Growth of the small airways and alveoli from childhood to the adult lung measured by aerosol-derived airway morphometry

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Zeman, Kirby L., and William D. Bennett. Growth of the small airways and alveoli from childhood to the adult lung measured by aerosol-derived airway morphometry. J Appl Physiol 100: 965–971, 2006. First published December 15, 2005; doi:10.1152/japplphysiol.00409.2005.—Understanding the human development of pulmonary air spaces is important for calculating the dose from exposure to inhaled materials as a function of age. We have measured, in vivo, the air space caliber of the small airways and alveoli at their natural full distension [total lung capacity (TLC)] by aerosol-derived airway morphometry in 53 children of age 6–22 yr and 59 adults of age 23–80 yr. Aerosol-derived airway morphometry utilizes the gravitational settling time of inhaled inert particles to infer the vertical distance necessary to produce the observed loss of particles to the airway surfaces at sequential depths into the lung. Previously, we identified anatomical features of the lung: the caliber of the transitional bronchioles [transitional effective air space dimension (EADtrans)], the mean linear dimension of the alveoli (EADmin), and a measure of conducting airway volume [volumetric lung depth (VLDtrans)]. In the present study, we found that EADmin increased with age, from \(184 \mu m\) at age 6 to \(231 \mu m\) at age 22, generally accounting for the increase in TLC observed over this age range. EADtrans did not increase with TLC, averaging \(572 \mu m\), but increased with subject age and height when the entire age range of 6–80 yr is included \([EAD_{\text{trans}} (\mu m) = 0.012 \text{[height (cm)]} \times \text{[age [yr]} + 508; P = 0.007\]. VLDtrans scaled linearly with lung volume, but VLDtrans relative to TLC did not change with age, averaging \(7.04 \pm 1.55\%\) of TLC. The data indicate that from childhood (age of 6 yr) to adulthood a constant number of respiratory units is maintained while both the smallest bronchioles and alveoli expand in size to produce the increased lung volume with increased age and height.

Postnatal lung development; aerosol-derived airway morphometry; lung volume

THE HUMAN LUNG UNDERGOES a continual postnatal growth and development of the air spaces through early adulthood. Understanding the range of physical changes is important for defining the characteristics of normal lung structure, interpreting lung function data, setting the parameters of assisted ventilation, and predicting the dose from exposure to inhaled materials, either therapeutic or pollutant, as a function of age. Modeling of the child lung is based on a small data set. In addition, it is especially difficult to obtain the in vivo measures of lung air spaces in children, either individually or for a large cohort. Aerosol-derived airway morphometry (ADAM) (5, 10, 30) has been shown to be useful for providing a noninvasive means to measure the size of the lung air spaces.

Briefly, ADAM uses the gravitational settling of small inhaled particles to infer the vertical distance [effective air space dimension (EAD)] that the particles must have settled to become lost to the airway wall. This method measures the dimensions of the air spaces as a function of the volumetric lung depth (VLD), i.e., the dimensions decrease as volume into the lung increases from the proximal to distal airways (Fig. 1). Hence, EADs are a volume average of the mean linear intercept at a depth populated predominantly by air spaces of its respective generation (22). For a list of abbreviations for terms used with ADAM, see Table 1.

In previous studies, we and others have shown that the dimension of the most distal air space generation, the alveolar region, can be reliably approximated by minimum EAD (EADmin) (6, 30). Small but significant changes in EADmin, or mean linear intercept of the peripheral air spaces, with age in adults can be detected by ADAM under the appropriate experimental conditions (6).

Also using ADAM, we were able to identify in vivo the transitional bronchioles: a region that partitions the lung into two general anatomical areas marked by a difference in branching pattern. We showed that the dimensions of the airways decrease in caliber with depth into the lung until a region is reached where there is an abrupt slowing of the caliber change with further lung depth (Fig. 1) (31). We demonstrated that the airway caliber at this point (EADtrans) was similar to that of the transitional bronchioles. The volume of gas required to reach these transitional bronchioles into the lung from the oropharynx was denoted VLDtrans and is analogous to the anatomical dead space of the conducting airways, only slightly greater in volume since it includes the transitional bronchioles. This volume (VLDtrans) was positively correlated with age.

