Clinical Roles of Lung Volumes Detected by Body Plethysmography and Helium Dilution in Asthmatic Patients: A Correlation and Diagnosis Analysis

Jian Luo1,*, Dan Liu2, Guo Chen3,*, Binmiao Liang3,* & Chuntao Liu1,*

Roles of lung volumes in asthma remain controversial. We aimed to evaluate the efficacy of lung volumes in differentiating asthma severity levels. Consecutive outpatients with chronic persistent asthma were enrolled, and body plethysmography (BP) and helium dilution (HD) were performed simultaneously to extract RV%pred, TLC%pred, and RV/TLC. Significant negative correlations were found between FEV1%pred and RV%pred (r = −0.557, P < 0.001), TLC%pred (r = −0.387, P < 0.001), and RV/TLC (r = −0.485, P < 0.001) measured by BP, as well as difference in volumes between these two techniques (ΔRV%pred, ΔTLC%pred and ΔRV/TLC). In mild and moderate asthma, AUC of RV%pred detected by BP and ΔTLC%pred was 0.723 (95%CI 0.571–0.874, P = 0.005) and 0.739 (95%CI 0.607–0.872, P = 0.002) with sensitivity and specificity being 79.41% and 88.24%, and 65.22% and 56.52% at cut-off of 145.40% and 14.23%, respectively. In moderate and severe asthma, AUC of RV%pred detected by BP and ΔTLC%pred was 0.782 (95%CI 0.671–0.893, P < 0.001) and 0.788 (95%CI 0.681–0.894, P < 0.002) with sensitivity and specificity being 77.78% and 97.22%, and 73.53% and 52.94% at cut-off of 179.85% and 20.22%, respectively. In conclusion, lung volumes are reliable complement of FEV1 in identifying asthma severity levels.

Asthma is a common, chronic airway disease with an increasing prevalence ranging from 1.8% to 14.5% of the population as varied by country and population1,2. It has been widely acknowledged that airway inflammation plays a central role in the development of asthma, which is clinically characterized by a pattern of respiratory symptoms and variable expiratory airflow limitation3. In spite of the extensive investment in treatment, much of the underlying pathogenesis of asthma remains unknown, and preventable deaths caused by asthma continue to occur, especially in patients with recurrent severe exacerbations4. Therefore, early and accurate identification of patients with risk of exacerbation and efficacious application of treatment may improve survival and quality of life in asthmatics.

Variable airflow limitation confirmed by positive bronchodilator reversibility test or positive bronchial challenge test is one of the prerequisite in establishing a diagnosis of asthma and in identifying potential exacerbation, of which forced expiratory volume in one second (FEV1) is the most commonly used and studied5,6. However, FEV1 is not necessarily associated with severity7. In recent decades, lung volumetric parameters such as residual volume (RV) and total lung capacity (TLC) have been demonstrated to be potential measures in evaluating asthma severity levels and treatment responses8–11. In addition, lung volumes especially RV reported in most studies were measured by body plethysmography (BP). BP remains as the gold standard but may lead to an overestimate of RV when in the presence of severe obstruction, due to the potential for the gas within all regions

1Department of Respiratory Diseases, West China School of Medicine and West China Hospital, Sichuan University, Chengdu, China. 2Department of Critical Care Medicine, West China School of Medicine and West China Hospital, Sichuan University, Chengdu, China. 3Department of Gerontology, Sichuan Academy of Medical Sciences and Sichuan Provincial People’s Hospital, Chengdu, China. *These authors contributed equally to this work. Correspondence and requests for materials should be addressed to B.L. (email: liangbinmiao@163.com) or C.L. (email: liuct0910@yahoo.com)
Duration of asthma (year) 4.5
Age (years) 52.0
Demographics
FEV1%pred (%) 84.1
Pre-bronchodilator
Spirometric parameters
Gender (Male, %) 6 (26.1) 18 (52.9) 24 (66.7) 0.010 0.058 0.003 0.330
FEV1 Change (mL) (in airway responsibility test) 29.7
PEF%pred (%) 70.1
Volumetric parameters
Table 1. Baseline characteristics in patients with mild, moderate and severe asthma. ANOVA, analysis of variance; FEV1, forced expiratory volume in one second; FEV1%pred, predicted percentage of forced expiratory volume in one second; FEV1/FVC, ratio of forced expiratory volume in one second to forced vital capacity; MMEF%pred, predicted percentage of maximal mid-expiratory flow; PEF%pred, predicted percentage of peak expiratory flow; RVhe%pred, predicted percentage of residual volume measured by helium dilution method; RVpleth%pred, predicted percentage of residual volume measured by body plethysmography; RV/TLCpleth, ratio of residual volume to total lung capacity measured by body plethysmography; TLCpleth%pred, predicted percentage of total lung capacity measured by body plethysmography; TLChe%pred, predicted percentage of total lung capacity measured by helium dilution method; RV/TLCpleth, ratio of residual volume to total lung capacity measured by body plethysmography; ΔRV/TLC, difference of ratio of residual volume to total lung capacity measured by body plethysmography and helium dilution method; ΔTLC%pred, predicted percentage of difference of total lung capacity between body plethysmography and helium dilution method.

