Registration-based Assessment of Regional Lung Function via Volumetric CT Images of Normals vs. Severe Asthmatics

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ABSTRACT

The purpose of this work is to explore the use of image registration-derived variables associated with computed tomographic (CT) imaging of the lung acquired at multiple volumes. As an evaluation of the utility of such an imaging approach, we explore two groups at the extremes of population ranging from normals to severe asthmatics. A mass preserving image registration technique is employed to match CT images at total lung capacity (TLC) and functional residual capacity (FRC) for assessment of regional air volume change and lung deformation between the two states. Fourteen normals and thirty severe asthmatics were analyzed via image registration-derived metrics together with their pulmonary function test (PFT) and CT-based air-trapping. Relative to the normals, the severe asthmatic group demonstrates reduced air volume change (consistent with air trapping) and more isotropic deformation in the basal lung regions, while demonstrating increased air volume change associated with increased anisotropic deformation in the apical lung regions. These differences are found despite the fact that both PFT-derived TLC and FRC in the two groups are near 100% of predicted values. Data suggest that reduced basal-lung air volume change in severe asthmatics is compensated by increased apical-lung air volume change and that relative increase in apical-lung air volume change in severe asthmatics is accompanied by enhanced anisotropic deformation. These data suggest that CT-based deformation, assessed via inspiration vs. expiration scans, provides a tool for distinguishing differences in lung mechanics when applied to the extreme ends of a population range.

Keyword: Lung Mechanics, Quantitative Computed Tomography, Image Registration, Air Trapping, Asthma
INTRODUCTION

Asthma affects more than 25 million people in the United States and can be characterized by different symptoms such as airflow obstruction, bronchial hyper-responsiveness and airway inflammation (8). Identification of phenotypes serving to separate non-severe asthmatics from severe asthmatics has been the focus of the NIH sponsored multi-center Severe Asthma Research Program (SARP) (12, 35, 40, 41, 54) and the search for phenotypes has included the acquisition of volumetric computed tomography (CT) scans of the lungs at total lung capacity (TLC) and functional residual capacity (FRC).

Imaging techniques such as hyperpolarized Magnetic Resonance Imaging (MRI) (1, 9, 16, 17, 49, 61), Positron Emission Tomography (PET) and Single Photon Emission CT (SPECT) (27, 29, 36, 43, 51) have been utilized for the exploration of functional defects and airway structural changes. Recently, hyperpolarized helium gas MRI has been compared with regional volume changes using paired lung volumes imaged via CT, and regional differences in lung function (expansion) were well matched (25). CT and MRI as tools for quantitative assessment of the lung have recently been reviewed (53). While each method provides unique pieces of information regarding lung structure and function, CT has the ability to relate detailed structure together with regional lung function (33). Over the past 30 years now, CT has been validated in regards to its ability to reflect regional air content of the lung (31), parenchymal destruction in chronic obstructive pulmonary disease (COPD) (15, 24).

Image matching methods as used here have recently demonstrated not only to reflect independent measures of regional volume changes (10, 22, 45, 58), but also to have shown the utility in differentiating airway vs. parenchymal phenotypes in a COPD population (23). In addition, the image matching derived variables via CT have been compared with different
modalities such as MRI, SPECT and Xenon-CT (11, 38, 45), and they have shown fairly
significant correlations. With the demonstration that image registration between two lung
volumes provides an accurate surrogate for regional lung function, we utilize CT image matching
to assess regional differences in lung function of severe asthmatics, relative to normals.

In this study, we apply a mass-preserving non-rigid registration method (57, 58) with two
breath-hold volumes (TLC and FRC) to study alteration of regional air volume change and lung
deformation. In the previous studies (57, 58), the method demonstrated the relatively accurate
results even in large deformation based on landmarks selected at vessel bifurcations. The
registration-derived variables can measure the features of the lung when deforming from one
static state to the other, unlike existing air trapping measures (7, 44) that are based on density
measures using a single volumetric image at FRC (or in other cases, residual volume, RV).

The purpose of this paper is to apply a newly emerging tool allowing for the matching of
lung volume pairs imaged via CT, and we have selected the normal and severe asthmatic groups
to evaluate the utility of such image registration methods in mapping alterations in regional lung
mechanics. In addition, we will correlate the registration-derived variables with existing
traditional measures, such as PFT’s measures and air-trapping, which have been commonly used
for the study of asthma, to illustrate the implications of registration-derived measurements.

METHODS

Human Subject Data Sets

Fourteen normal (10F) and thirty severe asthmatic (18F) subjects were chosen for this
study. Demographic and pulmonary function data are provided in Table 1. Both CT images of
normal subjects and severe asthmatics were acquired at the University of Pittsburgh as part of the
SARP consortium (12, 20, 40, 54). The associated human studies along with the imaging protocol were approved by the Institutional Review Board. CT images were gathered during coached breath-holds TLC and FRC in the supine position, and then were processed using the Pulmonary Workstation and Apollo software (VIDA Diagnostics, Coralville, Iowa). Scanning details are provided in Table 2. Major criteria used to define severe asthma are provided in (54), and include treatments with oral corticosteroids and high-dose inhaled corticosteroids besides minor criteria such as requirement for daily treatment with a controller medication of long-acting β-agonist, theophylline, or leukotriene antagonist.

Image Registration and Regional Air Volume Change

The intensity-based mass preserving image registration method (57, 58) was employed to match two CT lung images. Here, the CT images at TLC and FRC are used for the reference and floating images, respectively. The tissue and air fractions are estimated as follows.

\[ \beta_{\text{tissue}}(x) = \frac{I(x) - HU_{\text{air}}}{HU_{\text{tissue}} - HU_{\text{air}}} \quad \text{and} \quad \beta_{\text{air}}(x) = \frac{HU_{\text{tissue}} - I(x)}{HU_{\text{tissue}} - HU_{\text{air}}} \] (1)

where \( \beta_{\text{tissue}}(x), \beta_{\text{air}}(x), I(x), HU_{\text{air}} \) and \( HU_{\text{tissue}} \) denote tissue fraction, air fraction, Hounsfield unit (HU) of a voxel, HU of air, and HU of tissue, respectively. \( HU_{\text{air}} \) and \( HU_{\text{tissue}} \) are set to -1000 and 55, respectively (57, 58). The tissue volume \( V_{\text{tissue}}(x) \) and air volume \( V_{\text{air}}(x) \) are calculated by multiplying a local volume \( \nu(x) \) to the tissue and air fractions, respectively.

