Published in final edited form as:

Respirology. 2014 October ; 19(7): 1046–1051. doi:10.1111/resp.12347.

The Relationship Between the Baseline Alveolar Volume-to-Total Lung Capacity Ratio and Airway Responsiveness

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Abstract

Background and objective—Ventilation heterogeneity (VH) has been linked to airway responsiveness (AR) based on various measures of VH involving inert gas washout, forced oscillation and lung imaging. We explore whether VH at baseline, as measured by the simple ratio of single breath alveolar volume to plethysmographically determined total lung capacity (VA/TLC), would correlate with AR as measured by methacholine challenge testing.

Methods—We analyzed data from spirometry, lung volumes, diffusing capacity and methacholine challenge to derive the VA/TLC and the dose-response slope of FEV1 (DRS-FEV1) during methacholine challenge from 136 patients. We separated out airway closure vs. narrowing by examining the DRS for FVC (DRS-FVC) and the DRS for FEV1/FVC (DRS-FEV1/FVC), respectively. Similarly, we calculated the DRS for sGaw (DRS-sGaw) as another measure of airway narrowing. We performed statistical analysis using Spearman rank correlation and multifactor linear regression using a backward stepwise modeling procedure.

Results—We found that the DRS-FEV1 correlated with baseline VA/TLC ($\rho = -0.26$, $p < 0.01$), and VA/TLC and FEV1 were independently associated with DRS-FEV1 ($R^2 = 0.14$, $p = 0.01$). In addition, VA/TLC was associated with both airway narrowing and closure in response to methacholine.

Conclusions—These results confirm that baseline VA/TLC is associated with AR, and reflects both airway closure and airway narrowing following methacholine challenge.

Keywords

asthma; clinical respiratory medicine; respiratory function tests; respiratory mechanics; respiratory structure and function

Introduction

One of the defining features of asthma is airway hyperresponsiveness (AHR). AHR is the increased sensitivity and enhanced narrowing of the airways to stimuli that lead to bronchoconstriction. The mechanism of AHR is not well understood, but may be related to increased sensitivity of the airway smooth muscle to a contractile agonist, increased strength or velocity of smooth muscle shortening, airway wall thickening, or uncoupling of the airway from the surrounding parenchyma due to peribronchiolar inflammation.¹ In addition, the observation has been made that increased VH is an important determinant of AHR in asthma,²⁻⁶ and that airway closure appears to be a predominant process involved in AHR.⁷⁻¹⁰

Ventilation heterogeneity (VH) has traditionally been measured by a single breath or multiple breath inert gas washout technique (such as multiple breath nitrogen washout, MBNW), the forced oscillation technique (FOT),^{2-6, 11} or by various imaging modalities.^{8, 9, 12-17} Interestingly, a common measurement made in the clinical pulmonary function testing (PFT) lab also reflects VH. This measurement is the ratio of the single breath alveolar volume (VA) from the test for diffusing capacity of the lung for carbon monoxide (DLCO), to the total lung capacity (TLC) determined by body plethysmography or a multiple breath inert gas dilution technique, the VA/TLC¹⁸. In health, complete distribution of the inert gas during the brief 10 sec breath-hold of the DLCO test provides VA and TLC values that are essentially equal (VA/TLC = 85%);¹⁹ however, as VH increases, gas distribution during the measurement is reduced so that VA underestimates TLC (VA/TLC < 85%). Heterogeneous ventilation, as measured by reduced VA/TLC, is typically seen in patients with airways disease such as asthma and COPD¹⁸⁻²⁸, although the association of VA/TLC to AHR is unknown.

Since the VA/TLC represents a global measure of VH, we hypothesized that baseline VA/TLC would be associated with airways responsiveness (AR). We commonly measure lung volumes and specific airway conductance at baseline and at the end of the methacholine challenge test, and many patients also have concomitantly measured baseline DLCO (which includes VA) on the same day. Accordingly, we analyzed the baseline VA and TLC data and methacholine challenge data to explore the hypothesis that VA/TLC is correlated with AR. We also determined the relative contributions of airway narrowing vs. airway closure to the association between AR and baseline VA/TLC.

