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Detection of Age-Related Changes in Thoracic Structure and Function by Computed Tomography, Magnetic Resonance Imaging, and Positron Emission Tomography

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It is useful to understand the normal changes in structure and function in the thorax that occur with age. Thus, we present the following quantitative preliminary data obtained from retrospective quantitative analysis of computed tomography (CT) and positron emission tomography (PET) examinations in subjects 0 to 90 years of age: Mean lung standard uptake values were found to significantly increase with increasing age and with increasing body mass index (BMI). Mean lung attenuation was seen to statistically significantly decrease with increasing age in subjects who had a CT scan, had a nonsignificant tendency to decrease with increasing age in subjects with a PET/CT scan, had a nonsignificant tendency to increase with increasing BMI, and was seen to significantly increase with increasing mean lung standard uptake values. Mean lung volumes were not noted to significantly change with increasing age in adult subjects whether or not they were normalized to the craniocaudal thoracic lengths, although mean lung volumes significantly increased with increasing age in pediatric subjects. Mean lung volumes had a nonsignificant tendency to decrease with increasing BMI, although normalized mean lung volumes significantly decreased with increasing BMI. Lung metabolic volumetric products were not noted to significantly change with increasing BMI or with increasing age. In this work, we also review the literature regarding normal structural and functional changes in the thorax with age.

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Quantitative radiologic and scintigraphic imaging of the changes in structure and function of thoracic structures with age can provide normative data that can help one to distinguish the normal expected changes related to aging from those that are caused by pathology, although the spectrum of normal aging changes and pathologic changes may sometimes overlap. Furthermore, quantitative imaging of structure and function has the potential to lead to more reproducible assessment in both clinical and research settings, when compared with qualitative assessment.

Unfortunately, many previous reports that have studied changes in thoracic structure or function with aging have not fully represented subjects in all age groups (in particular the elderly) or subjects of female gender.[1-8] In addition, previous reports have predominantly focused on structure as seen with ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI), or on function as measured by pulmonary function testing (PFT) and spirometry.

In this article, we report quantitative preliminary data obtained from the retrospective quantitative analysis of CT and positron emission tomography (PET) examinations of the chest in subjects ages 0 to 90 years pertaining to changes in the lung volume, lung attenuation, and lung metabolism with age; report the relationship of lung volume and lung metab-

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olism to body mass index (BMI); and then review the literature regarding what the normal structural and functional changes in the thoracic structures are with age from childhood to adult life.

Materials and Methods

Institutional review board approval for retrospective data collection and image analysis along with a HIPAA waiver were obtained from the Hospital of the University of Pennsylvania's and the Children's Hospital of Philadelphia's Institutional Review Boards before study initiation.

Subjects and CT and PET Scanning Techniques

Positron Emission Tomography

Sixty-two consecutive subjects (35 men, 27 women) ages 19 to 88 years who had 2 ^{18}F-fluorodeoxyglucose (FDG)-PET scans at the Hospital of the University of Pennsylvania (HUP) during 2005 to 2006 and a normal thoracic CT scan within 1 year of the PET scan were included in our study. PET scans were most commonly performed for current or previous malignancy, but all subjects with a current or previous history of thoracic disease were excluded. Subjects with a history of prior chemotherapy, thoracic surgery, or radiotherapy were excluded. Subjects who had received radioiodine treatment for thyroid cancer more than 6 months before PET scanning were included if no morphologic abnormalities were seen on the previous CT scan.

PET was performed on a dedicated whole-body scanner (Allegro; Philips Medical Systems, Bothell, WA, or C-PET; ADAC UGM Medical Systems, Milpitas, CA). All subjects fasted for at least 4 hours to ensure a serum glucose level less than 140 mg/dL at the time of injection. After tracer injection, subjects rested on a comfortable chair during the FDG uptake period. PET was initiated 60 minutes after the administration of 140 μCi/kg (5.2 MBq/kg) of ^{18}F-FDG through an intravenous indwelling catheter inserted into an antecubital vein. Sequential overlapping scans were acquired from the base of the skull to the mid-thigh, including the neck, chest, abdomen, and pelvis. Transmission scans using a ^{137}Cs point source were interleaved between the multiple emission scans to correct for nonuniform attenuation. The images were reconstructed using an iterative reconstruction algorithm, and both attenuation-corrected and non–attenuation-corrected images were used.

Eight pediatric subjects (7 male, 2 female) ages 10 to 17 years who had 2 FDG-PET scans at the Children's Hospital of Philadelphia (CHOP) during 2004 to 2005 were included in our analysis. The PET scans were most commonly performed for current or previous malignancy, but all subjects with a current or previous history of lung disease were excluded. Subjects with a history of chemotherapy within 3 months of the PET scan were excluded as were subjects who had received previous pulmonary radiotherapy or surgery.

PET was performed in these subjects with a dedicated whole-body PET scanner (Allegro or C-PET). All subjects fasted for at least 4 hours, and serum glucose levels were less than 140 mg/dL in all subjects. All were asked to empty their bladders immediately before being scanned. No specific preparation was given to the subjects. PET was initiated 60 minutes after the intravenous administration of a dose of ^{18}F-FDG adjusted to the body weight (130 μCi/kg (4.8 MBq/kg) for the Allegro and 68 μCi/kg (2.5 MBq/kg) for the ADAC camera). Sequential overlapping scans were acquired to cover from the base of the skull to the mid-thighs, including the neck, chest, abdomen, and pelvis. Transmission scans obtained with a ^{137}Cs point source were interleaved between the multiple emission scans to correct for nonuniform attenuation. The images were reconstructed with an iterative reconstruction algorithm, and both attenuation-corrected and nonattenuation-corrected images were used.

Computed Tomography

Seventy-four consecutive subjects (42 men, 32 women) ages 16 to 89 years old who had unenhanced thoracic CT scans at HUP in 2005 were included in our study. Subjects with normal CT scans with exception of minimal or mild subsegmental atelectasis in a lung base and with no more than 2 benign-appearing subcentimeter pulmonary nodules were included, although subjects with emphysema, more severe atelectasis, pulmonary malignancy, or other pulmonary disease processes were excluded. Subjects with histories of previous chemotherapy, thoracic surgery, or radiotherapy obtained from radiology reports or with CT imaging findings of thoracic surgery or radiotherapy were excluded.

At HUP, all thoracic CT scans were performed without intravenous contrast material in the supine position during full inspiration on either a single detector CT scanner or on multidetector CT scanners with 4, 16, or 64 detector rows. Axial images were reconstructed with slice thicknesses of 7 mm or 5 mm if obtained from single detector or multidetector scanners, respectively.

Thirteen pediatric subjects ages 0.08 to 11 years who had thoracic CT scans after the intravenous administration of contrast material at CHOP during January 2005 to September 2005 were included in our study. Subjects with normal CT scans with exception of minimal or mild subsegmental atelectasis in a lung base were included, most of whom were scanned for clinical indications of trauma, abdominal pain, or Langerhans cell histiocytosis, although subjects with more severe atelectasis, pulmonary malignancy, or other pulmonary disease processes were excluded. Subjects with a history of previous chemotherapy, thoracic surgery, or radiotherapy were excluded.

At CHOP, all chest CT scans were performed using intravenous contrast material in the supine position during either free breathing or full inspiration (depending on subject age) on a multidetector CT scanner with 16 detector rows. Axial images were reconstructed with slice thicknesses of either 3 mm or 5 mm.

PET/CT

Eighteen consecutive subjects (8 men, 10 women) ages 20 to 76 years had PET/CT scans performed at the HUP in 2006. Subjects included in the study were selected with the same

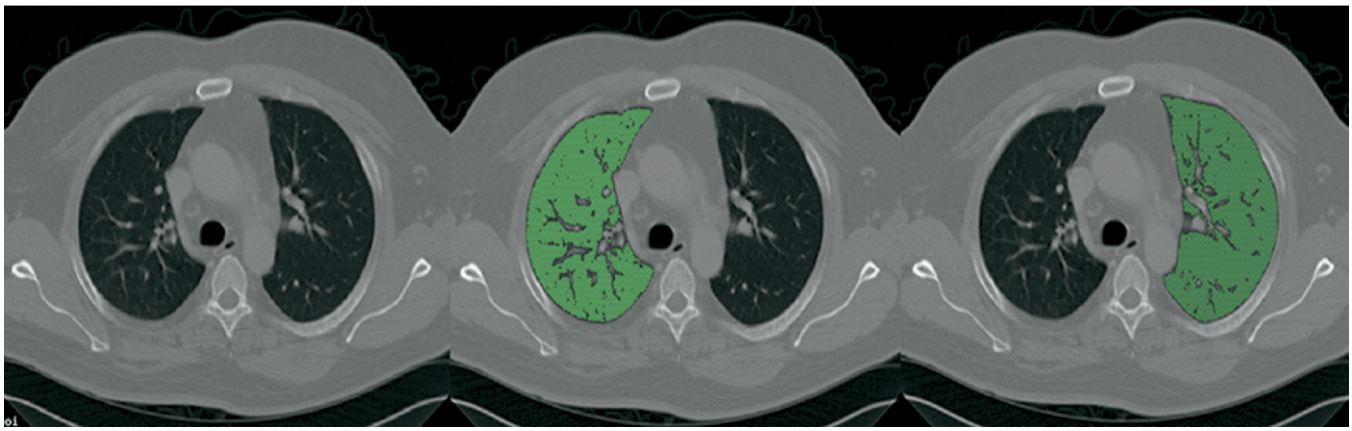

Figure 1 Axial CT image through lungs shows computer-assisted segmentation of right and left lungs.

criteria as those in the PET group described previously. Heights and weights were available for these subjects, which were recorded, and body mass indices (BMIs) were calculated as weight in kg divided by the square of the height in m.

