

Air Trapping Correlates with Increased Frequency of Albuterol Use and Severity of Wheeze in Persistent Asthma

Jose Joseph Vempilly, Belayneh A Abejie, Ali Rashidian, Vipul V Jain, and Nirav Bhakta

BACKGROUND: Symptoms of asthma have been shown to correlate poorly with spirometric variables of obstruction. We hypothesized that lung volume measurements might correlate with symptoms and frequency of rescue inhaler use in asthma. **METHODS:** Patients with persistent asthma on treatment for ≥ 12 months were enrolled from university-based clinics. The association between lung volumes, spirometry, asthma symptoms, and rescue inhaler use were explored by using linear modeling. **RESULTS:** Among the 120 subjects, 76% were women. The mean age \pm SD was 52 ± 15 y. With regard to ethnicity, 64% of the subjects were caucasian, 23% were Hispanic, and 13% were African-American. Twenty-one percent of the subjects reported chest pain. There was no significant correlation between asthma symptoms or rescue inhaler use to spirometry indices of obstruction. The residual volume percent of predicted showed a significant association with the wheeze score ($r = 0.32$, $P = .001$) and frequency of rescue inhaler use ($r = 0.35$, $P \leq .001$). Linear contrast analysis showed that the mean wheeze score ($P = .003$) and frequency of rescue inhaler ($P = .007$) use increased linearly from the lowest to the highest quartiles of residual volume. Furthermore, multiple regression analysis showed an association only to the residual volume percent predicted value to the pressurized metered-dose inhaler score and the wheeze score. **CONCLUSIONS:** Frequent albuterol use and wheezing may be a sign of unrelieved air trapping. Chest pain is a unique symptom in persistent asthma, and the pathogenesis requires further studies. Lung volume measurement added to routine spirometry can help identify patients with asthma and with air trapping. [Respir Care 0;0(0):1–●. © 0 Daedalus Enterprises]

Introduction

Asthma affects 334 million people globally, with an approximate prevalence of 7.7% of the population in the United States.¹ Common asthma symptoms include wheezing, shortness of breath, and coughing. Although asthma

symptoms induced by methacholine challenge have been shown to correlate with a fall in FEV₁,² clinical studies have failed to show a significant correlation between asthma symptoms and spirometry indices of obstruction.³⁻⁵ Lung volume abnormalities have been documented in adults with acute severe asthma.⁶ In children, lung volume abnormalities have been reported to be useful in assessing the severity of asthma.^{7,8}

A recent study observed a higher frequency of lung volume abnormalities compared with the frequency of spirometry abnormalities of airway obstruction in adults with persistent asthma.⁹ Therefore, we postulated that

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lung volume abnormalities, especially the magnitude of residual volume (RV) increase might show an association with asthma symptoms. To our knowledge, there is a paucity of literature that shows an association between lung volume abnormalities and the frequency of symptoms or the frequency on rescue inhaler use in adults with persistent asthma. Therefore, we explored the association between lung volume and spirometry measures of obstruction with the frequency of symptoms and the frequency of rescue inhaler use in patients with persistent asthma.

Methods

Physicians in pulmonary and internal medicine clinics identified patients with asthma diagnosed according to National Asthma Education Program guidelines¹⁰ as eligible for recruitment. After obtaining institutional review approved consent forms, 2 trained research coordinators interviewed these patients by using a study questionnaire. Any patients with the following conditions were excluded from the study: the presence of any debilitating systemic illness, such as malignancy, autoimmune disease, and chronic lung disease other than asthma. Furthermore, pregnancy, current smoking, or a history of smoking of >5 pack-years were all exclusion criteria for the study. Finally, patients who received oral or intravenous corticosteroids 2 weeks before the recruitment period, and patients who had a diffusion capacity of carbon monoxide < 70% of predicted value at recruitment were excluded. Among the study participants, 70% were using a combination of long-acting β -agonist with budesonide or fluticasone; 30% used inhaled fluticasone or beclomethasone alone. Thirty-two percent of the patients were also on montelukast in addition to inhaled steroids.

