limitation is thought to develop when flow-limiting choke points in the large airways (migrating upstream during expiration) increase the trans-pulmonary pressure with resultant decrease in airflow at the mouth (34, 35). Data investigating the functional narrowing behavior of individual central and peripheral airways in porcine airways suggest that changes in airway wall shape or dimensions, or luminal secretions exert a significant effect on airway flow, particularly in the small airways (36).

Limitations

Our study has inherent limitations due to its retrospective study design; we were not able to correlate patient symptoms with abnormal FEV₁/FVC ratio or RV/TLC ratio. Our study did not clearly differentiate prior smokers from current smokers. However, using strict DLCO inclusion criteria has limited the possibility of having included patients with significant COPD in our analyses. Further, a separate regression analysis demonstrated similar results in smokers and non-smokers. We utilized a robust multi-variable statistical analysis using the GLM model with interaction terms to account for variability in our predictor variable, thus eliminating some of the confounding effects. Finally, the role of exhaled nitric oxide has not been addressed in our retrospective study. A prospective study utilizing lung volumes measurement, exhaled nitric oxide, and oscillometry may help differentiate COPD phenotypes in asthmatics.

In conclusion, our data suggest that lung volumes in the form of elevated residual volume and RV/TLC ratio may be more sensitive in diagnosing airflow obstruction compared to spirometric criteria in asthma. Whereas bronchodilator response is a function of large airway narrowing from broncho-spasm, abnormal RV/TLC ratio may reflect distal airway closure from inflammation or loss of elastic recoil. A prospective study with assessment of lung volumes and their reversibility may help better understand the pathophysiology of airflow limitation in asthma.

ACKNOWLEDGMENTS

The authors thank Dale E Claes for importing lung function data and Fozia H Bashir for data collection. The authors do not have any financial or nonfinancial disclosures.

DECLARATION OF INTEREST

We declare that none of the authors of this study have any financial, consulting, and personal relationships with other people or organizations that could influence (bias) the author's work. We have not received any scientific writing assistance (use of an agency or freelance writer) or grant support from any source.

REFERENCES

1. Cerveri I, Corsico AG, Accordini S, Cervio G, Ansaldo E, Grosso A, Niniano R, Tsana Tegomo E, Anto JM, Kunzli N, Janson C, Sunyer J, Svanes C, Heinrich J, Schouten JP, Wjst M, Pozzi E, de Marco R. What defines airflow obstruction in asthma? *Eur Respir J* 2009 Sep; 34 (3):568–573.
2. Bateman ED, Hurd SS, Barnes PJ, Bousquet J, Drazen JM, FitzGerald M, Gibson P, Ohta K, O'Byrne P, Pedersen SE, Pizzichini E, Sullivan SD, Wenzel SE, Zar HJ. Global strategy for asthma management and prevention: GINA executive summary. *Eur Respir J* 2008 Jan; 31(1):143–178.