PET/CT imaging was initiated using a 16 detector row LYSO PET-CT (Gemini TF, Philips Medical Systems). A scout image was initially obtained for subject localization. Whole-body CT axial images were obtained using a low-dose protocol (50-150 mAs) with a 5-mm slice thickness after the administration of oral contrast material. Subsequently, 3D PET data were acquired using 3-minute table positions. The PET acquisition included a time-of-flight and a dead-time correction as well as online delayed coincidence subtraction to correct for random coincidences. Rescaled CT images were used to produce attenuation correction values for the PET emission reconstruction.

Image Analysis

PET Standard Uptake Value (SUV) Measurement

SUVs of the lungs were obtained from the PET scans of all available subjects. Manual outlines of the lung were made at 3 levels in each lung located one quarter, one half, and three quarters of the craniocaudal length from the lung apices, and computer-generated mean SUVs were recorded and averaged for each subject.

CT Lung Attenuation Measurement

Lung attenuation values (measured in Hounsfield units) were obtained from unenhanced thoracic CT scans in the following manner: 1 cm^2 regions of interest (ROIs) were manually placed in the lateral outer one-third of each lung at 3 levels (mid thoracic trachea, carina, and slightly below bifurcation of the bronchus intermedius with an attempt to avoid all visible airways and blood vessels). Attenuation values for these ROIs were recorded and averaged for each subject.

CT Lung Volume Measurement

The software system 3DVIEWNIX was used to segment all 13 CT images of the lungs in children, 12 of the adult PET/CT images, and 37 randomly selected CT images of adults over a wide age range to obtain separate left and right total lung volumes using the following steps: (1) The *Threshold* operation was used to segment the lung tissue from the rest of the tissue on the CT images. (2) Subsequently, the *Interactive2D* operation was used to manually remove areas that were not

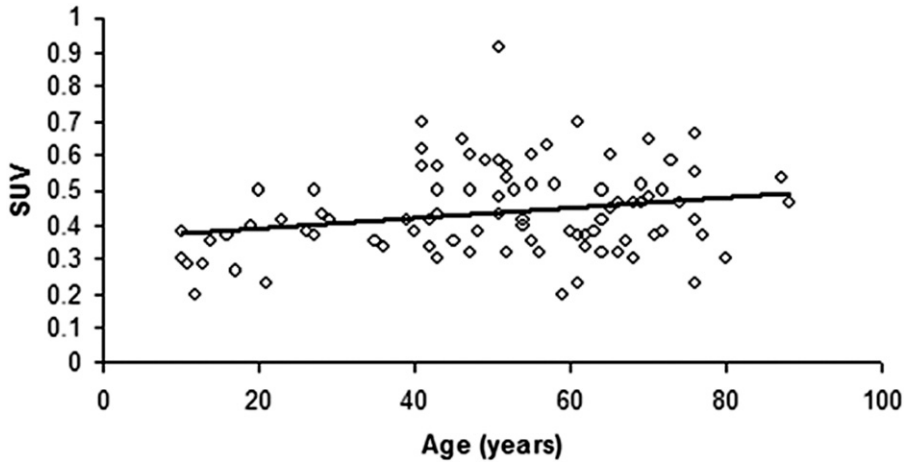

Figure 2 Change in mean lung SUV with increasing age. Linear regression curves, corresponding equations, Pearson *r* values, 95% CI values, and *P* values are listed in the Results section.

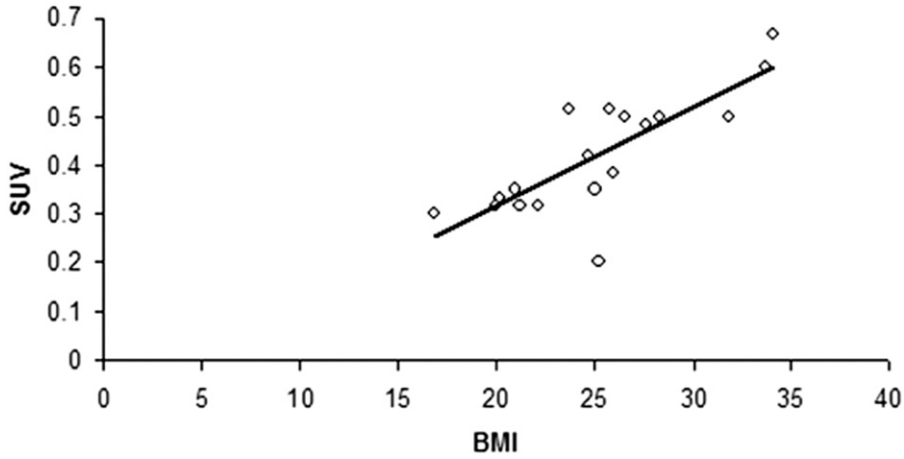

Figure 3 Change in mean lung SUV with increasing BMI in kg/m^2. Linear regression curves, corresponding equations, Pearson *r* values, 95% CI values, and *P* values are listed in the Results section.

part of the lungs including the airways. (3) The mask that was produced covered the lung areas only. Using *Interactive2D* once again, the left lung was removed and hence the mask for the right lung was obtained. (4) *Algebra* was used to obtain the left lung by subtracting the right lung mask from the entire lung mask.[9] Fig. 1 displays the segmentation results of an axial CT slice from one subject. Normalized lung volumes in adult subjects also were calculated by dividing lung volumes by the longitudinal distances between the superior endplate of the T1 vertebral body and the inferior endplate of the T12 vertebral body obtained from the CT images.

Data Analysis

Mean SUVs of the lungs were correlated with age and with BMI. Mean lung attenuations of the unenhanced lungs in adult subjects were correlated with age, BMI, and mean lung SUVs. Mean lung volumes were correlated with age as well as with BMI. Metabolic volumetric products (MVPs), defined as the product of lung SUVs and lung volumes (with units of SUV-mL) also were calculated and subsequently correlated with BMI and age. All scatterplots were performed with Microsoft Excel software (Microsoft Corporation, Redmond, WA). Linear regression curves and statistical analyses were performed with SPSS version 14.0 (SPSS Inc, Chicago, IL). Pearson *r* correlation values, 95% confidence intervals (CI), and 2-tailed *P* values were calculated, and statistical significance was considered to be present for *P* values <0.05.

Results

Mean lung SUVs were found to statistically significantly increase with increasing age in subjects undergoing PET and PET/CT (Pearson $r = 0.2329$; 95% CI = 0.02457–0.4218; $P = 0.029$; Fig. 2), and with increasing BMI (Pearson $r = 0.7863$; 95% CI = 0.5046–0.9167; $P = 0.0001$; Fig. 3). Mean lung attenuation was seen to statistically significantly decrease with increasing age in subjects who had a CT scan (Pearson $r = -0.3818$; 95% CI = -0.5614 to -0.1679; $P = 0.0008$; Fig. 4), and had a tendency to decrease with increasing age in subjects with a PET/CT scan without statistical significance (Pearson $r = -0.4111$; 95% CI = -0.7367 to 0.6910; $P = 0.0901$; Fig. 5).

Mean lung attenuation was not noted to statistically significantly change with increasing BMI although there was a tendency toward increasing mean lung attenuation with increasing BMI (Pearson $r = 0.369$; 95% CI -0.1183 to

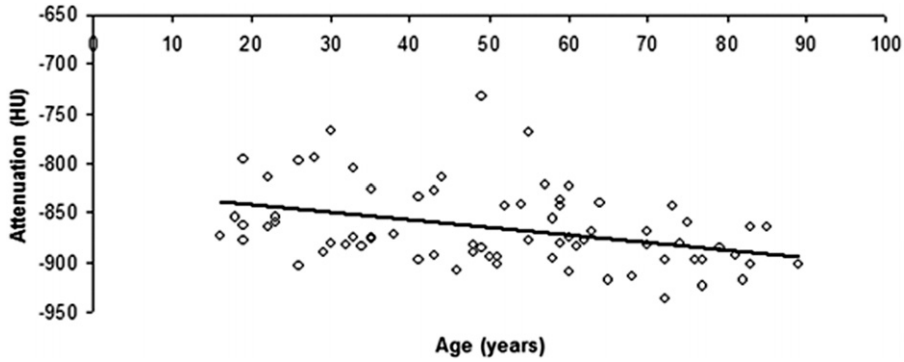

Figure 4 Change in mean lung attenuation in Hounsfield units from dedicated unenhanced chest CT examinations with increasing age. Linear regression curves, corresponding equations, Pearson *r* values, 95% CI values, and *P* values are listed in the Results section.