Methods

We analyzed all PFTs that included spirometry, lung volumes, DLCO and methacholine challenge that occurred over a 10-year period in the laboratory at Fletcher Allen Health Care, a tertiary care teaching hospital affiliated with the University of Vermont College of Medicine. The study was approved by the University of Vermont Committee on Human Research in the Medical Sciences (Study # M13-257). All testing was performed on the same equipment (MGC Diagnostics, Inc., Minneapolis, MN) according to standard guidelines.²⁹⁻³² First, baseline measurements of spirometry, lung volumes and specific airway conductance (sGaw) (by body plethysmography), and DLCO were made. The DLCO

was measured using a single breath technique, with VA calculated from the dilution of the inspired tracer gas. Then, methacholine challenge testing was performed by the 5 deep breath method using Provocholine® (Methapharm, Inc., Coral Springs, FL) in doubling concentrations from 0.03 to 16 mg/ml using a nebulizer controlled by a dosimeter to deliver 0.009 ml of solution per actuation. We calculated the provocative concentration causing a 20% fall in FEV1 (PC20) or a 40% fall in sGaw (PC40) and defined AHR as a PC20 or PC40 < 8 mg/ml. Because we were interested in VH and its contributing factors of airway narrowing and airway closure, we assessed the contribution to AR from airway narrowing as the change in FEV1/FVC and the contribution from airway closure as the change in FVC.⁷ This concept is derived from the idea that FEV1 reflects both airway closure and airway narrowing, represented by FVC and FEV1/FVC, respectively.^{33, 34} The proportion of change in FEV1 due to airway closure was expressed as the percent change in FVC divided by the percent change in FEV1 and termed the closing index.⁷ We also assessed the contribution to AR from airway narrowing as the change in sGaw.

In addition, based on this dose delivery schedule, we calculated the cumulative dose of methacholine, from which we calculated the dose response slope (DRS), defined as the percent fall in FEV1 divided by the cumulative dose of methacholine delivered (DRS-FEV1).^{35, 36} This allowed us to use the methacholine response data from all subjects, regardless of whether they met the conventional definition of AHR based on PC20 < 8 mg/ml. The DRS-FEV1 thus provided a continuous measure of generalized AR so that we could assess numerical correlation with VA/TLC. Since log DRS-FEV1 vs. log PC20 was directly correlated, we calculated the DRS-FEV1 at which PC20 = 8 in order to set a threshold value for determining AHR from the DRS data alone. This allowed inclusion of those patients who had a PC20 ≥ 8 mg/ml for FEV1, but achieved a PC40 < 8 mg/ml for sGaw, which we considered clinically to be consistent with AHR. We also calculated the DRS for airway narrowing and airway closure as the maximal change in FEV1/FVC (DRS – FEV1/FVC) and maximal change in FVC (DRS-FVC) divided by the cumulative dose of methacholine, respectively.⁷ In addition, we calculated the DRS for change in sGaw (DRS-sGaw) as another index of overall airway narrowing in response to methacholine.

We expressed normally distributed data as means (SD), and non-normally distributed data as medians (25-75th interquartile range, IQR). Data for PC20 and DRS became normally distributed after log transformation and are expressed as geometric mean (95% confidence interval, CI). Data for closing index and VA/TLC remained non-normally distributed even after log transformation. We added a constant of 3 to all DRS data in order to allow log transformation of those results – zero.³⁶ We performed statistical analysis using unpaired t-tests or Wilcoxon tests, Chi-Square test, and Spearman rank correlation, as appropriate, and multifactor linear regression using a backward stepwise modeling procedure. All data were analyzed using JMP Statistical Software (JMP® 9.0, SAS Institute, Inc., Cary, NC), and p-values < 0.05 were considered statistically significant.

Results

There were data available on a total of 142 patients, but 6 were excluded, five due to reaction to saline control, and one due to vocal cord dysfunction. The results of the

remaining 136 patients are shown in Tables 1-3. As shown in Table 1, most were being evaluated for shortness of breath or cough, or to specifically rule out asthma. For the group as a whole, spirometry, lung volumes, DLCO and sGaw were within normal limits. The VA/TLC was <0.85 in 17 (12%) subjects. Of the total, 43 subjects (32%) had AHR as defined by a $PC_{20} < 8$ mg/ml, and 53 (39%) on the basis of $PC_{40} < 8$ mg/ml. The DRS that corresponded to $PC_{20}=8$ mg/ml was $5.14 \text{ } \mu\text{mole}$. There was a significant correlation between having a low VA/TLC (<0.85) and AHR measured by PC_{20} or DRS-FEV1 > 5.14 ($\chi^2=13.65$, $p < 0.01$ and $\chi^2=7.85$, $p=0.01$, respectively), but not by PC_{40} ($\chi^2=1.11$, $p=0.29$). Comparing those with and without AHR based on DRS-FEV1 > 5.14 (Table 2), we found that participants with AHR were slightly older, had a lower FEV1, higher RV/TLC and lower VA/TLC, and a greater closing index. There was evidence of both airway narrowing and airway closure among the group with AHR, as shown by the changes in DRS-FEV1/FVC, DRS-FVC and DRS-sGaw.