The image registration method is to determine a spatial transformation that matches the two images by minimizing a cost function \( C \), so called the sum of squared tissue volume difference (SSTVD) as shown below.
\[ C = \sum_{x \in \Omega} \left( V_{\text{tissue}}^\text{ref}(x) - V_{\text{tissue}}^f(T(x)) \right)^2, \]  

(2)

where \( V_{\text{tissue}}^\text{ref}(x) \) is the local tissue volume of the reference image, while \( V_{\text{tissue}}^f(T(x)) \) is the local tissue volume of the floating image. \( T(x) \), known as the warping function, provides a transformation that maps a local volume at location \( x \) in the reference image to the corresponding location in the floating image. A multi-level B-spline transformation technique is adopted to describe the warping function \( T(x) \). The finest number of control grids in the entire image domain is selected as \( 32 \times 32 \times 32 \), which has been an optimal number when considering accuracy and computational cost (13, 58).

Once warping function \( T(x) \) is obtained, the corresponding local volume \( v^f(T(x)) \) at floating image is calculated as \( v^f(T(x)) = v^{\text{ref}}(x) / J \), where \( J \) is the determinant of Jacobian matrix.

At the floating image, the air fraction \( \beta_{\text{air}}^f(T(x)) \) is obtained by CT intensity value \( I(T(x)) \) (see Eq. 1), so that the air volume \( V_{\text{air}}^f(T(x)) \) is calculated as \( v^f(T(x))\beta_{\text{air}}^f(T(x)) \). As a result, the regional air volume change \( \Delta V_{\text{air}} \) is obtained by the air volume differences between the reference image and the floating image as follows (56).

\[ \Delta V_{\text{air}}(x) = V_{\text{air}}^\text{ref}(x) - V_{\text{air}}^f(T(x)) \]  

(3)

Lung Deformation

The volume change (measured by \( J \)) and the anisotropic deformation index \( (ADI) \) are employed to quantify lung deformation (2). To obtain \( J \) and \( ADI \), the deformation gradient tensor \( \mathbf{F} \) is defined as follows (37).

\[ \mathbf{F} = \nabla T, \]  

(4)
where $\nabla$ is the vector gradient operator. $\mathbf{F}$ could be decomposed into a rotation tensor ($\mathbf{R}$) and a stretch tensor ($\mathbf{U}$); $\mathbf{R}$ is orthogonal, whereas $\mathbf{U}$ is symmetric and positive definite.

$$\mathbf{F}^T \mathbf{F} = (\mathbf{RU})^T \mathbf{RU} = \mathbf{U}^T \mathbf{R}^T \mathbf{RU} = \mathbf{U}^T \mathbf{U}$$  \hfill (5)

$$\mathbf{F}^T \mathbf{Fs} = \lambda_i^* \mathbf{s}$$  \hfill (6)

$$\mathbf{Us} = \sqrt{\lambda_i^*} \mathbf{s} = \frac{1}{\lambda_i} \mathbf{s}$$  \hfill (7)

Cauchy-Green deformation tensor ($\mathbf{F}^T \mathbf{F}$) is symmetric and positive definite due to the orthogonality of $\mathbf{R}$ and the nature of $\mathbf{U}$, and $\mathbf{s}$ denotes the eigenvector, and $\lambda_i^*$ are the eigenvalues of the ($\mathbf{F}^T \mathbf{F}$) of each local volume from TLC to FRC. In Eq. 7, both $\lambda_i^*$ and $\lambda_i$ are positive, and $\lambda_i$ represent the principal strains along the principal directions of a deformed lung tissue element from FRC to TLC, where $\lambda_i = 1/\sqrt{\lambda_i^*}$ with $\lambda_1 > \lambda_2 > \lambda_3 > 0$. With the eigenvalues ($\lambda_1$, $\lambda_2$, $\lambda_3$), $J$ and $ADI$ are calculated as follows.

$$J = \lambda_1 \lambda_2 \lambda_3$$  \hfill (8)

$$ADI = \sqrt{\left(\frac{\lambda_1 - \lambda_2}{\lambda_2}\right)^2 + \left(\frac{\lambda_2 - \lambda_3}{\lambda_3}\right)^2},$$  \hfill (9)

**Physical Interpretation of $\Delta V_{air}$, $J$ and $ADI$**

The three registration-derived variables $\Delta V_{air}$, $J$ and $ADI$ are used to evaluate air volume change and lung deformation. First of all, $\Delta V_{air}$ reflects local air volume difference between the reference and floating images, measuring the amount of air entering (or leaving) a local region during inhalation (or exhalation). Second, $J$ is defined as the ratio of $v_{ref}^r(\mathbf{x})$ at TLC over $v^r(\mathbf{F}(\mathbf{x}))$...
at FRC. That is, if $J = 1$ at a local volume, the local volume remains unchanged between the two lung volumes. If $J < 1$, the volume decreases from FRC to TLC (i.e., contracts); while if $J > 1$, it increases (i.e. expands). Because the tissue volume inside a local volume can be assumed unchanged, the change of local volume is primarily due to the change of air volume. Basically, $\Delta V_{air}$ and $J$ are measures for air volume change excluding tissue volume and lung volume change including tissue volume, respectively. In fact, both variables exhibit similar characteristics because tissue volumes during lung deformation remain unchanged. However, $\Delta V_{air}$ is the volume difference while $J$ is the volume ratio, thus both would not have linear correlations.

The third variable $ADI$ provides information on the preferential deformation of local lung volume (2). For example, if a local volume is stretched isotropically in all directions, namely $\lambda_1 = \lambda_2 = \lambda_3$, Eq. 9 gives an $ADI$ value of zero. With increasing anisotropy, $ADI$ increases. An important feature of $ADI$ is its independence from $J$. That is, even if two local volumes have the same $J$, their $ADI$ values could be different (2). Note that $ADI$ measures the degree of anisotropy rather than the direction of anisotropy. Intrinsically, $\Delta V_{air}$ is derived from CT intensity $I(x)$ at each local volume (Eq. 1), whereas $J$ and $ADI$ are derived from eigenvalues of deformation gradient tensor (Eq. 4), so that $\Delta V_{air}$ could provide a discrete field sensitive to the local CT intensity, while $J$ and $ADI$ could generate more smoothed fields by the 1st order derivative of warping function.

Air Trapping

A voxel is regarded as an air-trapped voxel if the Hounsfield Unit of the voxel at FRC is below -856 (this number varies $\pm 6$ HU depending upon the studies) (7, 12). Air trapping percentage “$AirT\%$” is defined as the ratio of the number of air-trapped voxels over the number of voxels in the respective lobes (lobar $AirT\%$) or in the whole lung (total $AirT\%$). Lobar
contribution to total air-trapped voxels is denoted by “AirT*”, which is defined as the ratio of the number of air-trapped voxels in the lobe over the number of air-trapped voxels in the whole lung. Thus, the summation of AirT* values in the five lobes is equal to unity.