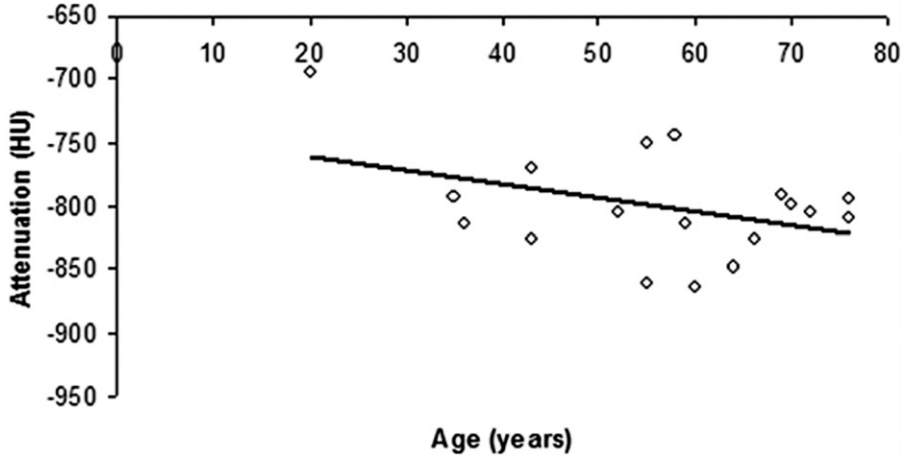

Figure 5 Change in mean lung attenuation in Hounsfield units from unenhanced CT portion of PET/CT examinations with increasing age. Linear regression curves, corresponding equations, Pearson *r* values, 95% CI values, and *P* values are listed in the Results section.

0.7131; $P = 0.1318$; Fig. 6). Mean lung attenuation was seen to statistically significantly increase with increasing mean lung SUVs (Pearson $r = 0.5247$; 95% CI = 0.07646–0.7965; $P = 0.0254$; Fig. 7).

Mean lung volumes were not noted to statistically significantly change with increasing age in adult subjects with CT or PET/CT scans grouped together (Pearson $r = 0.007167$; 95% CI = −0.2746 to 0.2878; $P = 0.961$; Fig. 8). Normalized mean lung volumes also were not noted to statistically significantly change with increasing age in adult subjects with CT or PET/CT scans grouped together (Pearson $r = 0.004374$; 95% CI = −0.2772 to 0.2853; $P = 0.9762$). Mean lung volumes statistically significantly increased with increasing age in pediatric subjects (Pearson $r = 0.9543$; 95% CI = 0.8504–0.9865; $P < 0.0001$; Fig. 9).

Mean lung volumes were not noted to statistically significantly change with increasing BMI, although there was a tendency for mean lung volumes to decrease with increasing BMI (Pearson $r = -0.5338$; 95% CI = −0.8480 to 0.05,804; $P = 0.0739$; Fig. 10). Normalized mean lung volumes were noted to statistically significantly decrease with increasing BMI (Pearson $r = -0.6245$; 95% CI = −0.8823 to 0.07,873; $P = 0.0299$).

Lung MVPs were not noted to statistically significantly change with increasing BMI (Pearson $r = 0.142$; 95% CI = −0.4704 to 0.6620; $P = 0.6599$; Fig. 11). Lung MVPs were not noted to statistically significantly change with increasing age (Pearson $r = 0.3668$; 95% CI = −0.2624 to 0.7772; $P = 0.2408$; Fig. 12).

Discussion

Changes in Structure and Function of the Lungs and Airways During Childhood

Many changes in structure and function occur in the pediatric lung. Although the number of conducting airways and pulmonary arteries does not increase with age after birth, there is only one-third to one-half of the adult number of alveoli present at birth.[10,11] Through septation of the primary

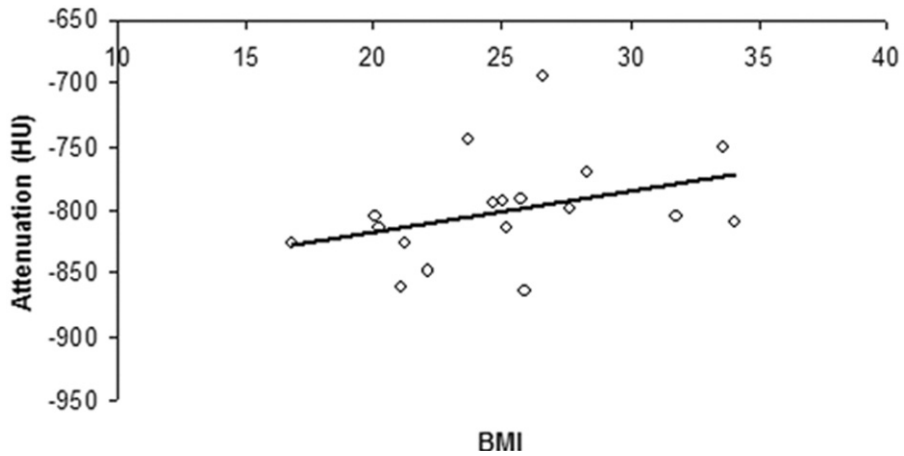

Figure 6 Change in mean lung attenuation in Hounsfield units with increasing BMI in kg/m^2. Linear regression curves, corresponding equations, Pearson *r* values, 95% CI values, and *P* values are listed in the Results section.

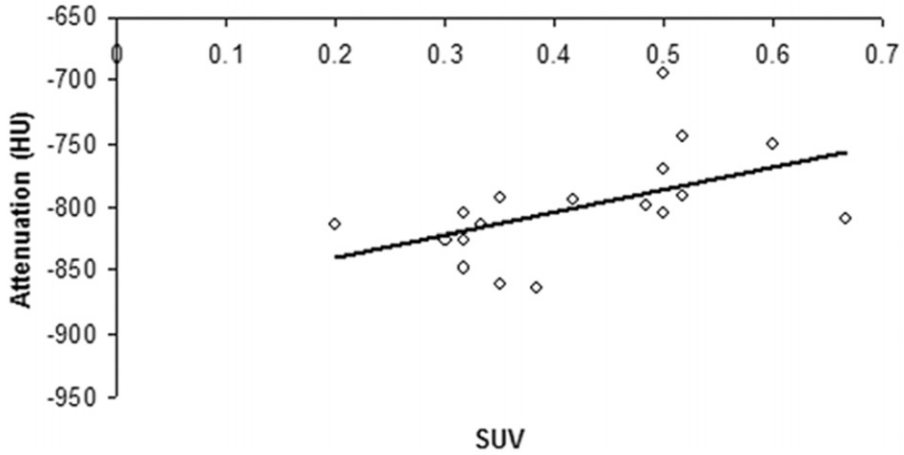

Figure 7 Change in mean lung attenuation in Hounsfield units with increasing mean lung SUV. Linear regression curves, corresponding equations, Pearson *r* values, 95% CI values, and *P* values are listed in the Results section.

saccules, the number of alveoli increases rapidly, probably reaching adult levels between 1.5 to 2 years of age, and almost always by 8 years of age.[12-16]

After this period of rapid alveolar addition is complete, lung growth continues to take place via an increase of the dimensions of structures already present.[12,15,16] As such, there is a substantial increase in the conductance of peripheral airways at about 2 years of age related to an increase in the caliber of the small conducting airways.[17]

During this growth period of increasing dimensions, there is also a progressive increase in the elastic recoil of the lungs with associated increased traction on the small airways resulting in increased forced expiratory flow relative to lung volumes.[18-22] Other changes include an increase in the outward recoil of the chest wall as well as greater strength of the respiratory muscles.[19] Through these changes, relative underdistention of the lung before 8 years of age is transformed to a relative overdistention thereafter.[23,24]

Although similar changes in the thorax tend to occur in all children, there is nevertheless a large variability in the size and function of the lungs. 80% of the explained variance between subjects for most indices of lung function including forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), total lung capacity (TLC), inspiratory capacity (IC), and pulmonary diffusing capacity of carbon monoxide (DLCO) is accounted for by differences in height. Differences in thoracic dimensions also play a small role, but this does not appear to be a factor in adults.[19]