All the subjects withheld long-acting β -agonists and inhaled corticosteroids for 24 h and long-acting muscarinic receptor blockers and leukotriene inhibitors for 48 h before lung function studies as per American Thoracic Society recommendations.¹¹ A reversibility study for spirometry indices was obtained after administration of 360 μ g of albuterol via pressurized metered-dose inhaler (pMDI). On inclusion to the study, all the subjects completed a questionnaire to describe the severity of their asthma symptoms and the frequency of rescue inhaler use 2 weeks before study enrollment. The following asthma symptoms experienced by the subjects were recorded on a Likert scale: tightness of chest or dyspnea, wheeze, cough, and chest pain were graded from 0 to 3, in which zero indicated no symptoms, and 1 to 3 indicated mild, moderate, and severe symptoms experienced 2 weeks before the day of the interview.

Baseline spirometry, diffusing capacity of the lung for carbon monoxide, and lung volume measurements were

QUICK LOOK

Current knowledge

There is a paucity of data on the association between asthma symptoms and lung function tests in subjects with persistent asthma. Spirometry does not correlate with asthma symptoms other than during an acute attack. Lung volume abnormality has been described as being useful in assessing the severity of asthma in children.

What this paper contributes to our knowledge

We described an association between wheeze and the frequency of pressurized metered-dose inhaler use to the degree of air trapping in subjects with persistent asthma. Furthermore, chest pain was a frequent symptom reported by subjects with persistent asthma. We described the plausible mechanism for chest pain and the association between asthma symptoms and lung volume abnormalities in this article.

done by using body plethysmography according to American Thoracic Society guidelines¹² (MGC Diagnostics, St. Paul, Minnesota) by 2 designated pulmonary function test (PFT) technicians. Of the 124 subjects recruited, 4 patients with a diffusing capacity of the lung for carbon monoxide of <70% predicted value and abnormal chest radiograph were excluded from the study.¹³ In addition to lung functions tests, serum IgE concentration and exhaled nitric oxide were measured only in the last 81 subjects due to budgetary issues. During the analysis, we used the following threshold values to define abnormal spirometric and lung volume measurements: FEV₁% predicted value of <80%, FEV₁/FVC < 70%, RV% predicted value >100%, RV to total lung capacity (TLC) of >35. The subjects with significant reversibility for FEV₁ or FVC \geq 12% and 200 mL were identified by using the American Thoracic Society guidelines.¹⁴

Statistical Analysis

We determined the correlation between the symptoms of asthma and the PFT variables by using the Spearman rho analysis. The dichotomous variable frequency in different groups was compared by using chi-square analysis. Linear contrast analysis was used to explore a linear association between the asthma symptom score and cumulative pMDI use 2 weeks before the recruitment to the binned quartile values of RV% predicted, and FEV₁% predicted values. The percent of predicted values for RV and FEV₁ binned into quartiles were used as a predictor variable in linear contrast

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Table 1. Demographics and Laboratory Tests in Study Participants

Variable	Age, y	BMI, kg/m ²	Duration of Asthma, y	Smoking Pack-Year	Serum IgE, IU/mL	Exhaled Nitric Oxide, ppb
Number of subjects	120	120	120	120	81	81
Mean	52.25	32.43	16.6	0.30	320.20	21.79
Median	53.00	31.98	12.0	0	69.00	14.00
Percentiles						
25	43.00	26.08	5.0	0	20.50	9.00
50	53.00	31.98	12.0	0	69.00	14.00
75	64.00	37.70	24.0	0	298.50	26.00