Data Type and Analysis

The aforementioned air volume change, volume change and anisotropic deformation index ($\Delta V_{air}$, $J$ and ADI) are calculated for each local volume. $\Delta V_{air}$, $J$ and ADI are then normalized by their respective medians of the same subject, denoted by $\Delta V_{air}^*$, $J^*$ and ADI*.

Their spatial distributions are presented by lobe, lung height and depth averaged over all subjects, as well as for the whole lungs of selected individual subjects. Here the normalized lung height $Z^*$ is measured from apical to basal ($Z^* = 0 – 1$), i.e. along the cranio-caudal axis, which is perpendicular to the normalized lung depth $Y^*$ from the non-dependent (ventral) region to the dependent (dorsal) region of the lung ($Y^* = 0 – 1$). When being presented by lobe (or lung height), $\Delta V_{air}^*$, $J^*$ and ADI* are the medians over all values in lobe (or at a given lung height). In this study, the left upper lobe, left lower lobe, right upper lobe, right middle lobe, and right lower lobe are denoted by LUL, LLL, RUL, RML and RLL, respectively. To distinguish the features of severe asthmatics from normals, a mixed Analysis of Variance (ANOVA) and independent T-tests are performed for significance check with software R (39); statistical significance is taken at $P < 0.05$ level.

RESULTS

Pulmonary Function Test (PFT)

Table 1 summarizes the PFT information for the forty-four subjects (14 normals and 30 severe asthmatics) analyzed in this study. The predicted values of TLC, FRC and RV are
calculated with the equation of Stocks and Quanjer (48), and the predicted values of FVC and
FEV₁ are obtained from the equation of Hankinson (26). The measured values are then divided
by the predicted values, yielding the “% predicted” values in the table. In severe asthmatics, the %
predicted values of both TLC and FRC are within the normal range and close to 100%. On the
other hand, the % predicted values of FVC, FEV₁, and FEV₁/FVC of severe asthma are
significantly smaller than those of normal subjects, as would be expected in severe asthma (40,
41). In addition, consistent with severe asthma (47), the % predicted values of RV and RV/TLC
in the severe asthmatics indicative of air-trapping are higher than those of normal subjects ($P$
<0.0005 and $P < 5.0 \times 10^{-6}$, respectively).

Validation of CT-based Lung Volumes

Fig.1 shows the linear correlations of lung volumes between upright PFT and supine CT. CT-based total lung volumes ($TLV$) including both air volume ($AV$) and tissue volume ($TV$) are
significantly correlated with PFT-based measures of TLC and FRC (see Figs. 1A and 1B). The
upright PFT volumes and supine CT-based $TLV$ are in similar ranges, being adjacent to the
identity line. On the other hand, as shown in Figs. 1C and 1D, CT-based $AV$ tends to be
consistently less than PFT volumes. Table 3 compares the ratios of CT-based $TLV$, $AV$ and
inspiratory capacity ($IC$) over PFT measurements between normals and severe asthmatics. In
normal subjects, the CT-based air volumes at TLC ($AV^{TLC}$) and FRC ($AV^{FRC}$) decrease about 24%
and 42% respectively, as compared to their corresponding PFT volumes. Similarly, $AV^{TLC}$ and
$AV^{FRC}$ in severe asthmatics decrease about 24% and 36% respectively relative to their
 corresponding PFT volumes. The CT-based $IC$ ($CT$) is reduced only 6% and 8% for normals and
severe asthmatics, respectively, as compared to PFT measurements. Hence, the ratios of CT
supine volumes to PFT upright volumes in severe asthmatics are not statistically different from
those of normal subjects as shown in Table 3.

Table 3 also shows that tissue volume differences between TLC and FRC are about 0.03
liter and 0.04 liter, whereas air volume differences between TLC and FRC are about 2.57 liter
and 2.32 liter for normals and severe asthmatics, respectively. The means of tissue volume
differences over TLC tissue volume are about 6% in both normals and severe asthmatics. As a
result, the difference of tissue volume between TLC and FRC is much smaller than that of air
volume, supporting the assumption of SSTVD that tissue volume change is negligible (see Table
3).

Mixed ANOVA (Analysis of Variance)

A mixed ANOVA test consisting of one between-subject variable and one within-subject
variable was performed for two independent groups (normals and severe asthmatics) and five
lung regions (LUL, LLL, RUL, RML and RLL), as shown in Table 4. The ANOVA test
evaluated six dependent variables, including lobar fraction of air volume change, $\Delta V_{air^*}$, $J^*$,
$ADI^*$, $AirT^\%$ and $AirT^\*$. For the between-subject variable “Groups”, $AirT^\%$ of severe asthmatics
is different from normal subjects ($P < 0.05$) in entire lungs. As a result, a follow-up T-test was
conducted to compare total $AirT^\%$ between normals and severe asthmatics (see Table 6). On the
other hand, the differences of lobar fraction of air volume change, $\Delta V_{air^*}$, $J^*$, $ADI^*$ and $AirT^*$
between normals and severe asthmatics are not significant. This is because the dependent
variables $\Delta V_{air^*}$, $J^*$ and $ADI^*$ were normalized by the respective medians, and the summations of
lobar fractions of air volume change and $AirT^\*$ values in the five lobes are equal to unity, as
described in the Methods section. For within-subject variable “Lung regions”, six dependent
variables indicate that each lobe has the different characteristics of air volume change, volume
change, anisotropic deformation and air trapping. The significant interactions between “Groups” and “Lung regions” of the lobar fraction of air volume change, $J^*$, $ADI^*$ and $AirT^*$ imply that the effect of severe asthmatic group can affect regional difference of air volume change, deformation and air trappings. Accordingly, the T-tests of these variables in five lobes of both normals and severe asthmatics were performed.

**Lobar Fraction of Air Volume Change**

Based upon lobar segmentation data, Fig. 2 shows the means and standard errors (±SE) of lobar fractions of air volume change (lobar air volume change / whole lung air volume change) for normals (black bars) and severe asthmatics (white bars). The T-test indicates that the difference of air volume change fraction in the upper and lower lobes between normals and severe asthmatics is significant ($P < 0.05$), especially in RUL ($P < 0.00005$). Fig. 3 also displays the ratios of air volume change to the left lung over the right lung $L/R|_v$ for normals (black bars) and severe asthmatics (white bars), and the ratios of air volume change to the upper lobes over the middle and lower lobes $U/(M+L)|_v$ ($P = 0.125$ for $L/R|_v$ and $P < 0.0005$ for $U/(M+L)|_v$). The difference of $U/(M+L)|_v$ is still observed in age-controlled ($P < 0.01$) and BMI-controlled ($P < 0.01$) subgroups, by controlling the sample number of severe asthmatics with age < 50 ($P = 0.33$ for age difference between 14 normals and 17 severe asthmatics) and BMI < 35 ($P = 0.25$ for BMI difference between 14 normals and 22 severe asthmatics), respectively. Thus, the difference between normals (black bar) and severe asthmatics (white bar) is significant in upper and lower lungs rather than left and right lungs.