Another 10% of the variability can be explained by differences in body fat as a percentage of body mass. Increased body fat reduces lung volume by occupying space locally and elevating the diaphragm. In contrast, increased muscle mass is associated with increased lung volumes for 2 reasons. First, increased muscle strength can directly increase inspiratory capacity. Second, habitually high levels of exercise activity tend to increase both lung growth as well as muscle growth, causing an indirect correlation between muscle mass and lung size. This activity-induced increase in lung growth is at least partially the result of increased production of growth hormone.[19,25]

Because of greater muscle strength, the inspiratory capacity of boys before puberty is approximately 7% greater than

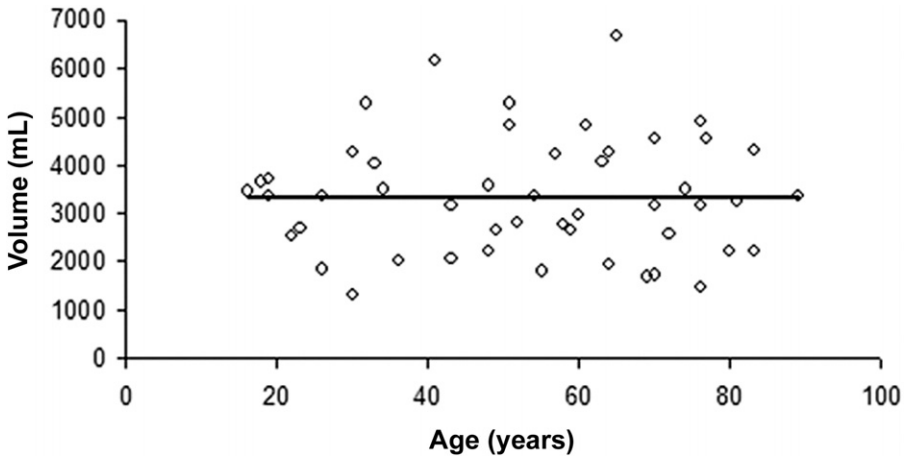

Figure 8 Change in adult mean lung volumes in milliliters with increasing age. Linear regression curves, corresponding equations, Pearson *r* values, 95% CI values, and *P* values are listed in the Results section.

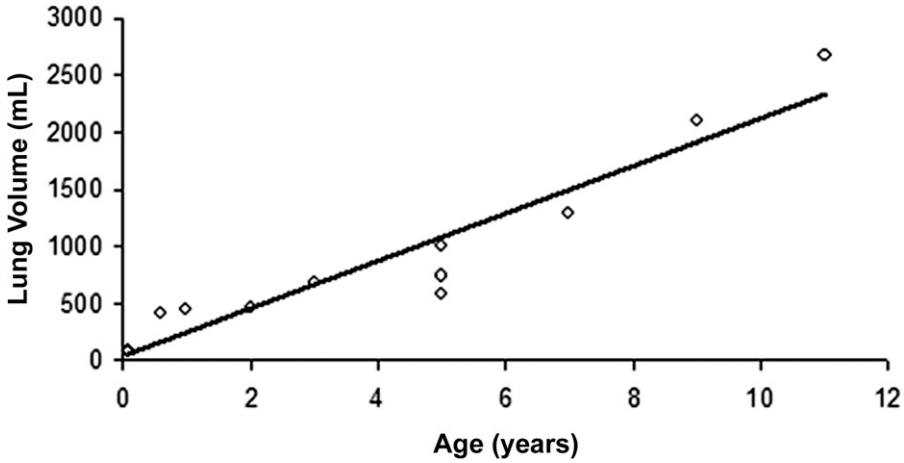

Figure 9 Change in pediatric mean lung volumes in milliliters with increasing age. Linear regression curves, corresponding equations, Pearson *r* values, 95% CI values, and *P* values are listed in the Results section.

girls of the same stature.[19,25,26] Residual and expiratory reserve volumes as well as forced expiratory flows are, however, similar in boys and girls. Considering that lung volumes are greater in boys, the equal flows suggest that the airways of girls may be shorter and wider, although it is controversial whether airway growth patterns and sizes differ between the sexes in infancy or later in childhood.[18,27-44]

Before puberty, the relationship between stature and lung function is relatively linear, whereas during puberty, lung function no longer increases proportionally to stature but tends to follow a more complex pattern, in part as the result of a differential growth in the length and width of the thoracic cavity compared with growth of other areas of the body.[19,26,45] Lung volumes tend to increase after adult stature has been reached as a result of prolonged increase in muscle strength, and lung function increases proportionally to trunk and chest dimensions rather than to stature.[45]

The increases in lung function associated with puberty were reported to occur in girls in the United Kingdom at an average age of 12 years old and average stature of 1526 mm.[26] There is a puberty-associated increase in FEV_1, FVC, and peak expiratory flow (PEF) of approximately 10%, and other indices change far less. FEV_1 may continue to increase by a small amount (~10 mL/yr), and FVC may decline with increases in fat although this is frequently reversed in early adult life.[19]

Puberty was reported to occur in boys in the United Kingdom at an average age of 14 years old and average stature of 1625 mm. Most indices of lung function are increased, averaging 16%.[19] FEV_1 and FVC continue to increase after puberty until approximately 25 years of age with cessation of longitudinal growth occurring at approximately 17 years. From 18 years on, a continued increase in lung function is largely the result of an increase in both the anterior-posterior and left-right dimensions of the thoracic cage.[19,45] In this stage of growth, the increase in lung tissue and collagen is less than the increase in lung volume. Muscle strength may continue to increase as well. The final mass of the lungs relative to body size and the mechanical properties of the lungs are similar in men and women.[19]

Imaging Correlation in Childhood

CT of the chest has made it possible to study lung structure in vivo.[39,46-50] Besides its common use in the evaluation of lung disease, CT also can be applied to the study of normal lung parenchyma, providing informative measurements of lung weight, gas volume, and lung expansion.[24,49,50]

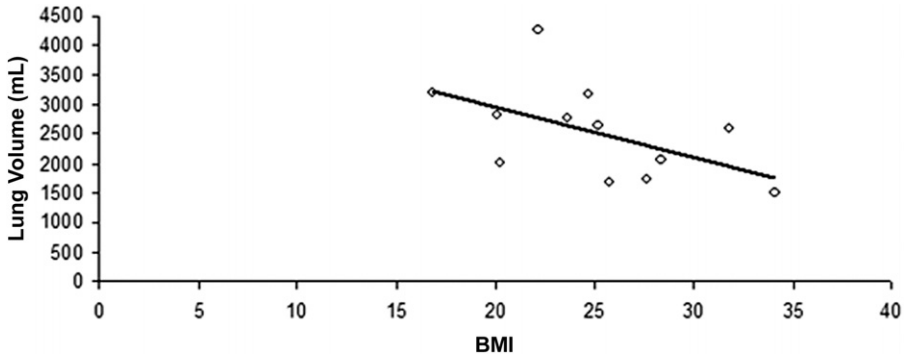

Figure 10 Change in mean lung volumes in milliliters with increasing BMI in kg/m^2. Linear regression curves, corresponding equations, Pearson r values, 95% CI values, and *P* values are listed in the Results section.

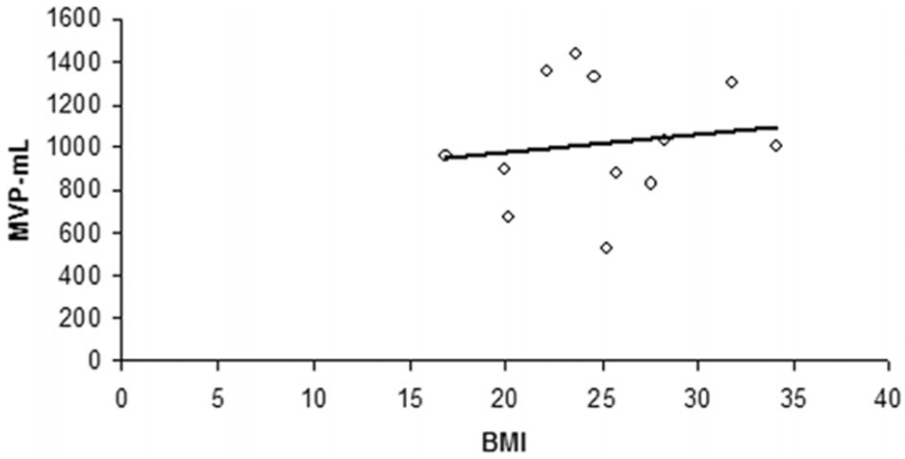

Figure 11 Change in lung MVP in SUV- milliliters with increasing BMI in kg/m^2. Linear regression curves, corresponding equations, Pearson *r* values, 95% CI values, and *P* values are listed in the Results section.

de Jong and coworkers studied changes in the airways, pulmonary parenchyma, and pulmonary arteries in children aged 0 to 17.2 years (the majority of whom were ages 0–2 years) with nonpulmonary malignancy who had normal CT scan reports, by using the degree of radiograph attenuation to estimate lung density, multiplying lung densities by lung volumes to calculate lung weights, and subsequently estimating lung expansion. CT scans were performed in these subjects after inflation of the lungs to 25 cm H_2O pressure.