In this study, we have used the EADmin, EADtrans, and VLDtrans values from ADAM to extend our analysis of changes in airway structure associated with changes in age from 6 through 80 yr. Alveolar dimensions at or near full distension have been measured by ex vivo or postmortem methods and have been shown to grow postnataally with age until ~22 yr of age (24, 25). The advantage of ADAM lies in its ability to study transitional bronchioles and alveolar morphometry in vivo and assess changes associated with development, aging, or disease. The present paper is interested in the normal growth of lungs and not the changes associated with the senescent lung. This article uses the data from 22 to 80 yr to illustrate the relative lack of lung growth in this age range over several decades of life, especially compared with the rapid changes in children and adolescents in only one decade. There is very little data, especially in vivo, in the literature to span this age range.

We hypothesized that our in vivo measurements by ADAM in a large group of healthy humans would corroborate limited

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photomultiplier tube. The subject was seated upright while tidally breathing filtered air through the mouthpiece.

A maneuver commenced at end inspiration of a tidal breath. The subject was instructed to exhale below FRC and then inhale all the way to TLC. At the same time, the three-way valve was switched to supply aerosol on demand, such that on the next inhalation the subject received the aerosol through the mouthpiece. The rate of inhalation was controlled by the subject matching a visual signal proportional to a target flow rate of 1 l/s. At end-inhalation of the aerosol at TLC, a solenoid valve was shut blocking flow, the subject was instructed to hold the breath for a preselected interval, and the solenoid valve was opened, followed by a controlled exhalation of 1 l/s to residual volume. The three-way valve was closed, ending the maneuver. The subject was removed from the mouthpiece for a rest. The maneuver was repeated until 5–10 correct maneuvers were completed, each with a unique breath-hold time. Breath-hold times were preselected by the investigator to distribute evenly for 0 s (i.e., no breath hold) to 10 s.

The concentration and flow data for each breath-hold maneuver were analyzed to obtain 1) the rate of decrease in exhaled aerosol concentration with breath-hold time and 2) the volumetric lung depth that the aerosol resided during the breath hold. The logarithm of the ratio of exhaled aerosol concentration ($C_e$) to the inhaled aerosol concentration ($C_i$) was calculated continuously for the entire exhaled volume for each breath-hold maneuver. The rate of decrease in $C_e$ as a result of particle settling during the breath holds was estimated by a least squares linear regression for the slope $d\ln(C_e/C_i)/dt$ for each exhaled volume increment, where $t$ is breath-hold time. Acceptable regression coefficients were >0.95 and were usually >0.97. EADs are inversely related to the slopes of the regression lines by a relationship derived from a model of infinitely long tubes randomly oriented in space (14):

\[
EAD = 1.273 \times V \frac{d\ln(C_e/C_i)}{dt}
\]

where $V$ is the particle settling velocity of the aerosol particles and $d\ln(C_e/C_i)/dt$ is the slope of the regression lines.

EADs were then associated with their volumetric depth into the lung by the exhaled volume through the principle of first in, last out. In other words, EADs that were calculated from the aerosol at the beginning of the exhalation were assumed to be representative of the proximal airways at that depth, and EADs calculated from the aerosol toward the end of the exhalation were representative of distal airways (Fig. 1). EAD$_{min}$ was determined from the data according to the description in Zeman and Bennett (30). EAD$_{trans}$ and VLD$_{trans}$ were determined from the data as described in Zeman et al. (31). Briefly (see Fig. 1), EAD$_{min}$ is the minimum value for the airway dimensions found at the greatest lung depth. EAD$_{trans}$ is determined by fitting two lines through the EAD data: one as a best fit through the proximal EADs and the other through the distal EADs. VLD$_{trans}$ is the volume contained in the airways to a depth into the lung where EAD$_{trans}$ is located. EAD$_{trans}$ is related to alveolar diameter, and EAD$_{trans}$ is related to transitional bronchiole caliber. VLD$_{trans}$ is related to anatomical dead space.

EAD measurements were made at full lung capacity (TLC) by requesting the subjects to inhale completely. Comparisons of these values were limited to those ex vivo procedures approximating lung distention at TLC. Typical means for ex vivo procedures to approximate the full lung volume was to infuse a fixative at 25-cmH$_2$O column or to inflate the lung sufficiently so that it would completely fill the thoracic cavity.