The primary outcome, DRS-FEV1 vs. baseline VA/TLC, showed a significant correlation (Figure 1). Furthermore, baseline VA/TLC correlated with DRS-FVC ($\rho = -0.26$, $p < 0.01$), the closing index ($\rho = -0.20$, $p = 0.02$) and DRS-sGaw ($\rho = -0.19$, $p = 0.03$), but not DRS-FEV1/FVC ($\rho = -0.13$, $p = 0.14$). The association of DRS-FEV1 and VA/TLC was not significant when examined separately among the cohort with AHR ($n = 61$, $\rho = -0.10$, $p = 0.44$), or without AHR ($n=75$, $\rho = -0.22$, $p = 0.53$).

When we analyzed the relationship of baseline physiological features of the entire cohort, we found significant correlations between baseline VA/TLC and FEV1 % predicted ($\rho = 0.35$, $p < 0.01$), FEV1/FVC ($\rho = 0.26$, $p < 0.01$) and RV/TLC ($\rho = -0.64$, $p < 0.01$) (Figure 2). We also explored the relationship of RV/TLC to the closing index, DRS-FEV1, DRS-FVC, DRS-FEV1/FVC and DRS-sGaw, and found significant correlations with all of these (data not shown). When modeled by multifactor linear regression, only FEV1% predicted and VA/TLC remained as determining factors of AR as measured by DRS-FEV1, with an adjusted R^2 of 0.14, $p=0.01$ (Table 3).

Discussion

The results of this study demonstrate that among a diverse group of patients baseline VH as measured by a lower VA/TLC is greater in patients with AHR compared to those without AHR, and VA/TLC is modestly correlated with AHR. In addition, baseline VA/TLC appears to be an independent determinant of AR. This is the first time that VA/TLC, a simple index of VH, has been related to AR. While we are not suggesting that VA/TLC can substitute for direct measures of AR such as PC_{20} or DRS, our findings are unique because they relate a commonly measured marker of VH derived from the clinical PFT lab, which contributes to our understanding of the pathophysiology of AR.

Ventilation heterogeneity has been linked to AR through many previous observations. Most of these studies have measured VH through imaging techniques,^{8, 9, 12-17} or using physiological measures including MBNW and FOT.^{2-6, 11} All of these techniques typically require specialized equipment and are not readily available to clinicians, although the MBNW and FOT are becoming more popular. In the current study, we used the simple

VA/TLC ratio as an indicator of VH present during the single 10-sec breath-hold maneuver part of determining DLCO. We used 85% as the lower limit of normal of VA/TLC.¹⁹ A low VA/TLC reflects VH, as supported by data showing that a low VA/TLC correlates with an increased inert gas phase III slope,²⁴ and VA as an estimate of TLC can be corrected for the degree of VH²² or airflow limitation.²⁵ As expected, in emphysema where there is a high degree of heterogeneous ventilation, VA/TLC underestimates total lung volume³⁷ and, conversely, is a good reflection of the amount of non-emphysematous lung on CT.²⁷ Although studies describing the relationship between VA and TLC go back many years²³, there has recently been renewed interest in the VA/TLC as a measure of VH.^{18, 38, 39}

Ventilation heterogeneity is well described in asthma and plays an important role in abnormal gas exchange.⁴⁰ However, it is unclear how VH is linked to AR. Computational modeling reveals that VH leads to overall increases in lung impedance^{41, 42} and instability of airways that can result in enhanced narrowing and closure in response to a bronchoconstricting stimulus, which may propagate up and down the airway tree in a positive feedback mechanism, thus resulting in AR.⁴³⁻⁴⁵ Increased baseline VH would also result in uneven deposition of any inhaled bronchoconstricting agonist, such as methacholine, leading to enhanced airway narrowing or closure at, or downstream from, sites of increased deposition.⁴⁶