**Spatial Characteristics of Averaged $\Delta V_{air}^*$, $J^*$ and $ADI^*$**

Fig. 4 shows that lobar air volume changes $\Delta V_{air}^*$, volume changes $J^*$ and anisotropic deformations $ADI^*$ in normals (black bars) and severe asthmatics (white bars) are significantly
different except for the RML. In normal subjects, $\Delta V_{air^*}$, $J^*$ and $ADI^*$ of the lower lobes are higher than those of the upper lobes as shown in Fig. 4, but the difference diminishes in severe asthmatics. The re-distributions of these quantities between upper and lower lobes in asthmatics are particularly evident in Fig. 5 where the data are presented by lung height along the basal-apical axis. Fig. 4 also shows that RML has the smallest air volume change ($A$) and volume change ($B$), but the highest anisotropic deformation ($C$) among five lobes in both normals and severe asthmatics.

Subject-Specific Distributions of $\Delta V_{air^*}$, $J^*$ and $ADI^*$

To illustrate and inspect the spatial distributions of $\Delta V_{air^*}$, $J^*$ and $ADI^*$ in individuals, a normal subject with a lobar air volume change ratio of $U/(M+L)|_v = 0.55$ and a severe asthmatic subject with $U/(M+L)|_v = 0.81$ were chosen because these $U/(M+L)|_v$ values are close to the respective group (normals and severe asthmatics) mean values. Both selected normal and severe asthmatic subjects have normal BMI, same sex and race, but the selected severe asthmatic subject has the characteristics of airflow obstruction (low FEV$_1$) and air trapping (high RV) (see Table 5). In addition, air volumes of two selected subjects, $AV^{TLC}$ and $AV^{FRC}$, are in the similar range. Fig. 6 shows the lobar distributions of normalized air volume change ($A$, $D$), volume change ($B$, $E$) and anisotropic deformation ($C$, $F$) for the selected two subjects. The selected normal subject exhibits the overall characteristics found in the normal group, and the selected asthmatic subject shows an obvious shift in the upper- and lower-lobe functions. As further shown in Fig. 6, the medians of $\Delta V_{air^*}$, $J^*$ and $ADI^*$ by lobe are fairly uniform in the severe asthmatic subjects except for the RML.

For the normal subject, Figs. 7A and 7B demonstrate that the apical-basal and ventral-dorsal gradients exist with larger $\Delta V_{air^*}$ and $J^*$ in the lower (80 %, near base) and dependent
(dorsal) regions while smaller $\Delta V_{air}^*$ and $J^*$ in the upper (20%, near apex) and non-dependent (ventral) regions. Fig. 7C shows anisotropic deformation in the lower regions of the normal subject, and relatively isotropic deformation in the upper regions. In contrast, for the severe asthmatic subject, Figs. 8A, 8B and 8C show increased heterogeneity of air volume change, volume change, and anisotropic deformation with the lack of regional characteristics. For example, higher air volume change, larger volume change and increased anisotropic deformation are found near the apex.

Air Trapping

Table 6 shows the means and standard errors (±SE) of total lung air trapping percentage ($AirT\%$) and lobar contribution of the air-trapped voxels ($AirT^*$) for normals and severe asthmatics. It is noted that the total $AirT\%$ of severe asthmatics is much higher than that of normals ($P < 0.005$), as observed in the ANOVA test. In addition, lobar contribution of air trapping ($AirT^*$) is mainly observed in the upper lobes of both normals and severe asthmatics, and $AirT^*$ is the highest in RML irrespective of asthma. Based on the T-test, the most statistically significant differences are mainly found in left lungs: LUL ($P < 0.05$), and LLL ($P < 0.01$). Specifically, $AirT^*$ increases in lower lobes of severe asthmatics relative to normals.

Fig. 9 shows the spatial distributions of air-trapped clusters (CT intensity < -856) in a normal subject and a severe asthmatic subject. Note that the two subjects are those discussed before in Figs. 6-8. Fig. 9 shows frontal (A, B), left lateral (C, D) and right lateral (E, F) views of the two subjects with a series of spheres embedded, representing the volume and location of contiguous air-trapped voxels. Air-trapped clusters are color coded by lobes. More air-trapped regions are found in the entire lung of asthmatic subject, as shown in Figs. 9B, 9D and 9F. The percentages of air-trapped voxels ($AirT\%$) in the entire lungs are 0.5% and 14%, and lower
lobar air-trapping contributions ($AirT^*$) are 24.7% and 36.8%, respectively for the normal and severe asthmatic subject.

**Tissue Fraction**

The tissue fractions ($\beta_{\text{tissue}}$, Eq. 1) are averaged with medians of fourteen normals and thirty severe asthmatics along ventral-dorsal and apical-basal axes to observe the differences of tissue fraction between normals and severe asthmatics. Figs. 10A and 10B show that tissue at TLC is almost uniformly distributed, and there seems to be little difference between normals and severe asthmatics at TLC. In contrast, at FRC, tissue fraction of severe asthmatics on both axes decreases at all vertical levels relative to normals. The difference is more evident near the dorsal regions ($Y^*=0.7-1$, Fig. 10A) and near the basal regions ($Z^*=0.7-1.0$, Fig. 10B). Since the summation of both air and tissue fractions is equal to unity, the decrease of tissue fraction implies an increase of air fraction.

The distributions of air volume at both TLC and warped FRC for the selected subjects are also displayed in Fig. 11 for comparison. The FRC image is warped into the TLC image domain by applying the transform for visual comparison. Similar to the distributions of tissue fractions at TLC, the air volumes at TLC for both normal and severe asthmatic subjects are uniformly distributed. Meanwhile, the difference in lung shape between normals and severe asthmatics is quantified by the ratio of apical-basal to ventral-dorsal lung extent at TLC. The ratios are 1.56 ($\pm0.05$, SE) and 1.36 ($\pm0.03$, SE) for normal and asthmatic subjects, respectively ($P < 0.005$). The morphological difference is still observed in both age-controlled and BMI-controlled asthmatic subjects ($P < 0.005$).
DISCUSSION

Comparison of CT- and PFT-based Volumes

In both normals and severe asthmatics, the CT-based total lung volume $TLV\ (CT)$ and air volume $AV\ (CT)$ are significantly correlated with the PFT-based volumes at both TLC and FRC (see Fig. 1). In addition, $TLV\ (CT)$ are in similar ranges (~90 %) with PFT volumes (see Table 3), being consistent with the studies of Brown et al. (5, 6). For air volume $AV(CT)$, about 20% and 40% reductions from PFT’s are measured at TLC and FRC, respectively, in both normals and severe asthmatics (see Table 3).