Data analysis. Correlations and regressions were analyzed using Systat for Macintosh 5.2 or by functions in Microsoft Excel 98. Unless otherwise noted, significance was set at $P < 0.05$ for an independent Student’s $t$-test when comparing two different groups, for least squares regression Pearson correlation, and for inclusion/exclusion in forward/backward regression.

Materials and methods

Subjects. The subjects were recruited from the general local population. There were a total of 109 subjects (50 male and 59 female subjects) ranging in age from 6 to 80 yr. All subjects had ADAM measurements made at an end-inspiratory lung volume of 100% of total lung capacity (TLC). Predicted forced expiratory volume in 1 s values were taken from Knudson et al. (18). Subjects were considered normal with predicted forced expiratory volume in 1 s and forced expiratory volume in 1 s to-forced vital capacity (FVC) ratio of $>80\%$. In each subject, we also measured forced expiratory volumes/flows and lung volumes, inspiratory capacity, and expiratory reserve volume by spirometry. Airway resistance (and specific airway resistance) and functional residual capacity (FRC) were measured by body plethysmography. TLC was defined as the sum of FRC and inspiratory capacity. Subjects had no smoking history, no history of lung disease, and no recent history of acute respiratory infection or viral illness within the previous 4 wk. Informed consent was obtained from each volunteer, and the study had the approval of the University of North Carolina Committee on the Protection of the Rights of Human Subjects.

EAD. The technique and theory used in these experiments is described below and in detail elsewhere (4, 23). In brief, the EADs were determined by analysis of exhaled aerosol recovery following inhalation of aerosol from FRC and breath holds for 0–10 s. Assuming the lung is composed of a system of randomly oriented tubes, the rate of decline (slope) of the particle recovery vs. breath-hold time is inversely proportional to the effective inner diameter of those tubes.

A 1-µm (mass median aerodynamic diameter) monodisperse aerosol (geometric standard deviation $= 1.1$) composed of carnauba wax was condensed on salt nuclei generated by a condensation aerosol generator (MAGE, TSI, Minneapolis, MN) and delivered to a mouthpiece via a three-way valve and a check valve. The mouthpiece was fitted with instrumentation to record flow by a pneumotach and aerosol concentration by light scattering from a He/Ne laser to a

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**Fig. 1.** This is sample data from 1 subject to illustrate the determination of minimum effective airway dimension (EAD$_{min}$), EAD at the point where EADs transition from 1 predictable logarithmic slope with lung depth to another lesser logarithmic slope with depth into the lung (EAD$_{trans}$), and volumetric lung depth (VLD) associated with EAD$_{trans}$ (VLD$_{trans}$). Arrows after, as found by others for alveolar intercept lengths. EAD$_{trans}$ is related to transitional bronchiole caliber. VLD$_{trans}$ is the volume contained in the airways to a depth into the lung where $EAD_{trans}$ is located. EAD$_{min}$ is related to alveolar diameter, and EADs decrease in size as depth into the lung increases. Dotted lines represent best fit based on the best simultaneous sum of regression coefficients for both lines. TLC, total lung capacity.
Table 1. List of definitions

<table>
<thead>
<tr>
<th>ADAM</th>
<th>Aerosol-derived air space morphometry</th>
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<tr>
<td>ADS</td>
<td>Anatomic dead space</td>
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<tr>
<td>EAD</td>
<td>Effective air space dimension: the theoretical distance a particle must gravitationally settle to be lost to the airway wall in the breath-hold time measured by ADAM. This is related to airway caliper, where the particle resided during the breath hold. EADs decrease in value distally with depth into the lung through the airways</td>
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<tr>
<td>EADmin</td>
<td>Minimum EAD value for a subject. See Fig. 1. This is related to alveolar diameter.</td>
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<tr>
<td>EADtrans</td>
<td>Value of EAD at the point where EADs transition from one predictable logarithmic slope with lung depth to another lesser logarithmic slope with depth into the lung. See Fig. 1. This is related to the caliber of the transitional bronchioles</td>
</tr>
<tr>
<td>rVLDtrans</td>
<td>VLDtrans relative to TLC. It is a measure of anatomical dead space relative to total lung size, expressed as percent</td>
</tr>
<tr>
<td>TLC</td>
<td>Total lung capacity</td>
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<tr>
<td>VLD</td>
<td>Volumetric lung depth: depth into the lung from the oropharynx to the airway generation that would cumulatively contain that volume of gas. See Fig. 1</td>
</tr>
<tr>
<td>VLDtrans</td>
<td>Volumetric depth into the lung associated with EADtrans. See Fig. 1. It is the gas volume contained within the airways to this depth into the lung and is similar to ADS</td>
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RESULTS

