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Lung Density Changes With Growth and Inflation

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BACKGROUND: With body growth from childhood, the lungs can enlarge by either increasing the volume of air in the periphery (as would occur with inspiration) or by increasing the number of peripheral acinar units. In the former case, the lung tissue density would decrease with inflation, whereas in the latter case, the lung density would be relatively constant as the lung grows. To address this fundamental structural issue, we measured the CT scan density in human subjects of widely varying size at two different lung volumes.

METHODS: Five hundred one subjects were enrolled in the study. They underwent a chest CT scan at full inspiration and another scan at end expiration. Spirometry, body plethysmography, and diffusing capacity of the lung for carbon monoxide were also measured.

RESULTS: There was a strong correlation between the size of the lungs measured at full inspiration on CT scan and the mean lung density ($r = -0.72$, $P = .001$). People with larger lungs had significantly lower mean lung density. These density changes among different subjects overlapped the density changes within subjects at different lung volumes.

CONCLUSIONS: Lung structure in subjects with larger lungs is different from that in subjects with smaller lungs. Tissue volume does not increase in proportion to lung size, as would be required if larger lungs just had more alveoli. These observations suggest that the growth of the lung into adulthood is not accompanied by new alveoli, but rather by enlargement of existing structures. The presence of greater air spaces in larger lungs could impact the occurrence and pathogenesis of spontaneous pneumothorax or COPD. CHEST 2015; 148(4):995-1002

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ABBREVIATIONS: FRC = functional residual capacity; HU = Hounsfield unit; RV = residual volume; TLC = total lung capacity

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It is widely presumed that the lung parenchyma in larger adults simply reflects more of the same lung structure that exists in smaller adults. If this is true, the density of the inflated lung should be uniform throughout a range of sizes across the adult population. Studies examining the growth and development of the postnatal human lung indicate that after birth, the lung grows in proportion to body size, but the production of new alveoli effectively ceases between 2 and 8 years of age.[1-5] However, the body continues to grow through adolescence and early adulthood. With that growth, the lungs can enlarge by either increasing the number of alveoli or by increasing the size of the alveoli. In the former case, the lung air density in the parenchyma of the larger lung would be expected to be the same as in a smaller lung, because the large lung would be just more of the same small lung. In the latter case, with larger peripheral airspaces, a larger lung would have a lower parenchymal density. Such information is of more than academic interest, because the size of the airspaces in the lung periphery could affect the septal tissue thickness and, thus, possibly impact the manifestation of different pulmonary pathologies. Indeed, it is known that spontaneous pneumothorax and its recurrence are significantly more common in tall subjects.[6-8] If the lung tissue is thinner in taller subjects with larger lung volumes at total lung capacity (TLC), then alveoli may be more likely to rupture.

In the current study, we test the hypothesis that larger lungs have the same structure as smaller lungs. This question has not been tested directly in a large cohort of subjects, but one postmortem histologic study reported measurements of the number of alveoli in lungs from six different-sized individuals.[9] Although the investigators concluded that larger lungs had more alveoli, given the wide variability in human populations, it would seem risky to make any firm conclusions about the number of alveoli in different size lungs from only six subjects.

On the other hand, CT scanning directly and unambiguously measures lung tissue density, expressed as Hounsfield units (HU) with a linear scale from 0 HU for water to −1,000 HU for air.[10] Thus, the amount of air and tissue in a given volume of lung can be quantified accurately.[11,12] Although such CT imaging can readily make lung parenchymal density measurements in vivo, this has not been evaluated systematically at known lung volumes in adult humans of various age and size.

Our current findings in a cohort of 500 human subjects show that people with larger lungs have lower parenchymal density, consistent with larger alveoli, regardless of whether the lungs are healthy or diseased. Perhaps even more remarkable, the decreased CT scan density with larger lung volume achieved by growth (among different subjects) closely recapitulated the calculated change in CT scan lung density with simple lung inflation (ie, within a subject). These results indicate that once alveolar septation is completed in early childhood, the lung enlarges by increasing the volume of existing peripheral acini, and that further alveolarization does not occur.