Their data showed only a small increase in lung expansion throughout childhood, substantial variability in lung expansion between subjects; a strong correlation of CT measured lung weight with subject height; an exponential association of airway wall, airway lumen (Fig. 13), and pulmonary artery areas with subject height; and a linear association of airway surface length/area ratio to alveolar surface/volume ratio (suggesting a close relationship of the growth of airways with the growth of alveoli; Fig. 14). There was also a strong correlation between the measured luminal areas of the trachea with those of all other measured airways. The authors noted an increase in lung expansion from about 3 mL/g at birth to 7.5 mL/g in adolescence. No differences in airways sizes were shown between males and females, although previous functional studies have indicated that males have smaller airways in infancy and larger airways after puberty than females, indicating either differences in smaller airways that cannot be measured with CT or error related to a small sample size.[51]

An earlier study had focused exclusively on the trachea analyzing length, anteroposterior diameter, transverse diameter, cross-sectional area, and contained volume. CT scans of 90 subjects younger than 20 years of age were used to relate these parameters to body height, and the resulting regressions had r values between 0.88 and 0.92. No differences were found between men and women.[52]

A study conducted by Gollogly and coworkers reviewed 1050 normal CT scans in subjects ages 0 to 24 years in an effort to establish normal CT determined lung volumes for children, by plotting the results as a function of age and sex (Fig. 15).[53] Similar to their data, our data showed that mean lung volumes increase with increasing age in pediatric subjects (Fig. 16). As an adjunct to pulmonary function testing, this normative quantitative assessment has the potential to

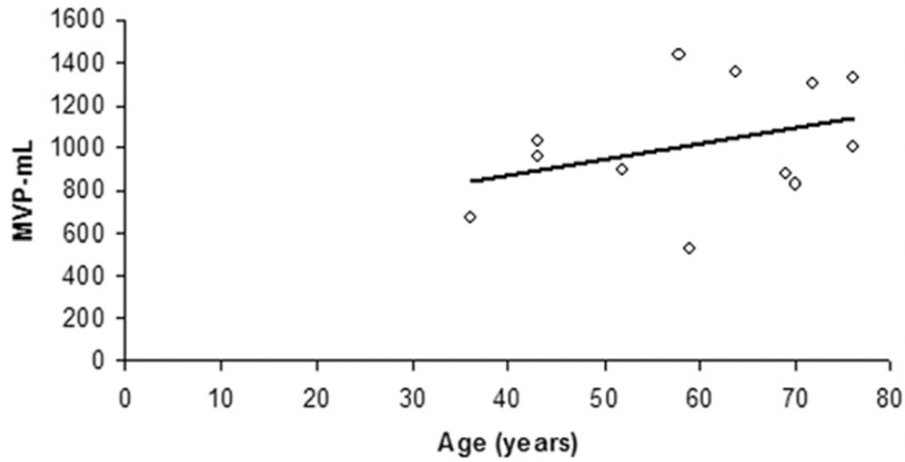

Figure 12 Change in lung MVP in SUV milliliters with increasing age. Linear regression curves, corresponding equations, Pearson *r* values, 95% CI values, and *P* values are listed in the Results section.

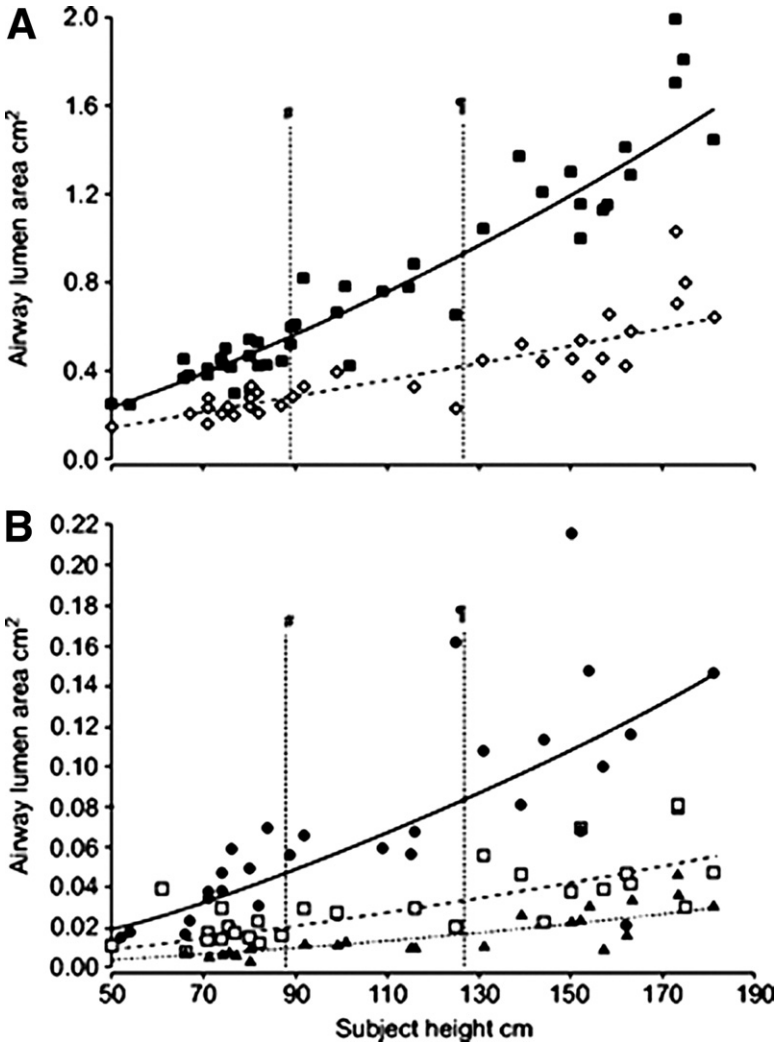

Figure 13 Changes in airway luminal areas with subject height: (A) Measurements of lumen area for trachea (■) and right bronchus intermedius (RBI; ◇) are plotted against subject height. Power-law regression lines are shown for trachea (—) and RBI (- - -). 95% confidence intervals are not shown. (B) Measurements of lumen area for right apical bronchus (RAB; ●), first branch after RAB (□) and second branch after RAB (▲) are plotted against subject height. Linear regression lines are shown for RAB (—), RAB1 (- - -), and RAB2 (· · ·). 95% confidence intervals are not shown. Data were grouped for males and females. Subjects' height at ~2 years (#) and 8 years (¶) of age is indicated by vertical dotted lines. (Reprinted with permission de Jong et al.[51])

increase the clinical utility of a CT scan of the chest in the evaluation of children with complex spinal deformities, who may be at risk of thoracic insufficiency syndrome.[53] They also pointed out that total lung parenchymal volume measured on CT is easily understood, is relative operator- and patient-independent, is noninvasive, and can be performed in children who may not be able to cooperate with pulmonary function testing. However, disadvantages of this approach include exposure to ionizing radiation from CT (which can potentially be overcome through use of MRI techniques) as well as variability of measurements related to free breathing in subjects who are scanned.

Imaging studies have made limited observations in other thoracic areas as well. One study examined the diaphragmatic crura on CT in 80 children of ages 0 to 15 years and reported that the diaphragmatic crura of younger children appear large, relative to body size and the diameters of the T12 vertebral body, compared with those of older children, and have a greater tendency to be nodular in appearance in children younger than 5 years of age than in older children. However, crural width was not seen to increase significantly with age.[54]

Changes in Structure and Function of the Lungs and Airways During Adulthood

Most of the functional changes accompanying aging of the lung can be explained by decreases in 3 factors: chest wall compliance, respiratory muscle performance, and pulmonary elastic recoil.[55] Chest wall compliance was shown to undergo a statistically significant decrease with increasing age in a study comparing the compliance of the chest wall in