BMI = body mass index
IgE = immunoglobulin E

Table 2. Base Line PFT Values in the Study Participants

Variable	PFT Value, Mean \pm SD
FEV ₁	2.43 \pm 0.81
FEV ₁ % predicted	85.42 \pm 19.16
FVC	3.26 \pm 0.97
FVC% predicted	90.06 \pm 14.88
FEV ₁ /FVC	74.70 \pm 10.53
RV, L	2.12 \pm 0.77
RV% predicted	112.41 \pm 32.57
TLC, L	5.40 \pm 1.26
TLC% predicted	99.18 \pm 13.31
RV/TLC	39.27 \pm 9.73

PFT = pulmonary function test
RV = residual volume
TLC = total lung capacity

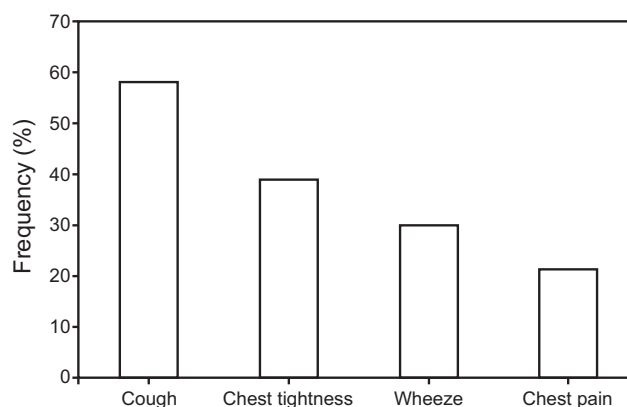


Fig. 1. Frequency of symptoms (%) among the study participants.

analysis. Multiple linear regression analyses were used to identify a better predictor variable between RV% and FEV₁% predicted values against the outcome variables total pMDI use and the mean wheeze score reported 2 weeks before enrollment. The addition of forced expiratory flow during the middle half of the FVC maneuver and peak expiratory flow value as additional predictor variables did not improve the model. Therefore, the best model was determined to be the one with FEV₁ and with RV as a predictor variable. The collinearity index Variance inflation factor value for FEV₁% and RV% in the model was 1.27, which suggests a lack of significant collinearity between FEV₁% and RV% values. We analyzed data by using SPSS 25 (SPSS, Chicago, Illinois). $P < .05$ was considered significant.

Results

Among the 120 study subjects, 76% were women, and the mean \pm SD age was 52 \pm 15 y. The mean value of relevant variables in the study subjects are shown in Table 1. The pretest PFT variables in the subjects are shown in Table 2. The reported frequencies of various asthma symptoms are shown in Figure 1. Twenty-five subjects (21%)

reported chest pain. The intensity of chest pain was mild in 7%, moderate in 10%, and severe in 4%. Chest pain was unilateral in 6% and bilateral in 15%. Chest pain as a symptom was more frequently observed in the male subjects (56% [11/30]) compared with the female subjects (16% [14/90]) ($P = .02$). There was no correlation between chest pain and the degree of air trapping (Table 3). In addition, there was no significant association between the presence of gastroesophageal symptoms and chest pain ($P = .37$). The frequency of abnormal spirometry and lung volume indices in patients are shown in Figure 2.

The bivariate correlation between asthma symptoms, rescue inhaler use, and PFT variables are shown in Table 4. There was no significant correlation between the symptoms of asthma and FEV₁ or FEV₁/FVC ratio. However, the severity of wheeze score correlated significantly with prebronchodilator RV ($P = .001$) and RV/TLC ($P = .04$). In addition, linear contrast analysis showed that the mean wheeze score and pMDI use (Fig. 3) increased linearly among the subjects with a higher quartile value of RV% predicted. However, there was no such linear increase in the mean frequency of wheeze scores or pMDI use among patients with higher FEV₁ % predicted quartile values (Fig. 4). Multiple linear regression analysis with FEV₁ and RV

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percent predicted value as predictors and wheeze score and pMDI use as separate outcome variables showed a significant correlation only to the RV% predicted value (Table 5).