Materials and Methods

All subjects were enrolled in one of three studies at our institution. None of the scans were performed for clinical purposes. All protocols were approved by the Johns Hopkins institutional review board (NA_00009980, NA_00020295, and NA_00011275), and written informed consents were obtained. One study examined the effects of losartan on COPD progression. The second study compared the lung function and lung morphology among a local cohort that included smokers and nonsmokers and individuals with and without HIV. The third study examined the effects of an nrf2 promoter on airway reactivity. It was interesting that the correlation among all the groups was similar. All the scans used for the current analysis were obtained at baseline for the three studies prior to any intervention. As each study was rolled out in sequence, we realized we may want to compare the data among the studies. Therefore, we intentionally used the exact same protocol and the same scanner. Bronchodilators were not used in any of the studies for the CT scan portion of the protocol. The same script was read for each subject. Gating was not used, nor were residual volume (RV) CT scan measurements made. A total of 501 subjects were enrolled in the three studies.

Study Design

All subjects underwent a chest CT scan at full lung inflation after coaching to maximize the inspiratory effort, and another scan at end expiration after additional coaching. In addition, subjects had spirometry, body plethysmography, and diffusing capacity of the lung for carbon monoxide measurements taken.

Acquisition of CT Scan Data

All scans were performed using a single spiral CT scanner (Definition 64) with settings of 120 kVp; milliamperes second was based on body size (small = 80, medium = 100, large = 145), with a rotation time of 0.5 s, pitch of 1.0, thickness of 0.75 mm, and interval of 0.5 mm. Images were reconstructed using a B35 and a B31 algorithm.

Lung Volume Measurement

Lung volumes were calculated using PW software (VIDA Diagnostics, Inc) based on the lung CT scans. The PW software calculates the total lung volume, as well as the lung air volume and the lung tissue volume. In addition, lung volumes were measured by body plethysmography, which was performed according to American Thoracic Society guidelines.[13]

Parenchymal Density Measurement

Parenchymal densities for the entire lung volumes for each subject were calculated using the PW software (VIDA Diagnostics).

Data Analysis

Data analysis was performed using JMP 7.0.1 software (SAS Institute Inc). Smoking history was measured in pack-years. The baseline data were compared among the three groups using one-way analysis of

variance and Tukey honestly significant differences for all pairs comparisons. Differences in the mean lung density by sex and race were compared separately using one-way analysis of variance. The relationships between the mean lung density and the demographic and pulmonary function data were analyzed separately by simple linear regression. Finally, multivariate models were constructed to measure the effects of each independent variable on mean lung density. Significance was accepted at $P \leq .05$.

Results

A total of 496 subjects were included in the analysis. Five subjects were excluded because of missing data. The study population was predominantly black (75%), consistent with the race mix of the local population. The subjects were divided into three groups: nonsmokers, defined as < 10 pack-year history; smokers without COPD, defined as smoking for > 10 pack-years and $FEV_1/FVC > 70$; and smokers with COPD, defined as smoking for > 10 pack-years and $FEV_1/FVC < 70$. The level of COPD was mild in the vast majority of the subjects. The mean emphysema score (% voxels < −950 HU) for all the subjects with COPD was only 5.8% ± 7.7% (mean ± SD), and 88% had < 15% emphysema on CT scan. With this small amount of emphysematous lung, the total mean density of the whole lung will not be greatly impacted. Table 1 shows the demographic and pulmonary function data. Lung volume as measured by CT scan and body plethysmography were strongly correlated overall ($r = 0.84$, $P < .0001$), as well as by group for the nonsmokers ($r = 0.87$, $P < .0001$), smokers without COPD ($r = 0.77$, $P < .0001$), and smokers with COPD ($r = 0.86$, $P < .0001$), consistent with findings of others.[14]