Ventilation heterogeneity is not necessarily specific to one disease, but could be induced by any process that leads to non-uniform airway caliber, such as variable airway smooth muscle contraction, airway wall inflammation or remodeling, intraluminal exudate or reductions in airway-parenchymal tethering. When asthmatic subjects with increased VH and AR are treated with inhaled corticosteroids, their degree of VH and AR is reduced, suggesting that at least some of their VH is due to airway inflammation.³ However, ventilation heterogeneity and AR are not normalized by inhaled corticosteroid therapy, suggesting that underlying structural abnormalities in the lungs exist that contribute to uneven ventilation.³ Interestingly, even when imposed on healthy subjects, VH leads to AR, thus supporting a mechanism independent of airway inflammation or any specific disease pathology.²

We found that VA/TLC was modestly correlated with AR. In addition, we divided the response into DRS-FEV1/FVC and DRS-FVC in order to determine whether the bronchoconstrictive response was more closely associated with airway narrowing or airway closure. Our results suggest that both effects were occurring, with a higher closing index among those with AHR suggesting that airway closure was the predominant response, similar to the findings from previous studies^{7, 33, 34}. In addition, baseline VA/TLC correlated with DRS-FVC but not DRS-FEV1/FVC, suggesting that this measure of baseline VH is associated with airway closure but not airway narrowing. However, baseline VA/TLC also correlated with DRS-sGaw, which may indicate an association with airway narrowing that is not revealed by the DRS-FEV1/FVC. We speculate that this may be due to the bronchodilating effect of the deep breath involved in measuring FEV1 and FVC that may mask any mild airway narrowing detected by sGaw⁴⁷.

Statistical modeling demonstrated that baseline VA/TLC and FEV1 %predicted were the only factors that contributed independently to AR. We suspect that baseline VA/TLC

contributed via its effects on airway narrowing and closure, as discussed, while baseline FEV1 likely contributed because it is a global measure of airway caliber that reflects many of the key factors associated with AR, such as reduced airway smooth muscle length, inflammation and remodeling.¹ In addition, FEV1 may independently contribute to AR simply on geometric grounds, with a lower FEV1 resulting in a greater percent change in airway diameter for a given degree of airway smooth muscle shortening⁴⁸. Of course, the low coefficient of determination ($R^2 = 0.14$) indicates that other factors not revealed by our study are also involved in the pathogenesis of AR.

There are some limitations to our study. First, we studied a mixed population of patients presenting to a tertiary care center for methacholine challenge testing. While the results of the study may therefore be relevant to the typical, unselected patient presenting to a clinical PFT lab, the results necessarily apply only to a general population. It would be interesting to analyze VA/TLC data in relation to AR among specified groups of patients with various phenotypes of asthma and COPD. Our inability to demonstrate a statistically significant association between DRS-FEV1 and VA/TLC among the cohort of patients with AHR in our population was likely due to the small sample size and clinical heterogeneity of this group. Second, our population overall had normal baseline lung function, and only very few had abnormalities of VA/TLC. Thus, the signal to detect a strong association between VA/TLC and AR may have been diluted by the predominance of normal individuals. Third, all the data are derived from methacholine challenge studies that used the 5 deep breath dosimeter method. The deep breaths associated with this method might have reduced AR among those patients with mild AHR,⁴⁹ thus diminishing the signal we were looking for. However, subjects must take a deep breath to measure VA and TLC, thus making the 5 deep breath more appropriate in the current analysis. Finally, the baseline VA/TLC, measured above FRC without forced exhalation, may not reflect the same mechanisms involved in AR that are inferred from the changes in FEV1 and FVC, which are measured during forced exhalation from TLC to RV.

In conclusion, this study demonstrates an association between AR and baseline VH as measured by VA/TLC in a population of patients referred for methacholine challenge testing. This suggests that a low baseline VA/TLC may be a physiological marker of AHR in selected patients. In addition, baseline VA/TLC may reflect the propensity for both airway closure and airway narrowing during methacholine challenge.

Acknowledgments

David Kaminsky was supported, in part, by NIH grant P30GM103532. David Chapman is a recipient of a CJ Martin Fellowship from the National Health and Medical Research Council of Australia (# 1053790).

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Summary at a Glance

We found that the baseline ratio of alveolar volume to total lung capacity (VA/TLC), as a measure of ventilation heterogeneity, correlates with airway responsiveness among a diverse group of patients undergoing methacholine challenge testing.

Figure 1.

The Relationship Between Baseline VA/TLC and DRS-FEV1. Closed circles = subjects with AHR defined by DRS-FEV1 > 5.14 % /μmole, open circles = subjects without AHR. Correlation analyzed by Spearman's rank order test.

Figure 2.