Discussion

Asthma is a syndrome characterized by chronic airway inflammation that causes expiratory air-flow limitation. Patients with asthma experience intermittent or persistent symptoms of wheeze, chest tightness, and cough, which have been attributed to air-flow obstruction and airway inflammation. In our cohort of subjects with stable persistent asthma, the most common symptom observed was cough. In addition to the classic symptoms, we observed chest pain in 21% of the subjects; this was a unique finding in subjects with persistent asthma on treatment compared with chest pain observed in the subjects with acute severe asthma.¹⁵ Previous studies failed to observe any correlation

between asthma symptoms and spirometry abnormalities, and our study confirmed these findings.^{4,5,9}

Although the presence of increased RV has been reported in severe asthma,¹⁶ our observation of a significant correlation between wheeze and abnormal RV and RV/TLC has not been reported before in subjects with persistent asthma. Furthermore, linear contrast analysis and multiple regression analysis showed only the RV to be significantly associated between the frequency of wheeze and pMDI use. A previous investigation documented the presence of an abnormal RV/TLC and increased RV in the presence of a normal FEV₁/FVC in asthma.⁹ The site of airway obstruction in asthma has been shown to mainly be in the peripheral airways when using the micromanometer technique.¹⁷ Furthermore, bronchodilator use has been shown to improve hyperinflation without significant improvement in FEV₁.¹⁸ Therefore, our finding of frequent use of albuterol rescue in the subjects with air trapping may be a reflection of the presence of small airway obstruction not captured by spirometry.¹⁹

Previous studies showed a high prevalence of chest pain (76%) in adults with acute severe asthma.¹⁶ Chest pain has been described as a dull aching-to-stabbing quality felt behind the sternum and subcostal area, and relieved by sitting forward and taking shallow breaths. Unexplained exercise-induced chest pain has also been observed in 40% of children with exercise-induced asthma.²⁰ For the majority of these children, the chest pain resolved with albuterol, which indicated air trapping as a possible mechanism for the chest pain. It is possible that breathing at a higher residual volume can lead to stress on rib joint mechanics, which can lead to dull or sharp chest pain in asthma. However, we were not

Table 3. Association between Chest Pain and RV% Predicted

Chest Pain	RV% Predicted, Quartile				Total
	Lowest	Second	Third	Highest	
Absent	22	24	25	24	95
Present	8	6	5	6	25
Total	30	30	30	30	120

$P = .37$.

RV = residual volume

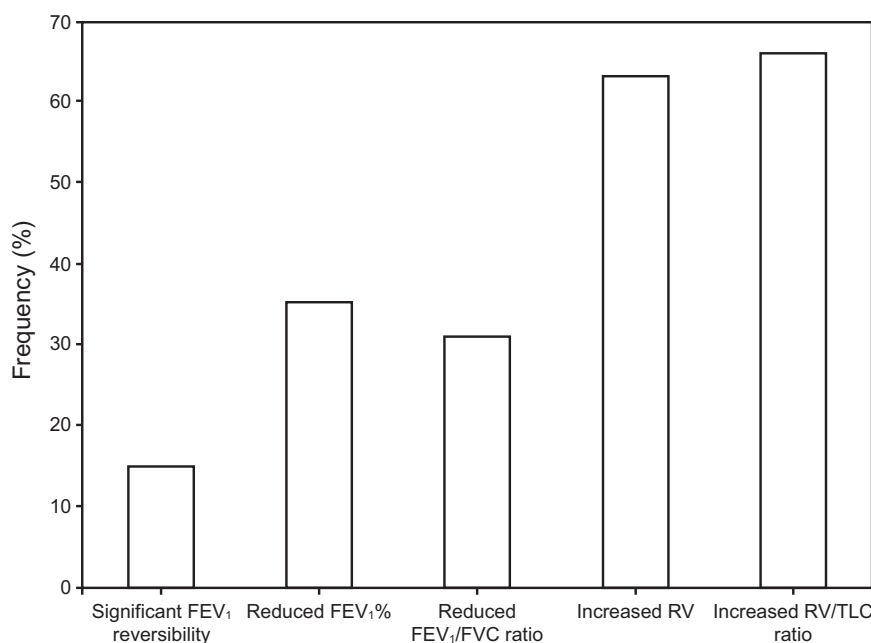


Fig. 2. Frequency of abnormal spirometry and lung volume variables in the study participants.