of the lung and airways to undergo unequal and asynchronous compression or decompression during panting maneuvers12-14. Helium dilution (HD) is an alternative method for measuring alveolar volume but may lead to an underestimate because gas contained within the poorly ventilated regions is not included in the helium estimate of lung volume3-15. In a small study by Woolcock and colleagues, functional residual capacity (FRC) and TLC were found to be significantly higher by plethysmography than those by dilution method, and the differences between these methods were the greatest when the FEV1 was lowest, and these differences decreased during clinical recovery16. Therefore, we hypothesized that the difference in volume between these two methods may provide additional clinical value in identifying individuals with differing asthma severity.

To test this hypothesis, we conducted a prospective correlation and diagnosis analysis in an attempt to further assess the correlation between lung volumes and FEV1, and the values of individual lung volumes as well as the corresponding differences between the two methods in distinguishing asthma severity.

Results
Demographics. A total of 93 patients (48 male and 45 female) were enrolled in our final analysis, of which 23 (24.73%) had mild asthma, 34 (36.6%) had moderate asthma, and 36 (38.7%) had severe asthma. The mean age of patients with mild, moderate, and severe asthma was 52.0, 53.4, and 54.4 years old, respectively; but there was no significant difference (P = 0.777). No difference was observed in the duration of asthma (4.5 ± 4.0 vs. 4.7 ± 2.5 vs. 6.1 ± 2.9 years, P = 0.083) or smoking history (6.7 ± 8.7 vs. 10.5 ± 12.4 vs. 10.9 ± 10.8 pack*year, P = 0.321) between groups (Table 1). Despite a significant difference of gender between different asthmatic severity groups (6 vs. 18 vs. 24, P = 0.010), the between group difference was only significant between patients with mild and severe asthma (P = 0.003) (Table 1).
Lung volumes differences between BP and HD and among different asthmatic severity levels.

Predicted percentage of RV (RV%pred) measured by BP was significantly higher than that by HD regardless of asthma severity (mild: 139.0 ± 38.1% vs. 87.8 ± 18.6%, \( P < 0.001 \); moderate: 164.2 ± 24.5% vs. 100.0 ± 20.0%, \( P < 0.001 \); severe: 198.1 ± 37.8% vs. 108.5 ± 28.6%, \( P < 0.001 \) (Fig. 1A). A similar pattern was seen in predicted percentage of TLC (TLC%pred) (mild: 108.9 ± 15.6% vs. 92.7 ± 13.8%, \( P = 0.001 \); moderate: 120.2 ± 12.2% vs. 97.5 ± 11.3%, \( P < 0.001 \); severe: 127.0 ± 13.3% vs. 94.5 ± 13.5%, \( P < 0.001 \) (Fig. 1B) and RV/TLC (mild: 45.9 ± 7.5% vs. 37.2 ± 8.0%, \( P < 0.001 \); moderate: 47.2 ± 7.2% vs. 36.4 ± 7.8%, \( P < 0.001 \); severe: 56.4 ± 9.1% vs. 40.6 ± 8.4%, \( P < 0.001 \) (Fig. 1C).

We also found a significant increasing trend of RV%pred (139.0 ± 38.1% vs. 164.2 ± 24.5% vs. 198.1 ± 37.8%, \( P < 0.001 \)), TLC%pred (108.8 ± 15.6% vs. 120.2 ± 12.2% vs. 127.0 ± 13.3%, \( P < 0.001 \)), and RV/TLC (45.9 ± 7.5% vs. 47.2 ± 7.2% vs. 56.4 ± 9.1%, \( P < 0.001 \)) measured by BP, rather than HD, as asthma severity levels (Table 1). In addition, a similar elevation of differences between BP and HD in predicted percentage of RV (\( \Delta \text{RV%pred} \)) and RV/TLC (\( \Delta \text{RV/TLC} \)) was also observed.