We used airway morphology measurements from ADAM to estimate alveolar diameter (EADmin), transitional bronchiolar caliber (EADtrans), and the volume of conducting airways anatomical dead space (VLDtrans). For a list of significant relationships between ADAM measures, see Table 2. We found that alveolar diameter in children, adolescents, and young adults increases with age (P = 0.003, n = 53) from our youngest subject measured at 6 yr to ~22 yr of age (Fig. 2A). The predicted alveolar diameter, calculated from this regression, is 184 μm at age 6, increasing to 231 μm at age 22. At ages older than 22 yr, alveolar diameter may tend to increase slightly with age, but not statistically significantly (P = 0.38), up to the limit of our oldest age of 80 yr (Fig. 2A). Alveolar diameter was calculated from this regression to be 257 μm at age 22, increasing to 288 μm at age 80. Alveolar diameter compares favorably with other direct microscopic ex vivo measurements of alveolar dimensions for the younger 6- to 22-yr-old subjects (Fig. 2B) and the older 23- to 80-yr-old subjects (Fig. 2C). In addition, the variability in alveolar measurements is similar to published data; the standard error of the measurement for the regression of alveolar diameter with age is similar to the standard error of the measurement calculated from the data given in the ex vivo references (compare vertical bars in Fig. 2A with vertical bars in Fig. 2, B and C). The increase in alveolar diameter associated with TLC could be approximated by a cubic function (P < 0.001; Fig. 3).

The average transitional bronchiolar caliper for the whole group, across all ages, was 572 ± 171 μm. Unlike alveolar diameter, there was no significant dependence of transitional bronchiolar caliber on age for the younger ages (6–22 yr). There was, however, a relationship between transitional bronchiolar caliber and an individual’s age and height if all subjects through the entire age range of 6–80 yr were included, with transitional bronchiolar caliber increasing with age \( \{EAD_{\text{trans}} (\mu m) = 2.00[\text{age (yr)}] + 510; P = 0.01\} \) (not shown) and height \( \{EAD_{\text{trans}} (\mu m) = 2.15[\text{height (cm)}] + 220; P = 0.03\} \) (Fig. 4). Transitional bronchiolar caliber did not increase with TLC.

For all subjects, the conducting airway gas volume significantly increased for the children, adolescents, and young adults \{6–22 yr; VLD_{\text{trans}} (ml) = 13.9[\text{age (yr)}] + 114; P < 0.001, not shown\}, reaching an average plateau of 420 ± 113 ml for the adults of age >22 yr. The increase in conducting airway gas volume for the children, adolescents, and young adults was exponential with height \( \{VLD_{\text{trans}} (ml) = 0.001[\text{height (cm)}]^{2.49}; P < 0.001\} \) (Fig. 5) and linear with TLC \{VLD_{\text{trans}} (ml) = 0.065[TLC (ml)] + 21.3; P < 0.001; not shown\}, yet conducting airway gas volume relative to TLC \( \{rVLD_{\text{trans}}\} \) remained a nearly constant proportion over the age range studied \( \{rVLD_{\text{trans}} = 7.04 \pm 1.55\%\} \) TLC. However, there is a hint that it may slightly decrease with increasing age: the average value for those under 19 yr old was 7.51 ± 1.79%, and for those aged 19–80 yr it was 6.90 ± 0.98%, but was not significantly different. On the other hand, \( rVLD_{\text{trans}} \) decreased with increasing height \( \{rVLD_{\text{trans}} = -0.022[\text{height (cm)}] + 10.631; P = 0.014\} \) (Fig. 6).