We found a strong correlation between the CT scan total lung volume and the mean lung density for the nonsmokers ($r = 0.70$, $P < .0001$) (Fig 1A), smokers without COPD ($r = 0.74$, $P < .0001$) (Fig 1B), and smokers with COPD ($r = 0.67$, $P < .0001$) (Fig 1C). A similarly strong correlation was found at functional residual capacity (FRC) in each of the groups (Fig 2). In each subject, the mean lung density would also decrease as the lung inflated from FRC to TLC. Figure 2 shows a composite graph that plots measurements of HU vs total lung volume in all subjects from all groups at TLC (red) and FRC (blue). As discussed subsequently, the FRC and TLC data comprise overlapping datasets along the same lung density continuum.

We performed a multivariate regression, with the mean lung density at TLC as the dependent variable and sex, race, age, log (pack-years), FEV_1/FVC, TLC, slow vital capacity, FRC, RV, RV/TLC, diffusing capacity of the lung for carbon monoxide, and total lung volume,

TABLE 1] Baseline Demographics and Pulmonary Function

Variable	Nonsmoker (< 10 Pack-y)	Smoker (− COPD)	Smoker (+ COPD)	Total
Male (female) sex	63 (51)	109 (55)	135 (83)	307 (189)
Age, y	44.8 ± 11.8	50.4 ± 6.6[a]	55.4 ± 9.7[a]	51.4 ± 10.2
Smoking, pack-y	2.9 ± 3.4	28 ± 16.9[a]	43.0 ± 26.9[a,b]	29.0 ± 25.6
Race,[c] black (white)	92 (22)	143 (21)	135 (83)[a,b]	370 (126)
FEV_1 % predicted	87 ± 16	91 ± 15	75 ± 16[a,b]	83 ± 17
FVC % predicted	92 ± 15	93 ± 16	74 ± 26[a,b]	84 ± 23
FEV_1/FVC	77 ± 9	78 ± 5	57 ± 10[a,b]	68 ± 13
TLC, L	5.4 ± 1.2	5.6 ± 1.1	6.0 ± 1.2[a,b]	5.8 ± 1.2
SVC, L	3.5 ± 1	3.8 ± 1	3.4 ± 1[b]	3.6 ± 1.0
FRC, L	3.2 ± 0.8	3.4 ± 0.8	3.9 ± 1[a,b]	3.6 ± 1.0
RV, L	1.8 ± 0.7	1.8 ± 0.6	2.6 ± 0.8[a,b]	2.2 ± 0.8
RV/TLC	0.34 ± 0.1	0.33 ± 0.1	0.44 ± 0.1[a,b]	0.38 ± 0.1
Dlco	21.8 ± 6.4	20.3 ± 6.4	17.6 ± 6.0[a,b]	19.5 ± 6.5
FEV_1 % predicted	87 ± 16	91 ± 15	75 ± 16[a,b]	83 ± 17

Data are presented as mean ± SD unless indicated otherwise. No adjustments were made for multiple tests. Dlco = diffusing capacity of the lung for carbon monoxide; FRC = functional residual capacity; RV = residual volume; SVC = slow vital capacity; TLC = total lung capacity.
[a] $P < .01$ vs nonsmokers.
[b] $P < .01$ vs smokers (− COPD).
[c] Five subjects did not identify any race.