It is known that supine CT-based air volumes are smaller than upright PFT measurements for several reasons. For example, the plethysmographic PFT includes dead space and gas in the abdomen, but CT only includes segmented lung regions. In addition, coaching TLC is difficult and the change of body posture from upright to supine can decrease lung volumes (6, 14, 52). The effect of body posture from upright to supine is particularly significant at FRC, resulting in about 30% reduction in PFT-based volumes (34, 42). Therefore, our analysis is consistent with previous studies, and further shows that the effect of body posture on air volume is uniform on both normal and severe asthmatic groups.

Characteristics of $\Delta V_{air}^*$, $J^*$ and $ADI^*$ in Normal Lungs

Existing studies (31, 32, 55) indicate that ventilation of the dependent region of normal lungs is higher than that of the non-dependent regions in the supine posture (known as vertical gradient) due to the gravity. In addition to this gradient, several researchers (3, 4, 19, 21) have reported an apical-to-basal (horizontal) gradient of ventilation existing in the supine posture. Our quantitative analysis also shows both vertical and horizontal gradients of air volume change.

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(ΔV_{air}^*) and volume change (J*) in the deep breathing of normal lungs. In fact, the gradient of air fraction shall inversely correlate with the gradient of tissue fraction. As shown in Fig. 10, the gradient of tissue fraction at FRC is greater than at TLC along both dorsal-to-ventral and basal-to-apical axes for normal subjects, consistent with the findings of others (31, 32, 46). Therefore, air volume change (ΔV_{air}^*) and volume change (J*) could depend on air-volume distribution at FRC as well as lobar size distribution at TLC because air volume at TLC is almost uniformly distributed (see Fig. 11).

Amelon et al. (2) demonstrated that the eigenvector corresponding to the principal eigenvalue (see Eq. 7) mainly orients to the apical-basal axis, being approximately normal to the diaphragm plane. Therefore, the increased anisotropy (ADI*) near basal regions may reflect the directionality of diaphragm movement as shown in Fig. 7C. In summary, in the case of normal subjects, relatively large volume change (ΔV_{air}^* and J*) and anisotropic deformation are observed in the basal and dependent regions, while relatively small volume change and isotropic deformation are observed in apical and non-dependent regions.

Characteristics of ΔV_{air}^*, J* and ADI* in Severe Asthmatic Lungs

The air volume change (ΔV_{air}^*) in normal lungs increases gradually from the apex to the base (from 20% to 80%) and from the ventral to dorsal lung regions, whereas it becomes fairly uniformly distributed in severe asthmatic subjects (see Figs. 5, 7 and 8). Quantitatively, the lobar air volume change ratio of U/(M+L)|v =0.78 in severe asthmatics is much higher than the air volume change ratio of 0.62 in normal subjects, as shown in Fig. 3B (P < 0.0005). Furthermore, the air volume change and volume change (J*) in severe asthmatics increase in the upper lobes, but decrease in the lower lobes as compared to normal subjects. Accordingly, we demonstrated that reduced air volume change in severe asthma mainly occurs in the lower lobes, which could
be substantiated by comparing the contours of air volume change captured near 80 % of the apical to basal distance as demonstrated in Figs. 7A and 8A. The relatively small anisotropic deformation ($ADI^*$) of the severe asthmatic subject near the basal region (80 % in Fig. 8C) might be due to the reduced directionality of diaphragm movement (see Table 1) in the asthmatic group. The geometric shape of the severe asthmatic lung at TLC exhibits reduced lung height (apical-basal) and increased lung depth (ventral-dorsal), which is also consistent with reduced $ADI^*$ in basal regions.

**Relationships between Air Trapping, PFT, $\Delta V_{air}^*$ and Tissue Fractions**

Air-trapping percentage ($AirT\%$) of severe asthmatics significantly increases as compared to normal subjects ($P < 0.005$), being consistent with existing studies (7). The result is also substantiated with the tissue fractions at FRC in severe asthmatics that are much smaller than in normal subjects on both dorsal-ventral and basal-apical axes as shown in Fig. 10. In addition to overall $AirT\%$, the lobar distributions of air-trapping fractions ($AirT^*$) at FRC are different between normal and severe asthmatic subjects (see Table 6). More specifically, air-trapping fraction in the lower lobes of the severe asthmatic subjects increases as compared to normal subjects (see $AirT^*$ in Table 6), being consistent with the finding of Fain et al. (20). Several imaging studies (1, 28-30, 50) reported that the areas of ventilation defect are observed mostly in the dependent and basal regions. Fig. 10A and 10B show that tissue fractions of severe asthmatics are much smaller than those of normals in gravitational dependent and basal regions, thus implying air trapping and reduced air volume change. The results are consistent with existing studies for ventilation defects, qualitatively.

The PFT analysis of the severe asthmatics demonstrated that air trapping (RV/TLC) is correlated with airflow obstruction (FEV$_1$/FVC). Thus, increased air trapping in the lower lobes
of severe asthmatic subjects may be correlated with reduced air volume change. The PFT results shown in Table 1 demonstrate that TLC and FRC volumes for both normal and severe asthmatic subjects are close to the predicted values, and CT-based lung volumes are not different between normals and severe asthmatics. Therefore, reduced air volume change in the lower lobes is compensated with increased air volume change from upper lung regions. Figs. 4A and 5A suggest that reduced air volume change in the lower lung may be correlated with relatively increased air volume change of upper lobes, resulting in elevated volume change and anisotropic deformation in the upper lobes. A recent study based on registration of three lung CT images acquired at different inflation levels (60) demonstrated that air volume change depends much more on the lower lobes than the upper lobes at the beginning of expiration from TLC. Since FEV$_1$ is measured during one second at the beginning of expiration from TLC, the reduced air volume change of lower lobes observed in severe asthmatics may contribute to the reduced FEV$_1$ measured in PFT.

Characteristics of RML

Among the five lobes, RML has the smallest air volume change, volume change and the highest ADI in both normal and severe asthmatic subjects. In addition, significant air trapping is also observed in RML. Intuitively RML has less freedom for deformation because it is bounded with both upper and lower lobes, resulting in smaller air volume change and volume change. The same constraint can also lead to more stretching and shearing, reflecting in a high anisotropic deformation. As noted before, $J$ and ADI are independent measures.