Correlation between lung volumes and FEV\(_1\)%pred. Significant negative correlations between FEV\(_1\)%pred and RV%pred (\( r = -0.557, P < 0.001 \)), TLC%pred (\( r = -0.387, P < 0.001 \)), and RV/TLC (\( r = -0.485, P < 0.001 \)) measured by BP, as well as \( \Delta \text{RV%pred} \) (\( r = -0.457, P < 0.001 \)), \( \Delta \text{TLC%pred} \) (\( r = -0.668, P < 0.001 \)), and \( \Delta \text{RV/TLC} \) (\( r = -0.375, P = 0.002 \)) were found (Table 2) and further illustrated in scatter plots (Figs 2 and 3). Nevertheless, such a correlation was not identified between FEV\(_1\)%pred and TLC%pred (\( r = 0.089, P = 0.396 \)) and RV/TLC (\( r = -0.176, P = 0.091 \)) measured by HD, except for RV%pred (\( r = -0.245, P = 0.018 \)).

Lung volumes in distinguishing asthmatic severity levels.

In distinguishing mild and moderate asthma, area under the curve (AUC) of RV%pred, TLC%pred and RV/TLC was 0.723 (95% confidence interval (CI) 0.571–0.874), 0.700 (95%CI 0.562–0.838) and 0.549 (95%CI 0.390–0.707), respectively; and significant differences were found in RV%pred (\( P = 0.005 \)) and TLC%pred (\( P = 0.011 \)) but not in RV/TLC (\( P = 0.537 \)) (Fig. 4A). With regard to volumes, a significant difference was only found in \( \Delta \text{TLC%pred} \) (AUC 0.739, 95%CI 0.607–0.872, \( P = 0.002 \)) (Fig. 4B). Similarly, in discriminating moderate and severe asthma, we found significant differences in RV%pred (AUC 0.782, 95%CI 0.671–0.893, \( P < 0.001 \)) and RV/TLC (AUC 0.788, 95%CI 0.680–0.895, \( P < 0.001 \)) (Fig. 4C), as well as in \( \Delta \text{RV%pred} \), \( \Delta \text{TLC%pred} \), and \( \Delta \text{RV/TLC} \) (Fig. 4D).

A cut-off of 145.4% and 179.9% in RV%pred exhibited a sensitivity and specificity of 79.41% and 77.78%, and 65.22% and 73.53%, respectively, in identifying different asthma severity levels; while a cut-off of 145.4% and 20.2% in \( \Delta \text{TLC%pred} \) was estimated to have a sensitivity and specificity of 88.24% and 97.22%, and 56.52% and 52.94%, respectively, to retrieve moderate and severe asthma from mild and moderate asthma. (Table 3).

Discussion

In our study, we found that lung volumes including RV%pred, TLC%pred and RV/TLC measured by BP were significantly higher than those measured by HD, and that the volumes measured by BP as well as the difference in volume between these techniques were positively correlated with increasing severity of asthma but negatively correlated with FEV\(_1\)%pred. Furthermore, we also identified that RV%pred measured by BP and \( \Delta \text{TLC%pred} \) could reliably distinguish both mild and moderate asthma and moderate and severe asthma with a high AUC and sensitivity.
BP measures thoracic gas volumes (TGV) on the basis of Boyle’s Law, which states that, under isothermal conditions, the product of gas volume and pressure is constant at any given moment, and results in an equation of TGV = −(ΔV/ΔP) × PA2 × (Pb/Pa), of which ΔV is the change in volume of the thorax before and after compression or rarefraction of the gas in thorax, ΔP is the change in the alveolar pressure measured at the airway opening under conditions of no flow during the panting maneuver, Pa1 and Pa2 are the alveolar pressure before and after compression or rarefraction of the gas in thorax under the assumption that pressure measured at the airway opening is representative of alveolar pressure, and Pb indicates the barometric pressure15. In comparison, HD measures lung volume from communicating regions of the lung only, and the FRC at the time the subject is connected to the spirometry apparatus of a known volume (Vapp) and helium fraction (FHe1) is calculated from the helium fraction at the time of equilibration (FHe2), as the following equation: FRC = Vapp × (FHe1 + FHe2)/FHe2. Therefore, lung volumes measured by HD rely on the gas volume exhaled by the patient; and consequently gas contained within the poorly ventilated regions is not incorporated in the heliometer estimate of lung volume, leading to higher volumes measured by BP compared with HD in patients with gas trapping14,17,19. Previous studies have also demonstrated that lung volumes measured by BP may be more sensitive than HD in distinguishing different levels of current asthma status16,20. In our study, we also found such a difference in lung volumes between BP and HD, and the difference between the two methods further increased with increasing severity, which we speculate to be a result of an increasing gas trapping as demonstrated by the decreasing FEV1%pred in our study.