DISCUSSION

We used ADAM techniques to measure human lung air spaces in vivo as a function of age from childhood to elder adult. From these measurements, EADmin, VLDtrans, and EADtrans have been derived. The effect of using the same inspiratory and expiratory volume flow rates (1 l/s) for testing all the subjects, with varying lung volumes, is unknown. The analysis of EAD is designed to account for flow-related dif-

Table 2. Correlation of morphometric measurements with combinations of age, TLC, height, and weight

<table>
<thead>
<tr>
<th>Age Range, yr</th>
<th>Relationship</th>
<th>( r^2 )</th>
<th>P Value</th>
</tr>
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<tbody>
<tr>
<td>6–20</td>
<td>EAD_{\text{trans}} (\mu m) = 7.25[\text{age (yr)}] − 1.35[\text{height (cm)}] + 318</td>
<td>0.27</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>6–28</td>
<td>EAD_{\text{trans}} (\mu m) = 1.53[\text{height (cm)}] − 10.3</td>
<td>0.17</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>6–28</td>
<td>EAD_{\text{trans}} (\mu m) = 0.80[\text{weight (kg)}] + 189</td>
<td>0.08</td>
<td>0.003</td>
</tr>
<tr>
<td>6–28</td>
<td>EAD_{\text{trans}} (\mu m) = 0.012[\text{age (yr)} \cdot \text{height (cm)}] + 508</td>
<td>0.26</td>
<td>0.007</td>
</tr>
<tr>
<td>6–22</td>
<td>VLD_{\text{trans}} (ml) = 13.9[\text{age (yr)}] + 114</td>
<td>0.21</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>6–20</td>
<td>VLD_{\text{trans}} (ml) = 0.001[\text{height (cm)}]^{2.49}</td>
<td>0.51</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>6–28</td>
<td>VLD_{\text{trans}} (ml) = 0.065[TLC (ml)] + 21.3</td>
<td>0.65</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>6–28</td>
<td>VLD_{\text{trans}} (ml) = 3.55[\text{weight (kg)}] + 140</td>
<td>0.33</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
ferences of impaction and gravitational deposition during the transport phase of the breathing of the aerosol. What is unknown is the biological dynamic response of an individual lung to this flow, i.e., heterogeneous flows within the lung due to regional changes of tissue compliance, airway obstruction/closure, etc. It is assumed that normal healthy lungs respond similarly for the first 30% of exhaled lung volume from a fully distended lung within the range of air velocity encountered for this study.

It was concluded by the Thurlbeck group (25) that significant differences between the sexes of younger subjects were not found for alveolar dimensions (between intercept distance), and this fact was used to group the subjects by age without regard to gender. Hence, the present study also combines the data from both sexes and discusses results as age-related changes.

Our in vivo measures for alveolar diameter, measured at TLC, from 6 to 80 yr of age (Fig. 2A) agree with those from the limited ex vivo postmortem measurements. The alveolar diameter at age 6 and 14 yr, 183–209 μm, agrees well with derived values of 186 and 217 μm at age 6 and 14 yr, respectively, calculated from our regression data and the regression equation for both males and females from Thurlbeck (25) (Fig. 2B). His values were derived from the regression of the mean linear intercept of alveolar dimensions with age obtained from microscopy of cadaverous lung sections (distended to 25-cmH2O column transpulmonary pressure with formalin, i.e., TLC) from 36 boys and 20 girls aged 1.5 mo to 14 yr. Our findings are also in close agreement with the mean linear intercept of alveolar dimensions with age obtained from microscopy of cadaverous lung sections (distended to fill the measured volume of the thoracic cavity) of a child at age 8 (8). The relatively constant alveolar diameter from age 22 through age 80, 252–292 μm (Fig. 2C), agrees well with the values of 245 and 283 μm at ages 25 and 79 yr, respectively, from a regression equation of size vs. age derived from the microscopic examination of 25 cadaverous lungs (26). Similar values of 251 μm (11) from two cadaverous lung casts, 250 μm from the stereoscopic examination of four acini specimens of the cast from a 50-yr-old male at end inspiration (24) and 280 μm from a single formalin-fixed cadaverous lung (distended to fill the measured volume of the thoracic cavity) of a child at age 8 (8), were also corroborated. Furthermore, our data confirm our hypothesis that alveolar diameter increases with age from 6 to near 22 yr, after which there is a limited change in this alveolar dimension for the rest of life. This is also in agreement with pulmonary function studies that show that the average lung volume increases postnatally until pulmonary maturation at age near 20–25 yr (21).