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Table 4. Bivariate Correlation between Study Variables in the Study Participants

Variable	Parameter	Cough	Wheeze	Dyspnea	pMDI Use	FEV ₁ %	RV %	FEV ₁ /FVC	RV/TLC
Cough	Coefficient	1	0.29*	0.14	0.16	0.09	0.01	0.01	0.01
	P	NA	.001	.12	.07	.29	.88	.90	.87
Wheeze	Coefficient	0.29*	1	0.55*	0.48*	-0.17	0.31*	-0.14	0.18†
	P	.001	NA	< .001	< .001	.06	.001	.12	.04
Dyspnea	Coefficient	0.14	0.55†	1	0.39*	-0.06	0.14	0.02	0.05
	P	.12	< .001	NA	< .001	.49	.10	.84	.53
pMDI use	Coefficient	0.16	0.48*	0.39*	1	-0.12	0.35*	-0.15	0.13
	P	.07	< .001	< .001	NA	.18	< .001	.09	.16
FEV ₁ %	Coefficient	0.09	-0.17	-0.06	-0.12	1	-0.45*	0.67†	-0.54*
	P	.29	.06	.49	.18	NA	< .001	< .001	< .001
RV%	Coefficient	0.01	0.31*	0.15	0.35*	-0.46*	1	-0.65*	0.52*
	P	.88	.001	.10	< .001	< .001	NA	< .001	< .001
FEV ₁ /FVC	Coefficient	0.01	-0.14	0.02	-0.15	0.67*	-0.65*	1	-0.52*
	P	.90	.12	.84	.09	< .001	< .001	NA	< .001
RV/TLC	Coefficient	0.01	0.18†	0.05	0.13	-0.55*	0.52*	-0.52*	1
	P	.87	.04	.53	.16	< .001	< .001	< .001	NA

* Correlation is significant at the .01 level (2-tailed).

† Correlation is significant at the .05 level (2-tailed).

pMDI = pressurized metered-dose inhaler

RV = residual volume

TLC = total lung capacity

NA = not applicable

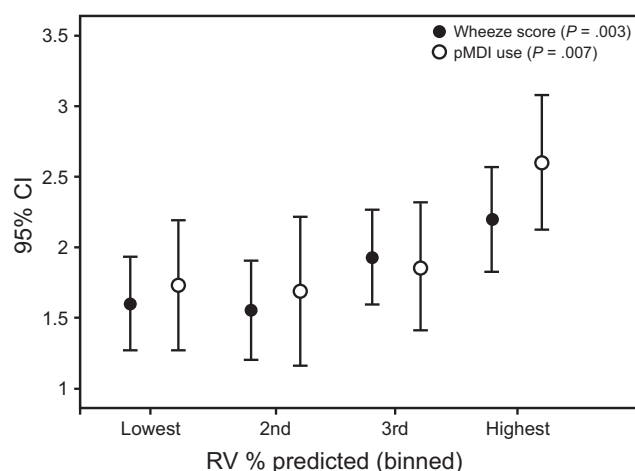


Fig. 3. Linear association between residual volume (RV) percent (quartiles) predicted value to mean wheeze score and mean pressurized metered-dose inhaler (pMDI) use. Wheeze score and pMDI use increased linearly with higher quartile values of RV.