FEV1 is commonly used as a gold standard to diagnose chronic airway diseases, including asthma, and to evaluate their severity in accordance with the measurements of bronchodilator reversibility test or bronchial provocation test18,20,22. Nevertheless, these classifications were derived from expert opinion and were not validated in clinical studies. An increasing number of clinical observations and studies have demonstrated that FEV1 is poorly related to symptoms23. Bacharier and his colleagues found in a prospective cohort study on 219 asthmatic children that FEV1%pred was not significantly different between severity levels of asthma (99.6% vs. 97.2% vs. 101.0% vs. 93.7% in mild intermittent and persistent, and moderate and severe persistent asthma, respectively, \( P = 0.375 \))24. In addition, Stănescu and his colleagues found a lung functional pattern with decreased VC and FEV1 but increased RV/TLC, therefore, the central phenomenon of this pattern is the increase in RV and RV/TLC, which resulted in the concomitant decrease of VC and FEV1, and the lack of correlation between FEV1 and asthma severity due to the following potential mechanisms: 1) loss of elastic recoil (extrinsic obstruction), Airways closed at the same transpulmonary pressure as in healthy people but at a higher lung volume, which limited further emptying of the lungs25; 2) small airways obliteration (intrinsic obstruction), small airways narrowed at a higher transpulmonary pressure that in healthy people, which limited further expiration26.

Meanwhile, studies have also demonstrated that in many patients with asthma, lung volume is increased. Sorkness and his colleagues analyzed the plethysmographic lung function in patients with no asthma, nonsevere asthma, and severe asthma; and they found that RV, TLC, and ratio of RV to TLC (RV/TLC) were significantly higher in patients with severe asthma than in patients without asthma, and that air trapping was a characteristic feature of severe asthma population27. Furthermore, Hartley et al. have elucidated that air trapping was significantly increased in patients with asthma, and multiple regression analyses showed that in asthma subgroups with postbronchodilator predicted percentage of forced expiratory volume (FEV1%pred) less than 80%, air trapping was a strong predictor of lung function impairment28. In addition, a recent study found that higher RV/TLC was a significant determinant of decreased deep inspiration-induced bronchodilation, which was strongly correlated

| Lung volumetric parameters | \( r \) | \( P \) |
|---------------------------|------|------|
| RVpleth%pred              | −0.557 | <0.001 |
| TLCpleth%pre              | −0.387 | <0.001 |
| RV/TLCpleth              | −0.485 | <0.001 |
| RVhe%pred                | −0.245 | 0.018  |
| TLChe%pre                | 0.089  | 0.396  |
| RV/TLChe                | −0.176 | 0.091  |
| ΔRV%pred                | −0.457 | <0.001 |
| ΔTLC%pre                | −0.668 | <0.001 |
| ΔRV/TLC                | −0.375 | <0.001 |

Table 2. Correlation analysis between lung volumes and FEV1%pred. FEV1%pred, predicted percentage of forced expiratory volume in one second; RVhe%pred, predicted percentage of residual volume measured by helium dilution method; RVpleth%pred, predicted percentage of residual volume measured by body plethysmography; RV/TLCpleth, ratio of RV to TLC measured by body plethysmography; RV/TLChe, ratio of RV to TLC measured by body plethysmography; TLChe%pred, predicted percentage of total lung capacity measured by body plethysmography; ΔRV%pred, predicted percentage of difference of residual volume between body plethysmography and heliometer dilution method; ΔRV/TLC, difference of ratio of residual volume to total lung capacity between body plethysmography and heliometer dilution method; ΔTLC%pred, predicted percentage of difference of total lung capacity between body plethysmography and heliometer dilution method.
with lower FEV₁ and airway distensibility²⁹. In the present study, we also found that lung volumetric parameters (RV, TLC and RV/TLC) varied significantly in asthmatics with different severity levels and revealed a significant negative correlation between lung volumes and FEV₁%pred. Hence, it seems reasonable to believe that lung volumetric parameters have potential diagnostic values in distinguishing asthmatic severity.