It was found that TLC correlated with nearly the third power of the alveolar diameter, EADmin, increase with age from 6 to 22 yr and thereafter remain nearly constant through age 80. Solid lines are regression of EADmin on age (regression a: EADmin (μm) = 2.97[age (yr)] + 166 for ages 6–22 yr; b: EADmin (μm) = 0.54[age (yr)] + 245 for ages 22–80 yr). Length of the lines in the horizontal direction extend over the range of ages included in analysis. Vertical bar is the standard error of estimate for the regression.

Fig. 2. A: alveolar dimensions, as measured by EADmin, increase with age from 6 to 22 yr and thereafter remain nearly constant through age 80. Solid lines are regression of EADmin on age (regression a: EADmin (μm) = 2.97[age (yr)] + 166 for ages 6–22 yr; b: EADmin (μm) = 0.54[age (yr)] + 245 for ages 22–80 yr). Length of the lines in the horizontal direction extend over the range of ages included in analysis. Vertical bar is the standard error of estimate for the regression. B: alveolar dimensions, as measured by EADmin, are compared with other ex vivo methods for the ages 6–22 yr. a, Regression line was analyzed from values given in Thurlbeck (25). Length of the line in the horizontal direction extends over the range of ages studied, and the vertical line is the standard error of estimate. b, Individual value (b) is from Dilly (7). C: alveolar dimensions, as measured by EADmin, for adults are compared with values obtained by Thurlbeck (Ref. 26; a), Haefeli-Bleuel and Weibel (Ref. 24; b), and Schreider and Raabe (Ref. 24; c). Length of the line in the horizontal direction extends over the range of ages studied, and the vertical bars are standard error of estimate (a), standard deviation (b), and range of values (c).
essentially complete by 1.5 yr of age, as indicated by cessation of alveolar septal maturation (29), and by 2 yr of age using counting techniques (25). Further lung growth, after age 2–3 yr, was observed to proceed by a lengthening of the interalveolar septa and the concomitant enlargement of the existing alveoli (28).

We have reported the relationships of alveolar dimensions, anatomical dead space volume, and transitional bronchiole caliber as dependent on height, using height as an indicator of body size rather than weight. We have found height to be a better indicator of the growth in body size when associated with growth in our lung parameters. A similar distinction had been observed by Thurlbeck (25). For example, from the fitted power function of $V_{\text{LD trans}}$ vs. height, we found $r = 0.72$ compared with the linear relationship of $V_{\text{LD trans}}$ vs. weight of $r = 0.57$. Comparing the expected cubic power relationship of our TLC vs. height, we find $r = 0.91$, with height having an exponent of 3.1. In contrast, the linear relationship of TLC vs. weight is still significant but less well correlated ($r = 0.77$).

We also inspected the $V_{\text{LD trans}}$-to-weight ratio (i.e., ml/kg) as a function of age and did not find a good relationship ($r = -0.13$). These data did, however, suggest a trend toward the youngest subjects having a higher ratio than the older subjects. Our study may be detecting the end of the growth of these airways since the study of anatomical dead space in infants and children by Numa and Newth (20) reported that the dead space relative to body mass decreased for the ages from birth to 14 yr, with very little of that change occurring after age 6.

The variability we found in alveolar dimension is generally larger than that found by stereoscopic and lung-cast analysis. The larger value probably represents the additional variability over stereological measurements due to the sum of the effects of in vivo subject performance of breathing maneuvers and the higher variability in flow and concentration measurements of ADAM. However, the range of alveolar dimension values from a single adult of the Schreider and Raabe study (24) is nearly the same as for our measurement of alveolar dimension for many adults (Fig. 2C). The Schreider and Raabe study mea-

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**Fig. 3.** Alveolar dimensions ($EAD_{\text{min}}$) scale with the cubed root of lung volume (TLC). Solid line is best exponential fit through the data of $EAD_{\text{min}}$ vs. TLC: $EAD_{\text{min}}$ ($\mu m$) = 10.0 [TLC (ml)]$^{-0.37}$; $r = 0.54$; $P < 0.001$.

**Fig. 4.** Size of the transitional bronchioles, as measured by $EAD_{\text{trans}}$, increases with body size, as defined by height. Solid line is best linear fit of $EAD_{\text{trans}}$ vs. height: $EAD_{\text{trans}}$ ($\mu m$) = 2.15[height (cm)] + 220; $r = 0.21$; $P = 0.03$.