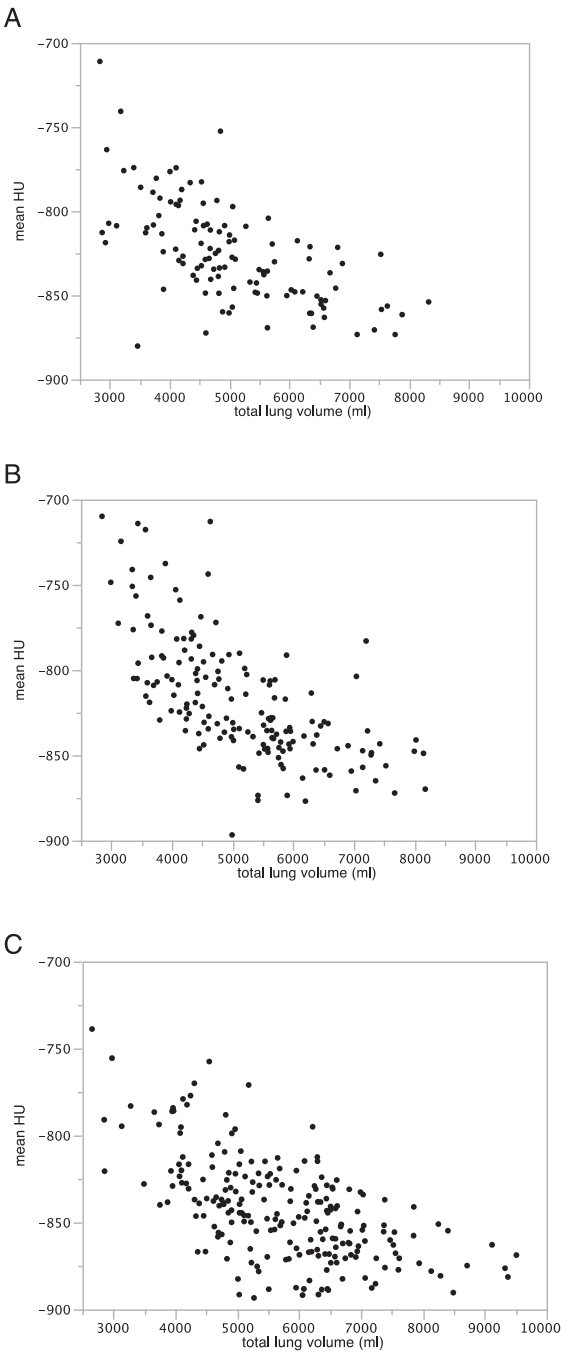

Figure 1 – *Relationship between mean lung density in HU and total lung volume at total lung capacity. A, For nonsmokers. B, For smokers without COPD. C, For smokers with COPD. The level of COPD was mild in the majority of subjects. The mean emphysema score (% voxels < −950 HU) for all subjects with COPD was only 5.8% ± 7.7% (mean ± SD), and 88% had < 15% emphysema on CT scan. With this small amount of emphysematous lung, the total mean density of the whole lung will not be greatly impacted. Each point represents one individual. HU = Hounsfield unit.*

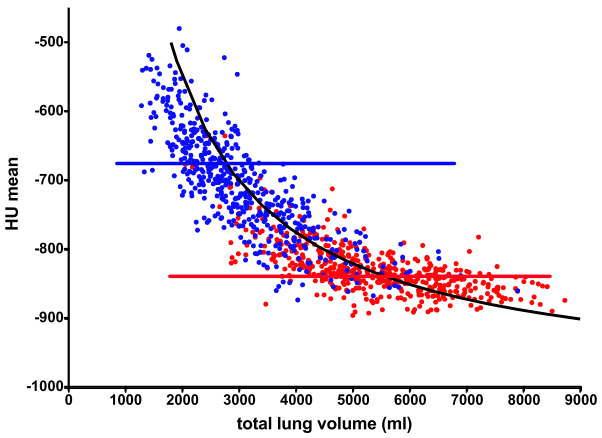

Figure 2 – *Relationship between mean lung density in HU and total lung volume for all subjects. The red points represent the lungs measured at total lung capacity (TLC). The blue points represent the lungs measured at functional residual capacity (FRC). The solid blue horizontal line represents the theoretical constant lung density over the range of lung sizes at FRC if larger lungs simply consisted of more alveoli of the same size. The solid red horizontal line represents the theoretical constant lung density over the range of lung sizes at TLC if there was no change in the alveolar size. The black line represents a simple calculation of lung density (HU) vs lung volume based on the lung density changes in a single lung as its air volume increases assuming an arbitrary fixed tissue (water) volume of 900 mL. Note the excellent fit of the data from all 500 subjects to this theoretical curve representing nothing more than air inflation of a lung. The fact that the FRC and TLC datasets overlap provides strong support for the idea that the alveoli in larger lungs are larger than those in smaller lungs. See Figure 1 legend for expansion of other abbreviation.*