In conclusion, air volume change and lung deformation of severe asthmatic lungs were studied and compared with those of normal lungs. In the case of normal subjects, air volume change, volume change and anisotropic deformation of lower lobes are higher than those of
severe asthmatic subjects. As a result, the dependence of air volume change on lower lobes is
greater than upper lobes. In contrast, in the case of severe asthmatic subjects, deformation of
lower lobes is limited as suggested by decreased volume change and reduced anisotropic
deformation, resulting in increased volume change and enhanced anisotropic deformation in the
upper lobes. This study also established some correlations between existing variables, such as
PFT and air trapping measure from a single CT image, and registration-based quantities derived
from two CT images, such as lobar fraction of air volume change, $\Delta V_{air}$, $J$, and $ADI$. These new
variables may potentially serve as sensitive measures for the study of asthmatic lungs.

Limitations and Future Study Directions

This study shall be extended to investigate the effects of age, BMI and the severity of asthma on
registration-derived variables in the future. In addition, B-spline cubic interpolation provides the
smoothed displacement field, which may result in more smoothed $J^*$ and $ADI^*$. Therefore, the
discontinuous effects of lobar slippage and boundary near diaphragm shall be investigated with
the lung physiology (18, 59). Furthermore, the trends of the $\Delta V_{air}^*$ and $J^*$ in Figs. 5A and 5B in
the range of $Z^* \approx 0.85-1$ are different, and the number of sample points in that region is much
smaller than other regions due to TLC lung geometry. Yin et al. (58) reported that the
registration errors in the regions near the diaphragm are greater than other regions. Thus, whether
the discrepancy in this region is physiological requires further investigation.

ACKNOWLEDGMENTS

The authors would like to thank Dr. Jiwoong Choi, Mr. Nathan E. Burnette, Ms. Wang
Lu, Dr. Kung-Sik Chan and Ms. Feiran Jiao for assisting with data acquisition and analysis.
This study was supported in part by NIH Grants R01-HL-094315 and S10-RR-022421.

Eric A. Hoffman is a shareholder in VIDA diagnostics that is commercializing lung image analysis software derived by the University of Iowa of Iowa lung imaging group.
REFERENCES


37. **Mase GT, Smelser R and Mase GE.** *Continuum mechanics for engineers* (series: *computational mechanics and applied analysis*). 2009.


**FIGURE CAPTIONS**

Fig. 1. Comparisons of A: Total lung volume at TLC ($TLV^{TLC}$), B: Total Lung volume at FRC ($TLV^{FRC}$), C: Air volume at TLC ($AV^{TLC}$) and D: Air volume at FRC ($AV^{FRC}$) from CT scans with the corresponding PFT volumes in normal (black symbols) and severe asthmatic (white symbols) subjects. Solid (normals) and dashed (severe asthmatics) lines indicate linear fitted regression lines.

Fig. 2. Means (±SE) of the fraction of air volume changes in normals (black bars) and severe asthmatics (white bars) by lobe.

Fig. 3. Means (±SE) of A: L/R|v ratio and B: U/(M+L)|v ratio of air volume change in normals (black bars) and severe asthmatics (white bars).

Fig. 4. Means (±SE) of A: air volume change ($\Delta V_{air}^{*}$; $P<0.05$ in LUL and RLL; $P=0.06$ at LLL; $P=0.07$ at RUL; $P=0.717$ at RML), B: volume change ($J^{*}$; $P<0.05$ in upper and lower lobes, and $P=0.183$ in RML) and C: anisotropic deformation ($ADI^{*}$; $P<0.05$ in upper and lower lobes, and $P=0.13$ in RML) in normals (black bars) and severe asthmatics (white bars).

Fig. 5. A: air volume change ($\Delta V_{air}^{*}$), B: volume change ($J^{*}$) and C: anisotropic deformation ($ADI^{*}$) between normals (solid) and severe asthmatics (dashed) along lung height (basal-apical axis); Values are normalized by the respective median of entire lung, and presented as means (± SE).

Fig. 6. Lobar distributions of normalized air volume change ($A$, $D$), volume change ($B$, $E$), and anisotropic deformation ($C$, $F$) for a selected normal subject (left side) and a selected severe asthmatic subject (right side). Normalized values are presented as box (bottom: 25 percentile, middle: median, up: 75 percentile) and whisker plots (bottom: 5 percentile, up: 95 percentiles).
Fig. 7. Distributions of: A, air volume change ($\Delta V_{air}^*$); B, volume change ($J^*$); C, anisotropic deformation ($ADI^*$) of a normal subject at 20 % (near apex), 40 %, 60 % and 80 % (near base) from apical to basal. In each slice, the left lungs are on the left and the right lungs are on the right.

Fig. 8. Distributions of: A, air volume change ($\Delta V_{air}^*$); B, volume change ($J^*$); C, anisotropic deformation ($ADI^*$) of a severe asthma subject at 20 % (near apex), 40 %, 60 % and 80 % (near base) from apical to basal. In each slice, the left lungs are on the left and the right lungs are on the right.

Fig. 9. Frontal views (A, B), Left lateral views (C, D) and right lateral views (E, F) of air-trapped regions captured by CT intensity at FRC image < -856 HU, from Apollo (Vida Diagnostics). A, C and E: $AirT\%$ of a normal subject: total, 0.5 %; LUL, 0.9 %; LLL, 0.2 %; RUL, 0.6 %; RML, 1.3 %; RLL, 0.3 % ($AirT^*$: LUL, 37.6 %; LLL, 7.8 %; RUL, 20.7 %; RML, 17.0 %; RLL, 16.9 %) and B, D and F: $AirT\%$ of a severe asthmatic subject: total, 14 %; LUL, 14.4 %; LLL, 5.0 %; RUL, 9.3 %; RML, 39.9 %; RLL, 14.9 % ($AirT^*$: LUL, 24.1 %; LLL, 7.8 %; RUL, 11.6 %; RML, 27.5 %; RLL, 29.0 %). Lobes are color-coded: LUL (green), LLL (blue), RUL (red), RML (purple) and RLL (orange).

Fig. 10. Means ($\pm$ SE) of tissue fraction in TLC and FRC; A: on dorsal-ventral axis, B: on basal-apical axis of both normals and severe asthmatics. The TLC curves for normals and severe asthmatics are difficult to distinguish because they are closely juxtaposed.