**Fig. 5.** Volume of the conducting airways, as measured by $V_{\text{LD trans}}$, increases with body size, as defined by height. Solid line is best exponential fit of $V_{\text{LD trans}}$ vs. height: $V_{\text{LD trans}}$ (ml) = 0.001[height (cm)]$^{2.49}$; $r = 0.72$.

**Fig. 6.** Volume of the conducting airways relative to TLC ($r_{V_{\text{LD trans}}}$) decreases with increasing height. Solid line is best linear fit: $r_{V_{\text{LD trans}}}$ (%TLC) = $-0.022$[height (cm)] + 10.631; $P = 0.014$. 
sured the alveolar dimensions of four acini of a single adult at near normal end inspiration. Therefore, the intersubject variability of alveolar dimensions is nearly the same as our inter-

subject variation. Some of the variation is undoubtedly actual biological variability due to genetic and environmental influences on normal development (9, 13, 16).

Because we did not see a significant difference in alveolar dimensions between male and female subjects, the larger TLC of male compared with female subjects of the same age is likely due to the increased number of alveoli in males rather than alveolar size (25). Add to this the fact that the number of alveolar units is developmentally determined by age of 2 or 3 yr, then gender differences in lung volume must be largely determined by that age, with a small component possibly due to differences in rates of alveolar enlargement to around age 22. Additional longitudinal studies, using the advantage of ADAM in vivo, would help determine the growth of the air spaces within individuals.

Unlike the alveolar dimensions, the dimensions of the transi-
tional bronchioles are not age dependent. However, there is a positive regression on body size as estimated by height (Fig. 4). Similar findings were inferred from pulmonary function and chest radiographs in a study of male twin adolescents (17), where it was found that overall lung size correlated with age but not functionally determined airway dimensions. Because height is strongly correlated with age in children and adoles-
cents, this implies that, for a given age, taller individuals possess larger transitional airways but do not change in caliber as they age. We also found that the conducting airway volume increases with age (data not shown), and especially with height (Fig. 5), as was also found by Hart et al. (12), whose relationship of anatomical dead space (V_D), measured at FRC, was found to be V_D (ml) = 0.0008[height (cm)]^{2.36}. This compares well to our relationship, measured at TLC, of VLD_{trans} (ml) = 0.001[height (cm)]^{2.49}. It must be reconciled that both conditions be met, i.e., 1) that the conducting airway volume increases with age in children and adolescents but also 2) that the diameter of the transitional bronchioles at the anatomical site detected by ADAM does not increase with height and age. The simplest interpretation would be that the transitional bronchioles do not grow in dimension after age 6, even though the dimensions of the airways proximal and distal to them grow through age 22. The more likely explanation, however, is that the bronchiolar tree enlarges with age and the bronchioles extend peripherally to accommodate the overall growth of the acinar air spaces. Furthermore, the anatomical site of the transitional bronchioles detected by ADAM is shifted slightly distally toward the alveolar ducts to maintain, on average, an apparent constant cross-sectional dimension.

There is a coefficient of variation of ~30% for alveolar dimensions measured by many techniques (Fig. 2). Some of the intersubject variability in these dimensions might be traced to deviations from normal lung development and growth, both fetal and postnatal. The fetal development of the lungs can deviate from normal due to many environmental and genetic factors. The branching process is under the control of a complex balance of chemoattractants, directing the outgrowth and elongation of the nascent pulmonary tree (see Ref. 1 for recent review) and transcription factors and other gene products (see Ref. 16 for recent review). Many environmental associations, such as low birth weight effects on the small to medium airways (2), hypoxia pre- or postnatal (13), nutrition (9), or combinations (15) have also been noted. However, the study of human branching abnormalities and air space development is hindered by the relative inaccessibility of the air spaces in individuals.

The use of ADAM allows convenient and rapid in vivo measurement of lung dimensions along with the ability to follow intraindividual alveolar changes for both normal and pathophysiological development. We have used this technol-

gy to corroborate ex vivo measurements of alveolar and respiratory bronchiole dimensions for a large age range from 6 to 80 yr. The alveolar dimensions increase with age postnatally until an age of ~22 yr, after which they remain nearly constant with age. They scale very closely to the cubed root of lung volume, thereby accounting for most of the differences in gas volume between individuals. The conducting airway volume also increases with both age and body size. The transitional bronchiole dimensions, however, do not increase with height and age.

DISCLOSURES

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