which were all significant on univariate analysis, as the independent variables. Controlling for the demographic and pulmonary function variables, the strongest predictor of mean lung density was the total lung CT scan volume at TLC (Table 2). In addition, controlling for the other variables, FEV_1/FVC and the log (pack-years) were significantly correlated with the mean lung density.

We also performed a multivariate regression analysis with the mean lung density at TLC as the outcome variable, and sex and CT scan total lung volume as the independent variables. For the smokers who had COPD, there was a significant difference in mean lung density among the male and female subjects ($P < .0001$). In fact, after controlling for lung volume, the mean lung density for the female smokers with COPD was lower than that for the males (−850 HU vs −838 HU, respectively, $P = .0023$).

Discussion

Our results (Figs 1, 2) clearly demonstrate that when lung volumes are at either FRC or TLC, larger lungs have a lower mean lung density. This observation leads to a direct rejection of the hypothesis that larger lungs are just more of the same structure as smaller lungs. Larger lungs are composed of larger alveoli. If the alveoli were all the same size in large and small lungs, it would be impossible for the CT scan density to be lower in people with larger lungs. Furthermore, the

TABLE 2] Multivariate Analysis for the Mean Lung Density (HU) at TLC

Variable	Estimate	SE	T Ratio	*P* Value
Intercept	−817.3809	28.00621	−29.19	<.0001
Sex, female	1.0941746	1.799365	0.61	.5435
Race, black	−1.519299	1.682665	−0.90	.3672
Age	−0.391073	0.156612	−2.50	.0130
Log, pack-y	7.8058712	3.91115	2.00	.0467
FEV_1/FVC	0.8688348	0.130925	6.64	<.0001
TLC	8.0173387	8.519061	0.94	.3473
SVC	3.8278465	7.683151	0.50	.6186
FRC	−2.376311	2.424763	−0.98	.3277
RV	6.1509496	12.01378	0.51	.6090
RV/TLC	5.7146478	54.95808	0.10	.9172
Dlco	−0.203828	0.229428	−0.89	.3749
CT scan total lung volume at TLC, cm^3	−0.022891	0.001913	−11.97	<.0001

HU = Hounsfield unit. See Table 1 legend for expansion of other abbreviations.

fact that the lung density data taken at TLC overlap the density data taken at FRC (Fig 2) suggests that the changes in lung density associated with lung sizes among individuals are the same as the changes in lung density seen with simple lung inflation within an individual.

This remarkable observation can be highlighted with a simple calculation of HU as lung density changes with lung inflation. If we start with a lung consisting of equal air and tissue (water) volumes of 900 mL, the tissue density would be 50% or −500 HU. If we now simply inflate this lung with air, keeping tissue volume constant, the predicted change in HU is shown by the black line in Figure 2. Although it may not be surprising that lung inflation within an individual would fall along this curve, the fact that the data from different size lungs in 500 different individuals at FRC or TLC also closely fit this curve is indeed a striking observation. If larger lungs in different people consisted of just more identical alveoli, then the density curves would be perfectly flat, as illustrated by the hypothetical horizontal lines in Figure 2. Thus, our evidence from CT scan density is entirely inconsistent with there being more alveoli in larger lungs. Furthermore, if alveoli are bigger, this could be manifested by thinner septal walls in vivo. As discussed subsequently, this fact could have important clinical manifestations.