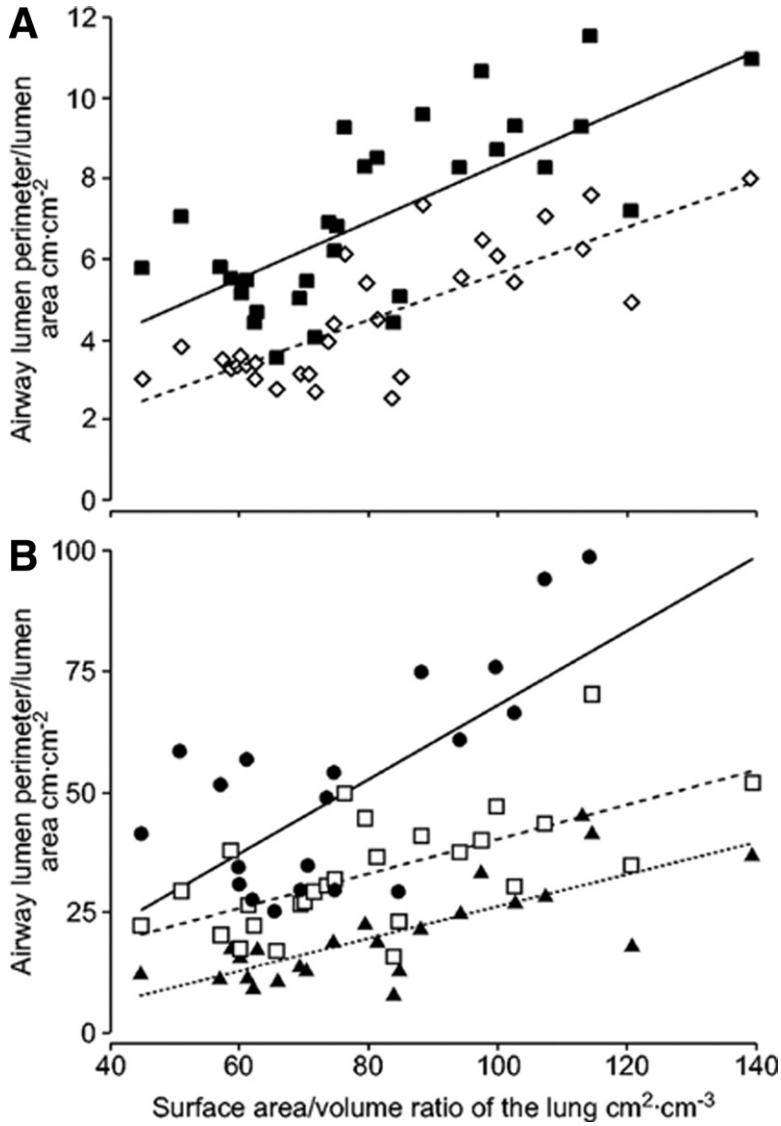

Figure 14 Changes in alveolar surface area/lung volume ratio versus airway lumen perimeter/airway lumen area ratio. (A) Measurements of lumen perimeter/area ratio for trachea (■) and right bronchus intermedius (RBI; ◇) are plotted against lung surface area/volume ratio. Regression line is shown for trachea (—) and RBI (- - -). 95% confidence intervals are not shown. (B) Measurements of lumen perimeter/area ratio for right apical bronchus (RAB; ●), RAB1 (□) and RAB2 (▲) are plotted against lung surface area/volume ratio. Linear regression line is shown for RAB (—), RAB1 (- - -), and RAB2 (· · ·). 95% confidence intervals are not shown. (Reprinted with permission de Jong et al.[51])

subjects ages 24 to 39 against those ages 55 to 75 years. In the upright position, mean rib cage compliance decreased from 0.164 L/cm H_2O in the younger subjects to 0.114 L/cm H_2O in the older subjects. Diaphragm-abdominal compliance concomitantly decreased from 0.032 L/cm H_2O to 0.020 L/cm H_2O. These reductions also were seen in the supine position.[56] Some of the factors contributing to a decrease in chest wall compliance can be observed radiologically, including calcification of the costal cartilages and chondrosternal junctions, as well as changes in shape of the thorax, which are often the result of partial or complete vertebral fractures with associated kyphosis secondary to osteoporosis.[55,57,58]

Respiratory muscle performance also is affected by changes in thoracic shape. Thoracic kyphosis leads to an increase in the anteroposterior diameter of the chest which, in turn, leads to flattening and decreased performance of the diaphragm.[58] This effect is accentuated by the diaphragm's increased relative contribution to mechanical ventilation in later life related to decreases in chest wall compliance.[55] Many studies also report that the respiratory muscles themselves have decreased strength in later life, although this is not ubiquitous.[55] Potential causes include decreased nutrition as well as age-associated alterations in skeletal muscle.[55,59] Skeletal muscle age-associated changes include a decrease in cross-sectional muscle fiber area (sarcopenia), a decrease in the number of muscle fibers, alterations in neuromuscular junctions, and loss of peripheral motor neurons, especially of type II fast-twitch muscle fibers.[55,60-65]

The decrease in elastic recoil of the lung parenchyma with increasing age is at least partially the result of an increase in

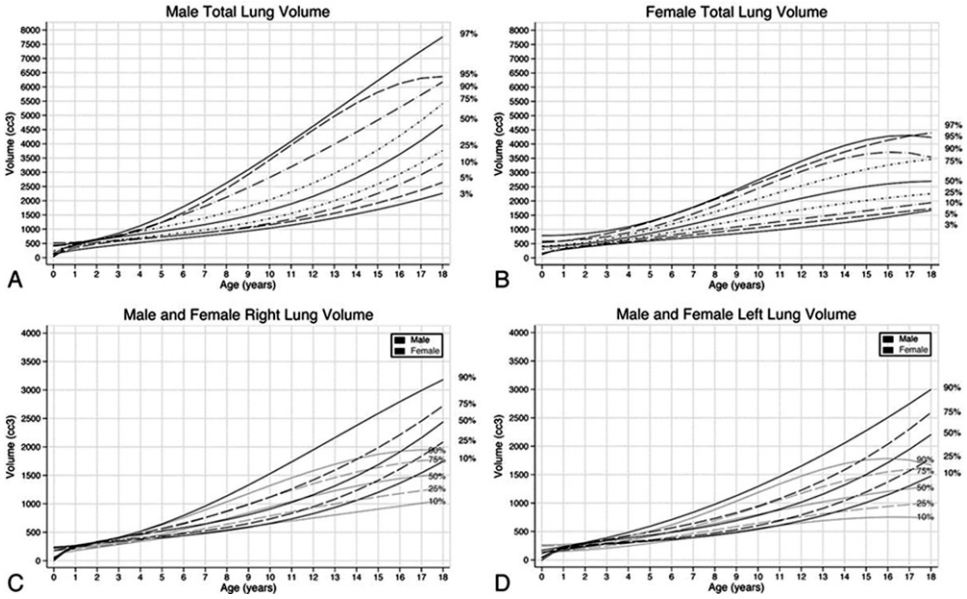

Figure 15 Changes in lung volume with increasing age in 1050 subjects with normal CT scans. (A) Smoothed data for total male lung volume as function of age from birth to 18 years of age. (B) Smoothed data for total female lung volume as function of age from birth to 18 years of age. (C) Smoothed data for right lung volume in male patients and female patients. (D) Smoothed data for left lung volume in male patients and female patients. (Reprinted with permission Gollogly et al.[53])

the ratio of elastin to collagen with increasing age.[66,67] This decrease in collagen content also may contribute to reduced expiratory airway diameter, with associated airflow limitation.[66]

Decreases in these 3 factors cause a variety of changes in the normal pulmonary function test values in the elderly. Decreased pulmonary elastic recoil and, to a lesser extent, decreased respiratory muscle performance generally lead to an increase in residual volume (RV) of approximately 50% from age 20 to 70. At the same time, there is generally a 25% reduction in vital capacity (VC), as well as a decrease in FEV_1.[55,66] Furthermore, there is an increase in functional residual capacity (FRC) with increasing age as the result of decreased pulmonary elastic recoil as well as increased elastic recoil of the chest wall. One study found FRC to increase from 50% to nearly 60% of TLC between 10 and 60 years old.[68] TLC itself tends not to change significantly with age if measurements are normalized to subject height.[69,70] FVC is estimated to begin to decline in the middle of the fourth decade of life.[71,72] Finally, maximum oxygen consumption (VO_{2max}) typically is decreased in the elderly.[66]

Declines in FEV_1 and FVC with increasing age may lead to a decrease in calculated FEV_1/FVC ratios in healthy elderly people, potentially resulting in the overdiagnosis of obstructive airway disease if the typical lower limit of 80% is applied to this population. In fact, data from the Cardiovascular Health Study suggest that the lower limit of normal in subjects ages 65 to 85 years should be adjusted to 56% to 64%.[73]

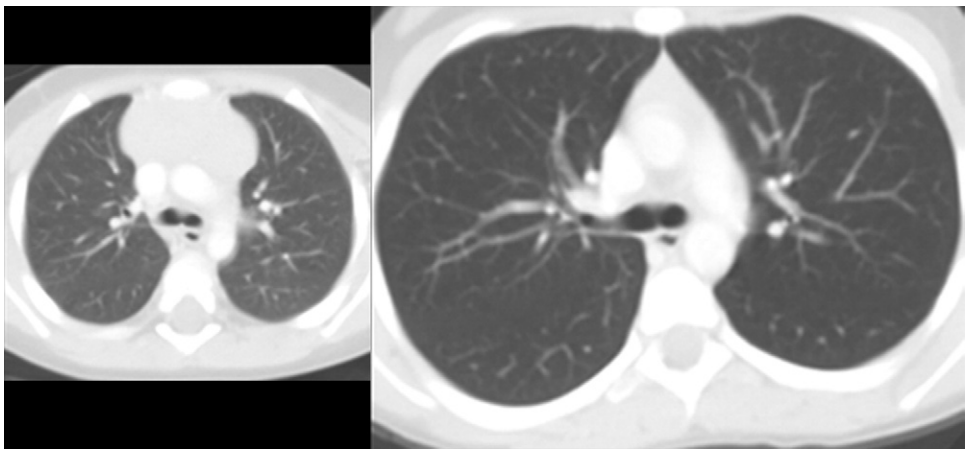

Figure 16 Representative axial unenhanced CT images from 6-year and 19-year old subjects demonstrate increase in mean lung volume with increasing age in pediatric subjects.