Fig. 11. Distribution of air volume normalized with the respective mean of: A, TLC; B, warped FRC image of a normal subject and C, TLC; D, warped FRC image of a severe asthmatic subject; For 3D visualization at TLC domains, we define about 30,000 parenchymal cubical
units to approximate lumped acini. Each cube consists of about 1,000 voxels given the current image resolutions.
Table 1. The demographic and PFT information of 14 normals and 30 severe asthmatics

<table>
<thead>
<tr>
<th></th>
<th>Normals</th>
<th>Severe Asthmatics</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (±SE)</td>
<td>Mean (±SE)</td>
<td>from T-test</td>
</tr>
<tr>
<td>Age, year</td>
<td>34.5 (±3.9)</td>
<td>47.2 (±2.2)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>BMI</td>
<td>25.6 (±1.5)</td>
<td>31.1 (±1.3)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Asthma duration</td>
<td>-</td>
<td>28.2 (±3.3)</td>
<td>-</td>
</tr>
<tr>
<td>Sex, No. (% Female)</td>
<td>10 (71%)</td>
<td>18 (60%)</td>
<td>-</td>
</tr>
<tr>
<td>Race, No. (White non-hispanic/African American/Other)</td>
<td>10/1/3 (71%/7%/21%)</td>
<td>25/3/2 (83%/10%/7%)</td>
<td>-</td>
</tr>
<tr>
<td>TLC, % predicted</td>
<td>96 (±3)</td>
<td>97 (±3)</td>
<td>0.75</td>
</tr>
<tr>
<td>FRC, % predicted</td>
<td>90 (±5)</td>
<td>102 (±5)</td>
<td>0.12</td>
</tr>
<tr>
<td>RV, % predicted</td>
<td>90 (±6)</td>
<td>134 (±9)</td>
<td>&lt; 0.0005</td>
</tr>
<tr>
<td>FVC, % predicted</td>
<td>98 (±2)</td>
<td>71 (±3)</td>
<td>&lt; 1.0×10^{-7}</td>
</tr>
<tr>
<td>FEV₁, % predicted</td>
<td>96 (±3)</td>
<td>55 (±4)</td>
<td>&lt; 1.0×10^{-10}</td>
</tr>
<tr>
<td>FEV₁/FVC × 100</td>
<td>81 (±1)</td>
<td>60 (±2)</td>
<td>&lt; 5.0×10^{-10}</td>
</tr>
<tr>
<td>RV/TLC × 100</td>
<td>27 (±2)</td>
<td>44 (±2)</td>
<td>&lt; 5.0×10^{-6}</td>
</tr>
</tbody>
</table>

* TLC, FRC and RV of 1 normal subject and 1 severe asthmatic subject were not available.
Table 2. The scanner and the scanning protocol used for both normals and severe asthmatics

<table>
<thead>
<tr>
<th>Scanner and protocol</th>
<th>GE VCT 64 slice</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Scanner model</strong></td>
<td>GE VCT 64 slice</td>
</tr>
<tr>
<td><strong>Scan type</strong></td>
<td>Helical</td>
</tr>
<tr>
<td><strong>Rotation time (s)</strong></td>
<td>0.5</td>
</tr>
<tr>
<td><strong>Detector configuration (channel # x mm)</strong></td>
<td>64 x 0.625 mm</td>
</tr>
<tr>
<td><strong>Pitch</strong></td>
<td>0.984</td>
</tr>
<tr>
<td><strong>Peak kilovoltage (kVp)</strong></td>
<td>120</td>
</tr>
<tr>
<td><strong>miliampere (mA)</strong></td>
<td>S-145, M-180, L-270</td>
</tr>
<tr>
<td><strong>Dose modulation</strong></td>
<td>Auto mA OFF</td>
</tr>
<tr>
<td><strong>Reconstruction Algorithm</strong></td>
<td>Standard or Detail</td>
</tr>
<tr>
<td><strong>Lung Algorithm</strong></td>
<td>None</td>
</tr>
<tr>
<td><strong>Additional Image filters</strong></td>
<td>No Selection</td>
</tr>
<tr>
<td><strong>Thickness (mm)</strong></td>
<td>0.625</td>
</tr>
<tr>
<td><strong>Interval (mm)</strong></td>
<td>0.5</td>
</tr>
<tr>
<td><strong>Iterative reconstruction (noise reduction algorithm)</strong></td>
<td>No Selection</td>
</tr>
<tr>
<td><strong>Scan Time (s)</strong></td>
<td>&lt; 10</td>
</tr>
<tr>
<td><strong>30cm length</strong></td>
<td></td>
</tr>
</tbody>
</table>

* mA was varied for SARP protocol based on BMI size (S: BMI < 20, M: 20 ≤ BMI ≤ 30, L: BMI > 30).*
Table 3. The comparison of the ratio of upright PFT volumes to supine CT volumes; air volumes, tissue volumes and tissue volume difference from supine CT between normals and severe asthmatics

<table>
<thead>
<tr>
<th></th>
<th>Normals Mean (±SE)</th>
<th>Severe Asthmatics Mean (±SE)</th>
<th>P from T-test</th>
</tr>
</thead>
<tbody>
<tr>
<td>$TLV^{TLC}(CT) / TLC(PFT) \times 100$</td>
<td>91 (±2)</td>
<td>91 (±2)</td>
<td>0.98</td>
</tr>
<tr>
<td>$TLV^{FRC}(CT) / FRC(PFT) \times 100$</td>
<td>88 (±3)</td>
<td>89 (±3)</td>
<td>0.76</td>
</tr>
<tr>
<td>$AV^{TLC}(CT) / TLC(PFT) \times 100$</td>
<td>76 (±2)</td>
<td>76 (±2)</td>
<td>0.98</td>
</tr>
<tr>
<td>$AV^{FRC}(CT) / FRC(PFT) \times 100$</td>
<td>58 (±4)</td>
<td>64 (±2)</td>
<td>0.23</td>
</tr>
<tr>
<td>$IC(CT) / IC(PFT) \times 100$</td>
<td>94 (±7)</td>
<td>92 (±4)</td>
<td>0.85</td>
</tr>
<tr>
<td>$AV^{TLC}$ (liter)</td>
<td>4.14 (±0.2)</td>
<td>4.27 (±0.2)</td>
<td>0.66</td>
</tr>
<tr>
<td>$AV^{FRC}$ (liter)</td>
<td>1.57 (±0.1)</td>
<td>1.95 (±0.1)</td>
<td>0.06</td>
</tr>
<tr>
<td>$TV^{TLC}$ (liter)</td>
<td>0.79 (±0.04)</td>
<td>0.79 (±0.03)</td>
<td>0.96</td>
</tr>
<tr>
<td>$TV^{FRC}$ (liter)</td>
<td>0.76 (±0.04)</td>
<td>0.75 (±0.02)</td>
<td>0.70</td>
</tr>
<tr>
<td>$\frac{TV^{TLC} - TV^{FRC}}{TV^{TLC}} \times 100$ (%)</td>
<td>6 (±1)</td>
<td>6 (±1)</td>
<td>0.72</td>
</tr>
</tbody>
</table>

* PFT volumes ($TLC$, $FRC$ and $IC$) of 1 normal subject and 1 severe asthmatic subject were not available. $TLV$, $AV$, $IC$ and $TV$ are total lung volume (air + tissue), air volume, inspiratory capacity and tissue volume, respectively.
Table 4. A mixed (between group and within group) analysis of variance (ANOVA) test is performed with normals vs severe asthmatics (between) and five lobes (repeated measures) as a grouping and a within variable, respectively.