Given these unambiguous data on lung density changes, how can the notion of increased alveolar number in larger lungs remain so prevalent? The answer, we believe, is a combination of two factors: The first is that to our knowledge there has not been a comprehensive study that has carefully examined average CT scan density at different lung volumes, and the second is that the method of assessing alveolar number histologically has a number of technical and subjective issues that could lead to significant errors, in addition to there being a limited number of postmortem lungs available. These issues related to histologic analysis have led to various results from human lungs.[2,9,15,16] For example, the morphologic data from 32 postmortem lungs presented by Angus and Thurlbeck[15] can be replotted to show a highly significant negative correlation between the average density of alveoli and the total lung volume, in milliliters ($r = -0.51$, $P = .003$), data very consistent with our findings in 500 subjects.

In contrast, a more recent histologic study of six human lungs[9] claimed that larger lungs are larger primarily because they have more alveoli. However, given the extent of the variability seen in CT scan density (HU) among the subjects with the same lung volume in our study, it would seem highly problematic to draw any conclusions about the number of alveoli in different size lungs from only six subjects. Perhaps more relevant is the earlier histologic study of lungs from 56 children (6 weeks to 14 years of age) by Thurlbeck,[4] in which it was shown that there was limited or no change in the number of alveoli after the age of 2 years. Such a cessation of alveolar septation in early childhood would then require alveolar enlargement with

any further lung growth, and this conclusion is strongly supported by our CT scan data presented here. CT imaging was used by de Jong et al[5,11] in children to show that, consistent with the histologic study of Thurlbeck,[4] the calculated alveolar number stopped increasing at very young ages.

There are some technical issues that warrant discussion. First, differences in scanner make and model can lead to differences in lung density measurements.[17] In our study, all subjects reported here were scanned on the same machine using the same protocol, so this variability was not an issue. In addition, all the subjects were coached with the same script to achieve TLC, and all the scans were analyzed by a single individual using the same software.

Second, one of the concerns in analyzing these in vivo data was that among subjects, airspaces expand to various degrees with lung inflation.[18] Thus, unless the lung volumes are matched carefully, it is not possible to compare CT scan densities from different individuals. TLC is based on a voluntary effort, and there is considerable variability in this effort among individuals that is likely greater in people with lung disease. In our study, we directly addressed the effect of volume variation by measuring CT scan density at two measured lung volumes in each subject. The CT scan density must decrease with lung inflation in an individual, and our data showed that the magnitude of this decreased density with lung inflation was similar to that seen in a larger lung from an unrelated individual (Fig 2). This surprising result supports the notion that the difference between small and large lungs in different-sized individuals is similar to the difference in lungs with lung inflation within an individual. Although it would be nice to be able to determine how the increased air is partitioned in the larger acini in the larger lungs, CT imaging currently does not have the ability to determine whether air is in the alveoli and alveolar ducts. HU over the whole lung measure average tissue density, which includes the acini, small airways, arteries, veins, capillaries, and epithelial lining fluid, but we have also measured similar CT scan density changes in small peripheral regions of interest consisting primarily of parenchyma (data not shown). Although, the data clearly show that the primary process of lung growth involves alveolar enlargement, given the variability in lung density at any lung volume that we observed in these human subjects, an increased alveolar number may contribute slightly to the increased lung volume in larger subjects.

For the subjects who smoked and had COPD, after controlling for the other independent variables, in addition to the total lung volume, the FEV_1/FVC, FEV_1 % predicted, and log (pack-years) cigarettes smoked were all correlated with the mean lung density. The positive correlation between the FEV_1/FVC and the mean lung density is consistent with the development of COPD and lung parenchymal destruction.[19] Only when the subjects had an $FEV_1/FVC < 70$ (COPD) did the increased airway obstruction correlate with the decreased mean lung density.