For the first time, to our knowledge, our study specifically evaluated the roles of lung volumetric parameters in differentiating levels of asthma severity. In an attempt to determine whether lung function measures were consistent with levels of asthma severity, Bacharier and his colleagues classified asthma severity via symptom frequency and medication use in 219 asthmatic children⁷. Although FEV₁%pred did not differ by severity, as we cited above, they found a significant negative correlation between asthma severity and ratio of FEV₁ to forced vital capacity (FEV₁/FVC) (mild: 86.3 ± 8.5 vs. moderate: 83.0 ± 10.3 vs. severe: 79.8 ± 11.8, P < 0.001). They attributed such a negative correlation to the dysanapsis, an incongruence between the growth of the airways and lung parenchyma, which worsened in asthma with airways smaller than the lung parenchyma and could resulted in higher lung volumes; but they did not examine related parameters such as RV or RV/TLC. In our study, we found that RV%pred...
measured by BP and ΔTLC%pred, with a high sensitivity ranging from 77.78% to 97.22% and specificity between 52.94% and 73.53%, could effectively differentiate asthma severity. We also detected that TLC% measured by BP had a sensitivity as high as 82.35% in distinguishing mild and moderate asthma. In discriminating moderate and severe asthma, we found a relatively low sensitivity of 63.89% with the P value being on the borderline, which might be attributed to the limited patient samples. By contrast, RV/TLC measured by BP, ΔRV%pred and ΔRV/TLC rendered high diagnostic values only in discriminating moderate and severe asthma, and the diagnostic specificity significantly surpassed the sensitivity (RV/TLC: 85.29% and 69.44%; ΔRV%pred: 85.29% and 58.33%), except for an equivalence in ΔRV/TLC (64.71% and 69.44%), which may result from the higher increase of gas trapping in severe asthma than that in mild asthma, as well as a similar increase of RV and TLC in mild asthma but a higher increase of RV than TLC in severe asthma. Nevertheless, a definitive conclusion of the influencing factors could not be drawn because we were unable to conduct spirometry in these patients before the onset of asthma to collect the baseline lung volumes.

Despite the findings, the present study had three limitations, which may need cautious interpretation of our results. For one thing, the number of participants is small, especially those with mild asthma, which may result in an inaccuracy of our findings. Secondly, the severity levels of asthma used in this study are based on outdated guidelines (NAEPP 1997), which lack assessment of beta2-agonist reliever use. The severity classification scheme better reflects what is currently termed asthma control according to the most recent guidelines introduced by the Global Initiative for Asthma (GINA). Thirdly, in addition to a diagnosis of asthma, a large proportion of the patients in this study have significant smoking history across all severity groups and persistent airflow limitation could not be entirely excluded, such that chronic obstructive pulmonary disease (COPD) may be a confounder.
Finally, we used FEV1 to identify asthma severity in our study, which might not entirely uncover the true relationship among FEV1, gas trapping and asthma severity.

Conclusions
In the diagnosis of asthma, body plethysmography is the optimal assessing method, and lung volumes assessed by body plethysmography as well as the difference between body plethysmography and helium dilution can differentiate between mild vs. severe, and moderate vs. severe asthma, but not mild vs. moderate asthma. Nevertheless, future investigations are still warranted to further reveal the correlation of lung volumes and asthma functional outcomes such as asthma controls, and to confirm the clinical applicability of lung volumes in discriminating asthma severity in clinical settings.

Methods
Study protocol was approved by the Institutional Ethical Committee for Clinical and Biomedical Research of West China Hospital (Sichuan, China), and all participants provided written informed consent. All methods were performed in accordance with the relevant guidelines and regulations released by the Chinese National Institutes of Health and the Clinical Trial Center of West China Hospital.

Patients. From January 2014 to April 2015, consecutive outpatients with chronic persistent asthma were enrolled in West China Hospital, Sichuan University. The diagnostic criteria of asthma were recommended by the Global Initiative for Asthma (GINA) 2012 guideline including: 1) recurrent respiratory symptoms with episodic breathlessness, wheeze, cough, and chest tightness, which were often triggered by incidental allergen exposure, seasonal variability and upper respiratory tract infection, and might resolve spontaneously or in response to medication; 2) airflow reversibility or airway responsiveness documented by lung function test, which was an increase in FEV1 of \( >12\% \) and \( >200 \) ml from baseline or a diurnal variation if peak expiratory flow (PEF) of \( >20\% \) or a fall in FEV1 from baseline of \( \geq 20\% \) with standard doses of methacholine\(^{22}\). We excluded patients with additional obstructive lung diseases, such as COPD, asthma-COPD overlap syndrome (ACOS), and cystic fibrosis.