The elderly tend to have decreased ventilatory responses to both hypoxia and hypercapnia, as well as a decreased cough reflex.[66] Moreover, studies have reported increases in both dead-space and shunt ventilation, with one source reporting that deadspace as a percentage of tidal volume (TV) doubles between 20 to 60 years of age as a result of decreased perfusion to an increasing number of alveoli.[66] With increasing age, as the walls of the small pulmonary arteries become stiffer and autonomic regulation decreases, blood flow becomes more pulsatile, and the vertical gradient of perfusion is lost.[74-77] Indeed, one study found that the percentage of normal or near-normal ventilation–perfusion scans performed to rule out pulmonary embolus decreased from 61% in those younger than 40 years of age to 11% in those older than 80 years.[78]

Gas exchange across the alveolar membrane decreases with age, largely as a result of increases in mean alveolar diameter, and DLCO generally decreases with increasing age.[2,3,8,69,79,80] Because the exchange of CO_2 and O_2 depends on alveolar ventilation, perfusion, and diffusion, the changes described previously are associated with a decrease in arterial partial oxygen pressures and an increase in the alveolar–arterial oxygen gradient.[66] However, studies have not found CO_2 diffusion to be affected; therefore, respiratory acidosis should continue to be considered pathological.[8,81,82]

Other structural pulmonary changes also have been noted in the elderly. Increasing airspace was noted to be associated with increasing age in a study of 16 autopsy specimens and 22 surgical specimens of nonsmokers.[83] These changes were reported to differ from those of emphysema in that the age-associated changes tend to be homogenous and are not associated with alveolar wall destruction.[55,84]

At the cellular level, an increase in the ratio of neutrophils to macrophages has been found in the bronchoalveolar fluid in subjects of increased age.[85] In addition, increases of interleukin-8, neutrophil elastase, and a variety of antiproteases also have been noted.[86] The clinical relevance of these changes is undetermined, although they may play a role in the increased susceptibility of the elderly to lower respiratory tract infections as well as to observed histological changes of the lung parenchyma.[66] Decreased mucociliary clearance, alterations in respiratory mechanics, comorbid conditions predisposing to aspiration, and other systemic immunologic changes also are potential contributors to the increased infection rate in the elderly.[87]

Imaging Correlation in Adulthood

Increasing airspace with increasing age was reported in a study using CT examinations of asymptomatic individuals.[88] In this study, thin-section CT was performed at both end inspiration and end expiration in 82 subjects (27 smokers and 55 nonsmokers). Air trapping measured on end expiratory images was found to have increased from 23% of subjects ages 21 to 30 years to 76% of those older than 61 years, in concordance with pathological findings. These findings are corroborated through a study reported by Fain and coworkers using diffusion-weighted ^{3}He MRI in healthy nonsmoker adults that showed that apparent diffusion coefficients in the lungs (which correlate with alveolar dimensions) increased with increasing age.[89] Our findings of decreasing mean lung attenuation with increasing age are consistent with these results as well. The subjects who underwent PET/CT had greater mean lung attenuations than those of the CT subjects, which likely is related to the fact that PET/CT scans were performed during quiet respiration whereas CT scans were performed at full inspiration.

According to one study, the trachea continues its growth into the adult period. This study examined the tracheas of 808 subjects between the second and eighth decades of life on posteroanterior and lateral chest radiographs and found both coronal and sagittal tracheal diameters to be larger in men than in women. In men, both dimensions were found to increase rapidly during the second and third decades of life and more slowly in the fourth decade, with coronal and sagittal diameters of 15.5 mm and 15.4 mm, respectively, in the second decade, and 19.5 mm and 20.3 mm, respectively, in the fifth decade. In women, tracheal growth over these 3 decades was more gradual with coronal and sagittal diameters of 14.4 mm and 14.5 mm, respectively, in the second decade and 16.6 mm and 16.8 mm, respectively, in the fifth decade. In both men and women, tracheal growth appeared to cease after the fourth decade.[90] Although these investigators found no correlation between tracheal dimensions and subject weight or height, others have found sagittal tracheal diameters to increase gradually with increasing height.[90,91]

Age, weight, and gender appear to have effects on the diaphragm as well. In a study that examined posteroanterior and lateral chest radiographs of 153 subjects with normal FEV_1 and TLC values, the right hemidiaphragm was noted to be both lower and flatter with increasing age. The right hemidiaphragm was found to be at a mean of 9.5 vertebral levels beneath the top of the first thoracic vertebra in subjects 19 to 37 years old and 10.1 vertebral levels lower in subjects 62 to 86 years old. Increasing weight tended to be associated with a higher and more curved hemidiaphragm, and whereas diaphragm position was not noted to change between men and women, the curvature was noted to be larger in men than in women.[92]

An increase in mean lung attenuation on CT is expected to lead to an increase in mean lung SUV on PET, as increased mean lung attenuation indicates a higher proportion of metabolically active tissue relative to airspace in a given volume of tissue. This relationship is supported by our data that show a positive correlation between mean lung attenuation and mean lung SUV.

Also, we have observed that mean lung attenuation had a tendency to increase with increasing BMI and that mean lung volumes had a tendency to decrease with increasing BMI, particularly when they were normalized for thoracic height, suggestive of restriction of the rib cage or lungs by excess fat deposition. This is supported by the observation that obesity alters chest wall compliance, reduces the effectiveness of respiratory muscle action, and can be associated with poor aeration of the lung bases, decreased functional reserve capacity, and decreased vital capacity.[93,94] Furthermore, fat

deposition in the mediastinum, pleural spaces, and above the diaphragm can reduce lung volumes, and abdominal fat has been noted to raise the diaphragm.[19] We also have observed that mean lung SUVs increase with increasing BMI, in keeping with the concomitant increase in mean lung attenuation and decrease in mean lung volume. This is further supported by our data that show that lung MVPs, which combine quantitative data values from PET and CT into single quantitative values, do not significantly change with increasing BMI.

Interestingly, although mean lung attenuation was shown to decrease with increasing age in our study, consistent with increases in airspace observed with increasing age as described previously, mean lung volume was not shown to significantly change with increasing age, and mean lung SUV was found to increase with increasing age.[55,83,84] The exact cause of this increase is mean lung SUV is not known, but it suggests that there may be increased inflammation in the lungs with increasing age, which may be related to the length of chronic exposure to environmental agents such as cigarette smoke or due to intrinsic increases in lung inflammation with aging. However, lung MVPs did not significantly change with increasing age.

Limitations of our study include its retrospective nature, a small study sample size, the potential for sampling error in our measurements, and inability to obtain height and weight information in the majority of subjects. In addition, although no emphysema was seen on CT scans used in our analysis, we did not have complete access to subject historical information regarding prior tobacco use or other environmental exposures. Furthermore, CT scans were performed on a variety of CT or PET/CT scanners using various scanning protocols and various levels of subject breath holding, potentially increasing the variability in measurements performed, although Brown and coworkers demonstrated that total lung volumes calculated from CT were strongly correlated (r = 0.90) with those measured by body plethysmography.[95] Finally, the relatively increased numbers of younger women and older men in our sample population may have biased our analyses. Despite these limitations, we believe that our data provide useful information for those interested in studying changes in the thorax with normal aging, and provide a basic methodological approach for future study of normal structural and functional changes in the lungs with aging and BMI.