When the data were analyzed by simple linear regression, we found a significant difference in mean lung density for men vs women (Table 3). However, in the multivariate model, controlling for the other variables, and specifically total lung volume, we found no difference between the male and female subjects ($P = .1778$) (Table 2). Although Thurlbeck[4] observed small differences between male and female children,[4] in the adults in our study we found no association between the mean lung density and the sex of the subject when controlling for total lung volume for the nonsmoking group and the smoking group without COPD ($P = .39$ and $P = .91$, respectively). However, in the smokers who had COPD, we found that women had a lower mean lung density than did men ($P = .0023$). This suggests that women may be at increased risk of lung destruction secondary to smoking, compared with men.

As mentioned previously, lung growth falls along the same curve as that which would be predicted for simple lung inflation, and this implies that the septal walls in larger lungs are likely thinner. This observation could provide the explanation as to why spontaneous pneumothorax and its recurrence are significantly more common in tall subjects.[6-8] If the septal tissue is thinner in taller subjects with larger lung volumes, then alveoli may be more likely to rupture. In fact, Chang et al[20] speculated that the cause of primary spontaneous pneumothorax in adolescents was related to the discrepancy between the rapid increase in chest height and lung growth. If the lung growth involves airspace enlargement with septal thinning, this would be entirely consistent with our current findings. Given this clinical manifestation, the possibility that lung size may also affect susceptibility to the destruction of alveoli in emphysema should be entertained.

Conclusions

In conclusion, we have obtained a unique dataset of CT images taken at two lung volumes from a large cohort of

TABLE 3] Correlations Between Mean Lung Density (HU) and Demographics and Pulmonary Function Variables

Variable	Nonsmoker (< 10 Pack-y)	Smoker (− COPD)	Smoker (+ COPD)
Male (female) sex	−836 (−811)	−826 (−797)	−848 (−834)
P value	< .0001	< .0001	.0008
Age, mean ± SD, y			
r	−0.016	−0.049	−0.27
P value	.87	.53	.0001
Smoking, $\log_{10}$, pack-y			
r	−0.18	−0.07	−0.21
P value	.18	.37	.0018
Race, black (white)	−823 (−834)	−816 (−822)	−836 (−853)
P value	.12	.47	< .0001
FEV_1 % predicted			
r	−0.15	−0.43	−0.16
P value	.11	< .0001	.02
FVC % predicted			
r	−0.35	−0.47	0.13
P value	.0002	< .0001	.5
FEV_1/FVC			
r	0.24	0.15	0.49
P value	.0095	.06	< .0001
TLC, L			
r	−0.43	−0.42	−0.43
P value	< .0001	< .0001	< .0001
SVC, L			
r	−0.47	−0.44	−0.19
P value	< .0001	< .0001	.006
FRC, L			
r	−0.36	−0.39	−0.42
P value	.0002	< .0001	< .0001
RV, L			
r	−0.11	−0.05	−0.42
P value	.27	.55	< .0001
RV/TLC			
r	0.24	0.26	−0.18
P value	.02	.0021	.01
DLCO			
r	0.46	−0.31	−0.06
P value	< .0001	.0001	.36
FEV_1 % predicted			
r	−0.15	−0.43	−0.16
P value	.11	< .0001	.02

No adjustments were made for multiple tests. See Table 1 and 2 legends for expansion of abbreviations.

healthy and diseased humans. The data demonstrate that among individuals of widely varying size, the lung parenchymal density was not constant but was highly dependent on the size of the lungs. These findings are entirely inconsistent with there being just more of the same acini in larger individuals. Rather, as the lung grows to adult size, the increased lung size must be caused by larger alveoli. In fact, the density changes with lung growth among different individuals overlap those changes within an individual with simple lung expansion, suggesting that varying lung size may involve little more than additional lung inflation. These observations do not support the idea that new alveoli can arise once the lungs have reached maturity. How the different lung structure with larger alveoli in larger lungs impacts the pathogenesis of COPD and other lung diseases remains to be shown.

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