Chronic persistence was defined as onset of asthmatic symptoms every week with various frequency or extent, and three severity levels were classified in accordance with the guideline released by National Asthma Education and Prevention Program (NAEPP) on the basis of daytime symptoms, night waking, activity limitation due to asthma, and FEV1%pred\(^{21}\): mild persistent (daytime symptoms \( \geq 1 \) episode/week but not daily presenting, night waking >2 episode/month but \( <1 \) episode/week, probable activity limitation, and FEV1%pred >80%), moderate persistent (daily daytime symptoms, night waking \( \geq 1 \) episode/week, activity limitation, and 60% \( \leq \) FEV1%pred \( \leq 80\% \)) and severe persistent (daily daytime symptoms, frequent night waking, activity limitation, and FEV1%pred \( <60\% \)).

Lung function test. To detect lung volumes (RV, TLC), BP and HD were performed in all enrolled patients using a calibrated equipment (JAEGER, Jaeger Corp, Germany), consisting of a mixing fan, carbon dioxide (CO2)

| Table 3. Cut-off points of RVpleth%pred and ΔRV%pred, TLCpleth%pred and ΔTLC%pred, RV/TLCpleth and ΔRV/TLC, and the corresponding sensitivity, specificity, PPV, NPV and LR in distinguishing different asthma severity levels. |
|------------------|-----------------|-----------------|-----------|-----------|------------|--------|--------|
|                  | Cut-off point   | Sensitivity     | Specificity | PPV       | NPV        | LR+    | LR−    |
| Mild vs. Moderate| RVpleth%pred    | 145.4           | 79.41       | 65.22     | 77.14      | 68.18  | 2.28   |
|                  | TLCpleth%pred   | 108.7           | 82.35       | 47.83     | 70.00      | 64.71  | 1.58   |
|                  | RV/TLCpleth     | 45.8            | 61.76       | 56.52     | 67.74      | 50.00  | 1.42   |
|                  | ΔRV%pred        | 42.0            | 85.29       | 43.48     | 69.05      | 66.67  | 1.51   |
|                  | ΔTLC%pred       | 14.2            | 88.24       | 56.52     | 75.00      | 76.47  | 2.03   |
|                  | ΔRV/TLC         | 3.1             | 91.18       | 30.43     | 65.96      | 70.00  | 1.31   |
| Moderate vs. Severe| RVpleth%pred   | 179.9           | 77.78       | 73.53     | 75.76      | 75.76  | 2.94   |
|                  | TLCpleth%pred   | 123.4           | 63.89       | 67.65     | 67.65      | 63.89  | 1.97   |
|                  | RV/TLCpleth     | 53.1            | 69.44       | 85.29     | 83.33      | 72.50  | 4.72   |
|                  | ΔRV%pred        | 88.5            | 58.33       | 85.29     | 80.75      | 65.91  | 3.97   |
|                  | ΔTLC%pred       | 20.2            | 97.22       | 52.94     | 68.63      | 94.74  | 2.07   |
|                  | ΔRV/TLC         | 11.7            | 69.44       | 64.71     | 67.57      | 66.67  | 1.97   |

LR, likelihood ratio; NPV, negative predictive value; PPV, positive predictive value; RVpleth%pred, predicted percentage of residual volume measured by body plethysmography; RV/TLCpleth, ratio of RV to TLC measured by body plethysmography; TLCpleth%pred, predicted percentage of total lung capacity measured by body plethysmography; ΔRV%pred, predicted percentage of difference of residual volume between body plethysmography and helium dilution method; ΔRV/TLC, difference of ration of residual volume to total lung capacity between body plethysmography and helium dilution method; ΔTLC%pred, predicted percentage of difference of total lung capacity between body plethysmography and helium dilution method.
absorber, oxygen (O₂) and helium supply, a gas inlet and outlet, and a water vapor absorber, and followed by MasterScreen Pulmonary Function Test (PFT) System to measure spirometry (FEV₁, FEF).

All test procedures complied with the standardizations recommended by American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines. BP contained a series of gentle pants at a frequency between 0.5 and 1.0 Hz to calculate lung volumes. When HD was used, patients were instructed to breathe for 30–60 seconds, and then switched them to the helium gas (turn in). The helium concentration was recorded every 15 seconds until the helium equilibration was complete (i.e. change of helium concentration is < 0.02% for 30 seconds). The participants were finally disconnected from the helium gas (turn out). Spirometry was conducted via three distinct phases to depict the flow-volume curves including: 1) maximal inspiration; 2) a “blast” of exhalation; and 3) continued complete exhalation until the volume-time curve showed no change in volume (< 0.025 L) for ≥ 1s and the subject had tried to exhale for ≥ 6 s.