3. Roberts SD, Farber MO, Knox KS, Phillips GS, Bhatt NY, Mastronarde JG, Wood KL. FEV₁/FVC ratio of 70% misclassifies patients with obstruction at the extremes of age. *Chest* 2006 Jul; 130(1):200–206.
4. Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, Coates A, van der Grinten CP, Gustafsson P, Hankinson J, Jensen R, Johnson DC, MacIntyre N, McKay R, Miller MR, Navajas D, Pedersen OF, Wanger J. Interpretative strategies for lung function tests. *Eur Respir J* 2005 Nov; 26(5):948–968.
5. Mohamed Hoesein FA, Zanen P, Sachs AP, Verheij TJ, Lammers JW, Broekhuizen BD. Spirometric thresholds for diagnosing COPD: 0.70 or LLN, pre- or post-dilator values? *COPD* 2011 Apr 11 .
6. Osborne ML, Vollmer WM, Pedula KL, Wilkins J, Buist AS, O'Hollaren M. Lack of correlation of symptoms with specialist-assessed long-term asthma severity. *Chest* 1999 Jan; 115(1):85–91.
7. Teeter JG, Bleecker ER. Relationship between airway obstruction and respiratory symptoms in adult asthmatics. *Chest* 1998 Feb; 113(2):272–277.
8. Enright P. Flawed interpretative strategies for lung function tests harm patients. *Eur Respir J* 2006 Jun; 27(6):1322–1323. Author reply 3–4.
9. Gjevre JA, Hurst TS, Taylor-Gjevre RM, Cockcroft DW. The American Thoracic Society's spirometric criteria alone is inadequate in asthma diagnosis. *Can Respir J* 2006 Nov–Dec; 13(8):433–437.
10. Cockcroft DW, Jokic R, Marciniuk DD, Fitzpatrick MF. The current dilemma with spirometric inclusion criteria for asthma drug trials. *Ann Allergy Asthma Immunol* 1997 Sep; 79(3):226–228.
11. Carroll N, Elliot J, Morton A, James A. The structure of large and small airways in nonfatal and fatal asthma. *Am Rev Respir Dis* 1993 Feb; 147(2):405–410.
12. Casale TB. The pathophysiology of small airway inflammation in asthma. *Postgrad Med* 2003 Feb; 113(2 Suppl):7–12.
13. Gelb AF, Schein A, Nussbaum E, Shinar CM, Aelony Y, Aharonian H, Zamel N. Risk factors for near-fatal asthma. *Chest* 2004 Oct; 126(4):1138–1146.
14. Anderson SD, McEvoy JD, Bianco S. Changes in lung volumes and airway resistance after exercise in asthmatic subjects. *Am Rev Respir Dis* 1972 Jul; 106(1):30–37.
15. Koch G. Terbutaline in bronchial asthma. Effect on lung volumes, ventilatory performance, pulmonary gas exchange and circulation at rest and during exercise. *Scand J Respir Dis* 1972; 53(4):187–195.
16. Mayfield JD, Paez PN, Nicholson DP. Static and dynamic lung volumes and ventilation-perfusion abnormality in adult asthma. *Thorax* 1971 Sep; 26(5):591–596.
17. Andrewes JF, Simmons DH. Lung volumes of normal and asthmatic children. *Pediatrics* 1959 Mar; 23(3):507–519.
18. Kraepelien S, Engstrom I, Karlberg P. Respiratory studies in children. II. Lung volumes in symptom-free asthmatic children, 6–14 years of age. *Acta Paediatr* 1958 Jul; 47(4):399–411.
19. Mahut B, Bokov P, Delclaux C. Abnormalities of plethysmographic lung volumes in asthmatic children. *Respir Med* 2010 Jul; 104(7):966–971.
20. Mahut B, Peiffer C, Bokov P, Beydon N, Delclaux C. Gas trapping is associated with severe exacerbation in asthmatic children. *Respir Med* 2010 Aug; 104(8):1230–1233.
21. Ruppel GL. What is the clinical value of lung volumes? *Respir Care* 2012 Jan; 57(1):26–35. Discussion-8.
22. Yanai M, Sekizawa K, Ohru T, Sasaki H, Takishima T. Site of airway obstruction in pulmonary disease: Direct measurement of intrabronchial pressure. *J Appl Physiol* 1992 Mar; 72(3):1016–1023.
23. Sorkness RL, Bleecker ER, Busse WW, Calhoun WJ, Castro M, Chung KF, Curran-Everett D, Erzurum SC, Gaston BM, Israel E, Jarjour NN, Moore WC, Peters SP, Teague WG, Wenzel SE. Lung function in adults with stable but severe asthma: Air trapping and incomplete reversal of obstruction with bronchodilation. *J Appl Physiol* 2008 Feb; 104(2):394–403.
24. Pellegrino R, Brusasco V. Lung hyperinflation and flow limitation in chronic airway obstruction. *Eur Respir J* 1997 Mar; 10(3):543–549.
25. Pyrgos G, Scichilone N, Toggias A, Brown RH. Bronchodilation response to deep inspirations in asthma is dependent on airway distensibility and air trapping. *J Appl Physiol* 2011 Feb; 110(2):472–479.
26. Brown RH, Pearse DB, Pyrgos G, Liu MC, Toggias A, Permutt S. The structural basis of airways hyperresponsiveness in asthma. *J Appl Physiol* 2006 Jul; 101(1):30–39.
27. Quadrelli SA, Roncoroni AJ, Montiel GC. Evaluation of bronchodilator response in patients with airway obstruction. *Respir Med* 1999 Sep; 93(9):630–636.
28. Sekiya K, Taniguchi M, Fukutomi Y, Mitsui C, Tanimoto H, Oshikata C, Tsuburai T, Tsurikisawa N, Hasegawa M, Akiyama K. Persistent airflow obstruction in young adult asthma patients. *Allergol Int* 2012 Mar; 61(1):143–148.
29. Simon MR, Chinchilli VM, Phillips BR, Sorkness CA, Lemanske RF Jr, Szeffler SJ, Taussig L, Bacharier LB, Morgan W. Forced expiratory flow between 25% and 75% of vital capacity and FEV₁/forced vital capacity ratio in relation to clinical and physiological parameters in asthmatic children with normal FEV₁ values. *J Allergy Clin Immunol*. [Research Support, N.I.H., Extramural] 2010 Sep; 126(3):527–34 e1–8.
30. Gelb AF, Licuanan J, Shinar CM, Zamel N. Unsuspected loss of lung elastic recoil in chronic persistent asthma. *Chest* 2002 Mar; 121(3):715–721.
31. Gelb AF, Zamel N. Unsuspected pseudophysiological emphysema in chronic persistent asthma. *Am J Respir Crit Care Med* 2000 Nov; 162(5):1778–1782.
32. Ciprandi G, Tosca MA, Capasso M. Forced expiratory flow between 25 and 75% of vital capacity might be a predictive factor for bronchial hyperreactivity in children with allergic rhinitis, asthma, or both. *Allergy Asthma Proc* 2011 Sep–Oct; 32(5):e22–e28.
33. Gibbons WJ, Sharma A, Loughheed D, Macklem PT. Detection of excessive bronchoconstriction in asthma. *Am J Respir Crit Care Med* 1996 Feb; 153(2):582–589.
34. Hyatt RE. Expiratory flow limitation. *J Appl Physiol* 1983 Jul; 55(1 Pt 1):1–7.
35. Spence DP, Graham DR, Jamieson G, Cheetham BM, Calverley PM, Earis JE. The relationship between wheezing and lung mechanics during methacholine-induced bronchoconstriction in asthmatic subjects. *Am J Respir Crit Care Med* 1996 Aug; 154(2 Pt 1):290–294.
36. Mitchell HW, Cvetkovski R, Sparrow MP, Gray PR, McFawn PK. Concurrent measurement of smooth muscle shortening, lumen narrowing and flow to acetylcholine in large and small porcine bronchi. *Eur Respir J* 1998 Nov; 12(5):1053–1061.