Changes in Structure and Function of the Thymus With Increasing Age

The thymus is a lymphoepithelial organ with the chief function of production and differentiation of T cells. During aging, the thymus involutes with loss of approximately 90% of its epithelial space by 50 years of age.[96,97] At the same time, there is a significant increase in the lipid composition of the thymus, eventually resulting in nearly complete lipomatous atrophy. At 40 to 50 years of age, only small variations, less than 1% per year, are observed in the thymus.[98] In fact, this process is one of the most profound consequences of aging in the human body, resulting in a reduced output of naïve T cells.[99] Together with changes in mature lymphocytes with aging, thymic involution is thought to be responsible for decreased immune function in the elderly.[100]

Classically, thymic involution was thought to begin, or at least accelerate, at puberty.[101-103] In fact, much work has been done to illustrate a link between sex steroids and thymic involution. More than 100 years ago, experiments demonstrated that castration results in increased thymic size, and several studies have since corroborated this finding.[102,104-106] In addition, exogenously administered sex steroids have been found to negatively impact thymopoiesis.[107] However, for various reasons, immunologists are beginning to reconsider the role puberty is thought to play in the involution process.[100]

One such reason is that the effects of gonadectomy are transient, and the thymus eventually involutes.[102,108] Another such reason is that loss of thymic tissue has been observed to actually begin in the first years of life. Necropsy results reported by Steinmann and coworkers show a continuous involution of the thymic epithelium from the first year of life to the end of life.[109,110] Yekeler and coworkers similarly observed, through ultrasonography, that the thymus begins to shrink between the ages of 4 to 6 months.[111] In addition, counts of the number of thymocytes per thymic lobe of children between 8 days to 8 years old have shown peak values to occur at 6 months of age.[112] As such, it is now thought that age-related intrinsic hematopoietic defects affect the proliferative and developmental potential of T cell precursors.[113] Recent experiments have better defined these precursors, and it is found that such cells decline in frequency and repopulation potential with age.[113-116]

Thymic sizes measured via ultrasonography were found, on average, to be larger in male infants than in female infants, but the difference was not statistically significant.[111] Statistically significant differences also were not found between breast-fed and formula-fed infants, although another study did find breast fed infants to have significantly larger thymic indices (defined as the product of the maximal transverse diameter and maximal sagittal area of the thymus), which could be related to immune modulating factors contained in human breast milk.[111,117,118] Statistically positive correlations also were found between birth weight and thymic index and between birth height and thymic index for term neonates.[111] Furthermore, maximum transverse diameter, anteroposterior dimensions, and longest craniocaudal dimensions all were found to be significantly greater in term infants than preterm infants.

The use of ultrasonography also has revealed a number of different shapes of the thymus on transverse scans, including rectangular or quadrilateral shape in 69%, oval or round shape in 12%, bilobar shape in 7%, drumstick or L-shape in 6%, and crescent shape in 6%. Similarly, on longitudinal scans a number of shapes were revealed, including triangular shape in 66%, teardrop shape in 16%, oval shape in 17%, and sickle shape in 1%. Symmetry was observed in 54%, with left predominance in 35% and right predominance in 11%. Echogenicity was homogeneous in 85% but slightly coarse and granular in 15%, less than that of liver and spleen in

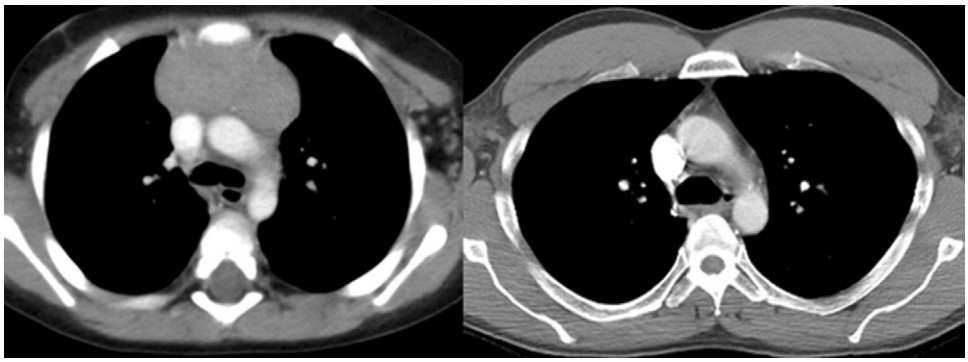

Figure 17 Representative axial unenhanced CT images show normal prominent oval soft-tissue attenuation thymus in anterior mediastinum of 6-year-old boy and diffuse fatty atrophy of thymus with triangular anterior mediastinal fat remaining in 40-year-old man.

73%, equal in 14%, and greater in 4%, and always less than that of the thyroid gland.[111]

CT and MRI also have been used to follow changes in the thymus with age as well. Both techniques are able to differentiate the thymus from mediastinal fat in subjects younger than 30 years of age.[119,120] In prepubertal subjects, the thymus typically has a quadrilateral shape with gently undulating convex lateral margins, although the margins may sometimes be flat or concave. During puberty, the thymus tends to assume a more triangular or arrowhead-like cross-sectional appearance. After puberty, the thymus is generally observed to undergo gradual focal or diffuse fatty atrophy, and its thickness has been shown to be inversely proportional to age (Fig. 17).[119,121-126]

Baron and coworkers were able to discern the thymus in 100% of subjects younger than 30 years of age, in 73% of subjects between 30 to 49 years of age, and in 17% of subjects of 50 years of age and older on CT. Sklair-Levy and coworkers reported that, in infants, the thymus tends to have greater attenuation than the chest wall and cardiac muscle whereas in older children, the attenuation of the thymus tends to be decrease to a level similar to that of skeletal muscle, and tends to be greater in males than in females. Moreover, in older subjects it approaches the attenuation of fat.[119,127]

On MRI, the signal intensity (SI) of the thymus is similar or slightly greater than that of skeletal muscle on T1-weighted images and greater than that of skeletal muscle on T2-weighted images in childhood, and there is no significant change in thymic SI on T1- or T2-weighted images with age in subjects younger than 30 years old.[120,126] A recent study by Inaoka and coworkers used chemical shift MRI techniques to depict changes in the physiologic fatty infiltration of the thymus with age. SI loss of the thymus, calculated via 1 minus the thymus/muscle SI ratio on opposed-phase T1-weighted images divided by the thymus/muscle SI ratio on in-phase T1-weighted images, was found to correlate well with increasing age but without significant difference between men and women. Mean SI loss was 0.8 for subjects under 11 years of age, 17.8 for subjects 11 to 15 years of age, 38.6 for subjects 16 to 20 years of age, and 42.0 for subjects 21 years of age or older.[121]

At one time, it was suggested that any thymic activity after puberty on 2-FDG-PET scanning could be considered as abnormal, but this is no longer felt to be the case.[128] Nakahara and coworkers found that 34% of 94 subjects between the ages of 18 and 29 years had increased FDG uptake within the thymus (Fig. 18). Interestingly, this study also demonstrated a correlation between increased thymic uptake and increased attenuation on CT, consistent with less fatty infiltration of the thymus.[129]

Because of the dynamic physiology of the thymus over the lifespan, FDG-PET cannot always be used in isolation to differentiate between the normal and pathological thymus, and structural imaging using CT or MRI remains helpful in this regard. The thymus may involute or hypertrophy in reaction to events throughout the lifespan. For example, stress may lead to thymic involution, although the thymus may rebound and even exceed prestress levels on recovery.[130,131] Additionally, pregnancy and lactation may also cause thymic involu-

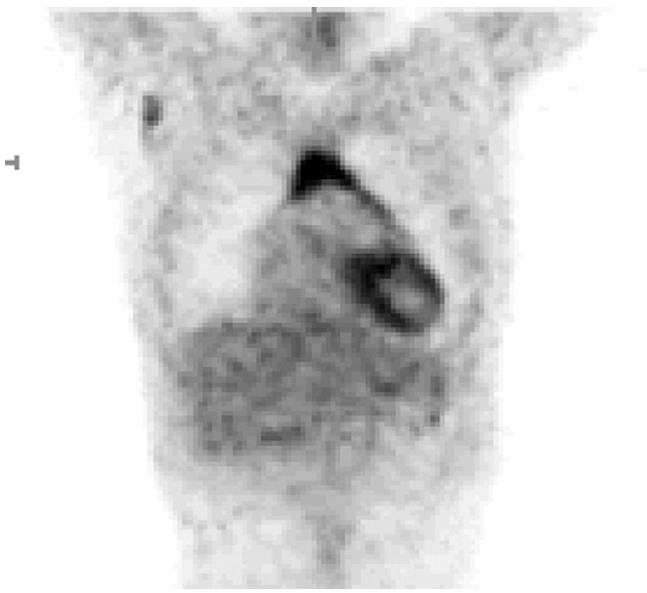

Figure 18 Coronal PET image of 15-year-old male reveals triangular shaped FDG uptake in normal thymus.

tion.[132] On the other hand, chemotherapy and radioiodine therapy can both lead to thymic hyperplasia and increased FDG uptake.[133,134]

Conclusion

Quantitative radiologic and scintigraphic cross-sectional imaging of the thorax, mainly through CT, MRI, and PET imaging, can generate useful information about normal changes in thoracic structure and function with age. Such information can be used as a normative baseline to assess subjects of any age in the clinical setting who undergo CT, MRI, or PET imaging of the thorax, and may serve as an aid to those investigators involved in research related to the aging process. In this article, we have reported quantitative preliminary data retrospectively obtained from CT and PET imaging of the thorax regarding changes in lung volume, lung attenuation, lung metabolism with age and BMI, and have reviewed the literature regarding reported changes in normal thoracic structure and function as well. It is our hope that some of the basic methodological approaches we have presented will serve as a springboard for future prospective studies of normal thoracic structural and functional changes with age.

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