<table>
<thead>
<tr>
<th>ANOVA (F-test, P value)</th>
<th>Groups (normals vs. asthmatics)</th>
<th>Lung regions (LUL, LLL, RUL, RML and RLL)</th>
<th>Interactions (Groups × Lung regions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventilation Fraction</td>
<td>0.69</td>
<td>&lt; 5 × 10^{-22}</td>
<td>&lt; 0.005</td>
</tr>
<tr>
<td>$\Delta V_{air}^*$</td>
<td>0.94</td>
<td>&lt; 5.0 × 10^{-7}</td>
<td>0.13</td>
</tr>
<tr>
<td>$J^*$</td>
<td>0.90</td>
<td>&lt; 5.0 × 10^{-15}</td>
<td>&lt; 0.005</td>
</tr>
<tr>
<td>$ADI^*$</td>
<td>0.07</td>
<td>&lt; 1.0 × 10^{-5}</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>$AirT%$</td>
<td>&lt; 0.05</td>
<td>&lt; 0.05</td>
<td>0.07</td>
</tr>
<tr>
<td>$AirT^*$</td>
<td>0.49</td>
<td>&lt; 5 × 10^{-8}</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

* Type III error is employed for F-test, and sphericity is corrected by Greenhouse-Geiser epsilon.
Table 5. The demographic, PFT and CT volume information of the selected normal and severe asthmatic subjects

<table>
<thead>
<tr>
<th></th>
<th>A selected normal</th>
<th>A selected severe asthmatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, year</td>
<td>57.3</td>
<td>47.7</td>
</tr>
<tr>
<td>BMI</td>
<td>19.7</td>
<td>23.9</td>
</tr>
<tr>
<td>Asthma duration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>Female</td>
<td>Female</td>
</tr>
<tr>
<td>Race</td>
<td>White non-hispanic</td>
<td>White non-hispanic</td>
</tr>
<tr>
<td>TCL, % predicted</td>
<td>93</td>
<td>127</td>
</tr>
<tr>
<td>FRC, % predicted</td>
<td>92</td>
<td>115</td>
</tr>
<tr>
<td>RV, % predicted</td>
<td>88</td>
<td>151</td>
</tr>
<tr>
<td>FVC, % predicted</td>
<td>92</td>
<td>80</td>
</tr>
<tr>
<td>FEV1, % predicted</td>
<td>95</td>
<td>40</td>
</tr>
<tr>
<td>FEV1/FVC × 100</td>
<td>80</td>
<td>40</td>
</tr>
<tr>
<td>RV/TLC × 100</td>
<td>36</td>
<td>42</td>
</tr>
<tr>
<td>$AV_{TLC}^{CT}$ / $TLC(PFT) \times 100$</td>
<td>78</td>
<td>78</td>
</tr>
<tr>
<td>$AV_{FRC}^{CT}$ / $FRC(PFT) \times 100$</td>
<td>56</td>
<td>62</td>
</tr>
<tr>
<td>$IC(CT)$ / $IC(PFT) \times 100$</td>
<td>105</td>
<td>95</td>
</tr>
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</table>
Table 6. Means (±SE) of total lung air-trapping percentage (AirT%) and lobar contribution of air-trapped voxels (AirT*): A voxel at FRC image is treated as an air-trapped region if its CT intensity <−856 HU.

<table>
<thead>
<tr>
<th></th>
<th>Normals</th>
<th>Severe Asthmatics</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (±SE)</td>
<td>Mean (±SE)</td>
<td>T-test</td>
</tr>
<tr>
<td>Air trapping percentage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Total AirT%), %</td>
<td>3.4 (±1.2)</td>
<td>10.9 (±1.9)</td>
<td>&lt; 0.005</td>
</tr>
<tr>
<td>LUL</td>
<td>33.7 (±2.9)</td>
<td>24.8 (±1.8)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>LLL</td>
<td>9.3 (±1.6)</td>
<td>15.7 (±1.6)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>RUL</td>
<td>16.2 (±2.0)</td>
<td>19.2 (±1.6)</td>
<td>0.258</td>
</tr>
<tr>
<td>RML</td>
<td>30.2 (±3.8)</td>
<td>25.9 (±2.2)</td>
<td>0.349</td>
</tr>
<tr>
<td>RLL</td>
<td>10.6 (±1.6)</td>
<td>14.4 (±1.3)</td>
<td>0.075</td>
</tr>
</tbody>
</table>

* The difference between AirT% and AirT* is described in the section of Method: Air Trapping.
<table>
<thead>
<tr>
<th></th>
<th>Normals</th>
<th>Severe asthmatics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$TLV$ ($CT$)</td>
<td>$AV$ ($CT$)</td>
</tr>
<tr>
<td>TLC (PFT)</td>
<td>$r=0.83$ ($P&lt;0.0005$)</td>
<td>$r=0.78$ ($P&lt;0.001$)</td>
</tr>
<tr>
<td>FRC (PFT)</td>
<td>$r=0.85$ ($P&lt;1\times10^{-4}$)</td>
<td>$r=0.86$ ($P&lt;5\times10^{-5}$)</td>
</tr>
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</table>
![Graph showing data comparison between Normal and Severe Asthmatic groups.](image)

<table>
<thead>
<tr>
<th>Region</th>
<th>Normal Percentage</th>
<th>Severe Asthmatic Percentage</th>
<th>P (T-test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LUL</td>
<td>20%</td>
<td>25%</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>LLL</td>
<td>25%</td>
<td>22%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>RUL</td>
<td>15%</td>
<td>17%</td>
<td>&lt;0.00005</td>
</tr>
<tr>
<td>RML</td>
<td>5%</td>
<td>9%</td>
<td>0.961</td>
</tr>
<tr>
<td>RLL</td>
<td>5%</td>
<td>30%</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>
\[ L/R | \nu \]

- Normal
- Asthmatic

\[ U/(M+L) | \nu \]

- Normal
- Asthmatic

\[ P \text{ (T-test)} \]

- 0.125
- < 0.0005