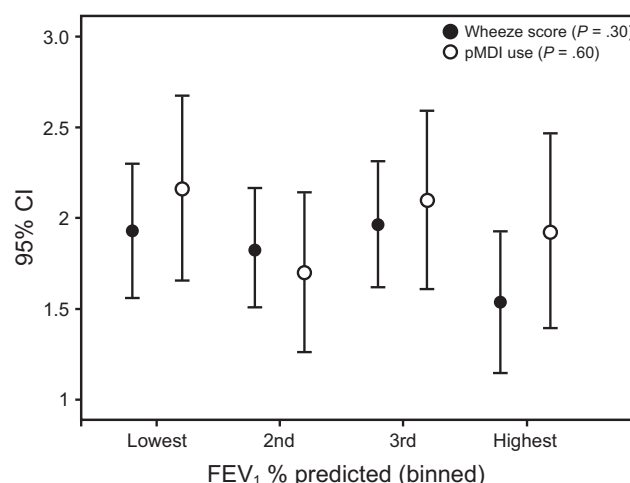


Fig. 4. Linear association between FEV₁% predicted (quartile value) to mean wheeze score and daily pressurized metered-dose inhaler (pMDI) use. There was no linear association between the 2 variables.

able to show any correlation between increased RV or RV/TLC and chest pain. It is possible that the lack of association between chest pain and short acting beta agonist (SABA) use may be a result of the instructions given to subjects to use SABA for dyspnea, cough, and wheeze only. Therefore, chest pain as a symptom needs further investigation to understand its pathogenesis.

Clinicians have been using a combination of clinical symptoms, signs, and FEV₁ reversibility to SABA in the

diagnosis of asthma. A yearly spirometry testing has been advocated to monitor disease progression and the efficacy of treatment in asthma. In our study, only a small proportion of the subjects (24%) demonstrated a low FEV₁/FVC, a key finding for airway obstruction in asthma. However, a significantly higher percentage of subjects (66%) showed an abnormal RV/TLC. This finding indicated the presence of unresolved air trapping, even in the presence

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Table 5. Linear Regression Analysis, Showing Factors Affected: Outcome Variables

Outcome Variable	Unstandardized Coefficients		Standardized Coefficients	P value	B, 95% CI
	B	Standard Error	β		
Wheeze*					
Constant	0.964	±0.666		.15	−0.355 to 2.284
FEV ₁ % predicted	−0.002	±0.005	−0.041	.69	−0.012 to 0.008
RV% predicted	0.009	±0.003	0.294	.004	0.003–0.015
pMDI use†					
Constant	−0.092	±0.908		.92	−1.890 to 1.707
FEV ₁ % predicted	0.003	±0.007	0.047	.63	−0.010 to 0.017
RV% predicted	0.016	±0.004	0.370	<.001	0.007–0.024

* $r = 0.32$, ANOVA $P = .002$ (r refers to regression coefficient and ANOVA was used for P value calculation).

† $r = 0.35$, ANOVA $P = .001$.

RV = residual volume

pMDI = pressurized metered-dose inhaler

of a normal spirometry index for obstruction in asthma (Fig. 2).⁹ The modest association observed between the wheeze score and rescue inhaler use and the increased RV supported our previous findings that lung volume measurements can provide a better understanding with regard to the pathophysiology of unresolved asthma symptoms. These findings also strengthen previous observations that spirometry measurements could miss detecting small airway dysfunction in asthma.^{21–23} Furthermore, our results were consistent with the observation from a randomized controlled trial that showed no improvement in outcome or quality of life from routine use of spirometry testing in children with asthma.¹⁹

Conclusions

The results of this study, like the previous studies, underscored the importance of lung volume measurements in addition to spirometry to accurately detect unresolved airway obstruction and air trapping in asthma. The association between the frequency of rescue SABA use and wheeze to increased RV and RV/TLC in the absence of spirometric indices, including FEV₁ reversibility, needs validation from a larger study by using a Likert scale symptom scoring protocol.

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