The Relationship Between Baseline VA/TLC and Baseline FEV₁ (A), FEV₁/FVC (B) and RV/TLC (C). All correlations analyzed by Spearman's rank order test.

Table 1
Demographic Features of Study Participants

Demographics n=136	
Age (yrs) *	52 (14)
Gender (%M/F)	41/59
BMI (kg/m ²) *	30 (7)
Smoking status (% current/former/never)	7/29/51
Pack-yrs smoking (among current + former) *	9 (22)
Indication for PFTs (n (%))	
Shortness of breath	62 (45)
Cough	32(23)
Rule out asthma	35(26)
Wheezing	2(2)
Underlying diagnosis listed (n (%))	
Asthma	65(48)
COPD	6 (4)
Interstitial Lung Disease	3 (2)
Cardiac disease	50(37)
Hypertension	49(36)
Diabetes	19 (14)
Other	3 (2)
None	57 (42)
Baseline Pulmonary Function Tests *	
FEV1 (L, % predicted)	2.73 (0.77) (86 (14))
FVC (L, % predicted)	3.56 (1.0) (87 (14))
FEV1/FVC	0.77 (0.70)
TLC (L, % predicted)	5.80 (1.20) (100 (14))
FRC (L, % predicted)	3.01 (0.80) (97 (23))
RV (L, % predicted)	2.19 (0.67) (113 (29))
RV/TLC	0.38 (0.10)
sGaw (L/cmH20-sec) †	0.21 (0.17-0.26)
VA/TLC †	0.94 (0.89-0.99)
Methacholine Challenge	
PC20 (mg/ml) ‡, §	12.39 (10.26-15.0)
DRS-FEV1 +3 (% /μmole) §	8.32 (7.08-9.77)
DRS-FVC + 3 (% /μmole) §	6.61 (5.75-7.76)
DRS-FEV/FVC + 3 (% /μmole) §	4.68 (4.07-5.37)
Closing Index †	0.66 (0.36-0.85)

Demographics n=136	
PC40 (mg/ml) [‡] , § n= 130	9.77 (7.94-12.02)
DRS-sGaw + 3 (% /μmole) §	12.59 (10.23-15.85)

* mean (standard deviation)

[‡] median (25-75 interquartile range)

[‡] calculation of overall PC20 or PC40 assumes all participants with PC20 or PC40 > 16 had PC20 or PC40 = 25.

§ geometric mean (95% confidence interval)

Table 2
Characteristics of Participants with and without Airway Hyperresponsiveness

Characteristics	With AHR (DRS-FEV1 > 5.14 % /μmole)	Without AHR (DRS-FEV1 ≤ 5.14 % /μmole)	P-value
N (%)	61 (45)	75 (55)	
Age (yrs) *	55 (13)	49 (14)	0.01
Gender (M/F%)	36/64	45/55	0.27
BMI (kg/m ²) *	30 (7)	29 (6)	0.29
FEV1% *	84 (14)	89 (14)	0.02
FVC% *	86 (14)	90 (14)	0.06
FEV1/FVC *	0.75 (0.07)	0.78 (0.07)	0.13
PC20 (mg/ml) †	5.37 (3.47-7.24)	> 16	---
DRS-FEV1 + 3 (% /μmole) †	19.50 (15.85-23.99)	4.17 (3.89-4.37)	<0.01
DRS-FEV1/FVC + 3 (% /μmole) †	7.08 (5.50-9.33)	3.31 (3.09-3.55)	<0.01
DRS-FVC + 3 (% /μmole) †	14.13 (11.48-17.38)	3.63 (3.39-3.80)	<0.01
DRS-sGaw + 3 (% /μmole) †	36.31 (27.54-43.77)	6.03 (5.01-7.24)	<0.01
Closing Index ‡	0.71 (0.59-0.85)	0.50 (0.00-0.85)	0.01
RV/TLC *	0.41 (0.10)	0.36 (0.08)	<0.01
VA/TLC ‡	0.93 (0.86-0.98)	0.95 (0.91-0.99)	0.01

* mean (standard deviation)

† geometric mean (95% confidence interval)

‡ median (25-75 interquartile range)

Table 3
Parameter Estimates for Multifactor Regression Modeling of DRS-FEV1 *

Parameter	Estimate	Std Error	P-value
FEV1 %predicted	-0.0061	0.0025	0.02
VA/TLC	-1.193	0.4231	0.01

* adjusted R² for model = 0.14, P = 0.01