Spirometrics were detected as predicted percentage of FEV₁ (FEV₁, %pred), PEF (PEF %pred), and maximal mid-expiratory flow (MMEF %pred); while lung volumes were displayed as predicted percentage of RV (RV %pred) and TLC (TLC %pred), and RV/TLC. Differences in lung volumes between BP and HD were calculated as predicted percentage of RV (△RV %pred), TLC (△TLC %pred) and RV/TLC (△RV/TLC).

**Statistical analysis.** Continuous data were reported as mean and standard deviation (SD), while dichotomous data were reported as frequency and proportion. SPSS 21.0 (Copyright (c) SPSS Inc. 1989–2007) was used to test the hypothesis with a two-sided P value of < 0.05 indicating statistical significance. Baseline lung function measures, such as FEV₁, %pred, PEF %pred, MMEF %pred, RV %pred, TLC %pred, RV/TLC, △RV %pred, △TLC %pred, and △RV/TLC %pred differences, were compared among three severity levels using One-way Analysis of Variance (ANOVA) and Least-Significant Difference (LSD) posthoc tests. Student-t test was conducted to compare the RV %pred, TLC %pred and RV/TLC between BP and HD. Correlation analysis was performed to calculate r value between lung volumetric parameters (RV %pred, TLC %pred, RV/TLC, △RV %pred, △TLC %pred, and △RV/TLC) and FEV₁ %pred. We depicted receiver operating characteristic (ROC) curves and calculated area under the curve (AUC) to evaluate the accuracy of RV %pred, TLC %pred, RV/TLC, △RV %pred, △TLC %pred, and △RV/TLC in discriminating different asthmatic severity levels. Cutoff points were defined as the point when Youden’s index (= sensitivity + specificity -1) reached the maximum, and the sensitivity, specificity, positive predictive values (PPV’s), negative predictive values (NPV’s) as well as likelihood ratios (LRs) were also calculated in different severity levels.

**References**

1. Gaviola, C. et al. Urbanisation but not biomass fuel smoke exposure is associated with asthma prevalence in four resource-limited settings. *Thorax* 71, 154–160 (2016).
2. Jousilahti, P., Haohtela, T., Laatikainen, T., Mäkelä, M. & Vartiainen, E. Asthma and respiratory allergy prevalence is still increasing among Finnish young adults. *Eur Respir J* 47, 985–987 (2016).
3. Global Strategy for Asthma Management and Prevention. Global Initiative for Asthma (GINA). Available at: www.ginasthma.org. (Accessed: 11st August 2015).
4. Bush, A., Kleinert, S. & Pavord, I. D. The asthma in 2015 and beyond: a Lancet Commission. *Lancet* 385, 1273–1275 (2015).
5. Fuhlbrigge, A. L. et al. FEV₁ (1) is associated with risk of asthma attacks in a pediatric population. *J Allergy Clin Immunol* 107, 61–67 (2001).
6. Kitch, B. T. et al. A single measure of FEV1 is associated with risk of asthma attacks in long-term follow-up. *Chest* 126, 1875–1882 (2004).
7. Bacharier, L. B. et al. Classifying asthma severity in children: mismatch between symptoms, medication use, and lung function. *Am J Respir Crit Care Med* 170, 426–432 (2004).
8. Kraemer, R., Meister, B., Schaad, U. B. & Rossi, E. Reversibility of lung function abnormalities in children with perennial asthma. *J Pediatr* 102, 347–350 (1983).
9. Miller, A. & Palecki, A. Restrictive impairment in patients with asthma. *Respir Med* 101, 272–276 (2007).
10. Stänescu, D. Small airways obstruction syndrome. *Chest* 116, 231–233 (1999).
11. Stänescu, D. & Veriter, C. A normal FEV1/VC ratio does not exclude airway obstruction. *Respiration* 71, 348–352 (2004).
12. Wanger, J. et al. Standardisation of the measurement of lung volumes. *Eur Respir J* 26, 531–522 (2005).
13. Coertjens, P. C. et al. Can the single-breath helium dilution method predict lung volumes as measured by whole-body plethysmography? *J Bras Pneumol* 39, 675–685 (2013).
14. O’Donnell, C. R. et al. Comparison of plethysmographic and helium dilution lung volumes: which is best for COPD? *Chest* 137, 1108–1115 (2010).
15. Kilburn, K. H., Miller, A. & Warshaw, R. H. Measuring lung volumes in advanced asbestososis: comparability of plethysmographic and radiographic versus helium rebreathing and single breath methods. *Respir Med* 87, 115–120 (1993).
16. Woolcock, A. J., Re buck, A. S., Cade, J. E. & Read, J. Lung volume changes in asthma measured concurrently by two methods. *Am Rev Respir Dis* 104, 703–709 (1971).
17. Coates, A. L., Peslin, R., Rodenstein, D. & Stocks, J. Measurement of lung volumes by plethysmography. *Eur Respir J* 10, 1415–1427 (1997).
18. Meneely, G. R. & Kaltreider, N. L. The volume of the lung determined by helium. Description of the method and comparison with other procedures. *J Clin Invest* 28, 129–139 (1949).
19. Stocks, J. & Quanjer, P. H. Reference values for residual volume, the subject’s residual capacity and total lung capacity. ATS Workshop on Lung Volume Measurements. Official Statement of The European Respiratory Society. *Eur Respir J* 8, 492–506 (1995).
20. Jarenbäck, L., Ankerst, J., Bjermar, L. & Tuveaas, E. Flow-Volume Parameters in COPD Related to Extended Measurements of Lung Volume, Diffusion, and Resistance. *Palm Med* 2013, 782052 (2013).
21. National Heart, Lung, and Blood Institute. Expert panel report 2: guidelines for the diagnosis and management of asthma (EPR-2 1997). Available at: www.nhlbi.nih.gov/guidelines/archives/epr2/asthgdln_archive.pdf. Accessed September 19, 2007.
22. Global Strategy for Asthma Management and Prevention. Global Initiative for Asthma (GINA). Available at: www.ginasthma.org. (Accessed: 13rd March 2012).
23. The Childhood Asthma Management Program Research Group. Long-term effects of budesonide or nedocromil in children with asthma. *N Engl J Med* 343, 1054–1063 (2000).
24. Mahut, B., Peiffer, C., Bokov, P., Beydon, N. & Delclaux, C. Gas trapping is associated with severe exacerbation in asthmatic children. *Respir Med* 104, 1230–1233 (2010).
25. Leith, D. E. & Mead, J. Mechanisms determining residual volume of the lungs in normal subjects. *J Appl Physiol* 23, 221–227 (1967).
26. Holland, J., Milic-Emili, J., Macklem, P. T. & Bates, D. V. Regional distribution of pulmonary ventilation and perfusion in elderly subjects. *J Clin Invest* 47, 81–92 (1966).
27. Sorkness, R. L. et al. Lung function in adults with stable but severe asthma: air trapping and incomplete reversal of obstruction with bronchodilation. *J Appl Physiol* (1985). 104, 394–403 (2008).
28. Hartley, R. A. et al. Relationship between lung function and quantitative computed tomographic parameters of airway remodeling, air trapping, and emphysema in patients with asthma and chronic obstructive pulmonary disease: A single-center study. *J Allergy Clin Immunol* 137, 1413–1422 (2016).
29. Pyrgos, G., Scichilone, N., Togias, A. & Brown, R. H. Bronchodilation response to deep inspirations in asthma is dependent on airway distensibility and air trapping. *J Appl Physiol* (1985) 110, 472–479 (2011).
30. Miller, M. R. et al. Standardisation of spirometry. *Eur Respir J* 26, 319–338 (2005).

Acknowledgements

This study was partly supported by Sichuan Science and Technology Agency Grant (2014SZ0010) and Ministry of Science and Technology of the People's Republic of China (2015BAI12B10). We thank Professor Dongtao Lin (College of Foreign Languages and cultures, Sichuan University), who is specialized in biomedical writing and editing, for copyediting this manuscript.

Author Contributions

J.L. and B.M.L. were responsible for study design and conception, and drafting the article; J.L. and G.C. revised the article critically for important intellectual content, such as statistical analysis and discussion; J.L., G.C. and D.L. were responsible for acquisition, analysis and interpretation of data; B.M.L. and C.T.L. provided final approval of the version to be published and were responsible for all aspects of the work to ensure that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved. All authors read and approved the final manuscript.

Additional Information

Competing financial interests: The authors declare no competing financial interests.

How to cite this article: Luo, J. et al. Clinical Roles of Lung Volumes Detected by Body Plethysmography and Helium Dilution in Asthmatic Patients: A Correlation and Diagnosis Analysis. *Sci. Rep.* 7, 40870; doi: 10.1038/srep40870 (2017).

Publisher's note: Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

This work is licensed under a Creative Commons Attribution 4.0 International License. The images or other third party material in this article are included in the article’s Creative Commons license, unless indicated otherwise in the credit line; if the material is not included under the Creative Commons license, users will need to obtain permission from the license holder to reproduce the material. To view a copy of this license, visit http://creativecommons.org/licenses/by/4.0/

© The Author(s) 2017