Anatomical variability in the upper tracheobronchial tree: sex-based differences and implications for personalized inhalation therapies

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Abstract

The morphometry of the large conducting airways is presumed to have a strong effect on the regional deposition of inhaled aerosol particles. Nevertheless, sex-based differences have not been fully quantified and are still largely ignored in designing inhalation therapies. To this end, we retrospectively analyzed high-resolution computed tomography scans for 185 individuals (90 women, 95 men) in the age range of 12–89 yr to determine airway luminal areas, airway lengths, and bifurcation angles. Only subjects free of chronic airway disease were considered. In men, luminal areas of the upper conducting airways were, on average, ~30–50% larger when compared with those in women, with the largest differences found in the trachea (289.72 ± 54.25 vs. 193.50 ± 42.37 mm² for men and women, respectively). The ratio of the largest luminal area in men to the smallest luminal area in women (in any given segment) ranged between 4.5 and 8.6, the largest differences being found in the lobar bronchi. Sex-based differences were minor in the case of bifurcation angles (e.g., average main bifurcation angle: 93.04 ± 9.58° vs. 91.03 ± 9.81° for men and women, respectively), but large intersubject variability was found irrespective of sex (e.g., range of main bifurcation angle: 65.04°–122.01° vs. 69.46°–113.94° for men and women, respectively). Bronchial segments were shorter by ~5%–20% in women relative to men, the largest differences being located in the upper lobes. False discovery rate analysis revealed statistically significant associations among morphometric measures of the right lung in women (but not in men), suggesting two phenotypes among women that we attribute to the smaller female thoracic volume.

NEW & NOTEWORTHY We found significant sex-based morphometric differences in the central airways of healthy men and women that were only mildly attenuated in subsets matched for lung volume. Lumen areas were significantly larger in men (~30–50%). Large variability (~75–87%) in airway bifurcation angles (60°–122°) was found irrespective of sex. The branching pattern of the right main and right upper bronchi in women (but not in men) follows two phenotypes modulated by lung volume.

anatomy; morphometry; population study; sex-based differences; upper airways

INTRODUCTION

The human respiratory system exhibits an incredible variability in airway morphology, both in terms of size and shape (1–5). Large variability can be found even among healthy individuals (6, 7). Figure 1 portrays the variability in the general population by showcasing the upper tracheobronchial airways of 10 adults that have been three-dimensional (3-D)-reconstructed from computed tomography (CT) scans. As one can imagine, intersubject variability becomes more pronounced when individuals are compared across specific population segments representing differences based on age, sex, and disease type and stage. Although recognized, this intersubject variability is rarely taken into account when devising therapeutic approaches and pharmaceutical products for drug delivery to the lungs (8). For example, despite the growing interest in personalized medicine, therapeutic aerosols are currently delivered to the lungs of patients using devices that are, to a large extent, based on “one-size-fits-all” approaches (9). Similarly, it would seem reasonable to assume that anatomical airway variability could translate to significant differences in the effects of exposure to environmental aerosol pollutants (10). A question that needs to be addressed is whether there are patterns (phenotypes) in airway morphology that could be correlated to patterns of regional aerosol deposition. If such patterns could be identified, they could then be further linked to hot spots of airway disease or to drug delivery effectiveness. The answer to this question is
not obvious, but if such patterns and correlations could indeed be established, the impact would be significant.

The "Human Respiratory Tract Model for Radiological Protection" or ICRP model (11) and its variants are still widely used as the basis for estimation of deposition and pharmacokinetics in the human lung. The ICRP model, however, assumes a morphometric model for an adult male or "reference man" and uses scale factors based on body height to adjust the dimensions for other subjects, including women and children. Furthermore, this scaling is applied only to cross-sectional areas and lengths. Bifurcation angles are assumed to be insensitive, thus fixed mean values are used based on a symmetric branching assumption. Although the ICRP model has been successful and widely used, it represents a sizable simplification, partly made necessary by the thoracic imaging limitations in the early 1990s. As we will show in this study, the range of anatomical variability that we have documented among healthy subjects cannot be reproduced from an ideal "reference man" simply with the use of scaling factors.

Modern medical imaging affords us a view of the respiratory system with fine anatomical detail, at least for the upper tracheobronchial tree (12, 13). At the same time, high-fidelity computational fluid-particle methods (14, 15) have evolved to the point where they can estimate regional aerosol deposition patterns with incredible detail. These parallel developments offer an opportunity that was till recently not available: to leverage these tools in unison to explore patterns of regional deposition that are expressions of underlying anatomical phenotypes. This can be done for the general population or for specific subpopulations based on determinants such as sex, age, or airway health status. Furthermore, with the advent of artificial intelligence tools, the opportunity to search for underlying patterns is even more compelling. Given a sufficiently large sample of airway geometries, a series of computational fluid-particle dynamics simulations could be performed to explore potential links between airway anatomical phenotypes and regional deposition patterns. At a higher level, one can imagine performing such large-scale in silico population studies for different groups of patients and then comparing, in a statistical sense, deposition patterns across such segments of the population.

In view of these considerations, we have embarked on a long-term effort to establish a sizable database of subject airway geometries in the form of chest CT scans. We believe that we have reached a stage where significant further progress in pulmonary patient care can only be achieved through open collaboration among researchers. Thus, we plan to eventually make the database that we are building freely available to other researchers within the restrictions required for proper anonymization and patient data protection. Here, we present our first analysis of the characteristics of a sample of 185 subjects who have been cleared of chronic airway disease. The choice to first analyze individuals who are free of airway disease is motivated by the need to establish the baseline against which subpopulations of patients with specific disease can then be compared.

MATERIALS AND METHODS

Materials: Population Sample

We have used computed tomography (CT) reconstructions of the tracheobronchial airways of 194 individuals (99 males and 95 females). Subject age ranged from 12 to 89 yr old. Each individual was CT scanned at maximum inspiration.
following the same standardized protocol at a single medical diagnostic center (Prognosis Advanced Diagnostic Center). The data were obtained retrospectively from hospital subjects who had previously been scanned as part of receiving medical care but who the radiologists had classified as being free of chronic respiratory disease or acute disease (e.g., trauma). All samples were reported as being free of airway abnormalities and remodeling. Consent was given to use these CT data for research purposes, and before analysis, all CT data were fully anonymized to comply with the Helsinki Declaration (16). After analyzing the reconstructed airways, nine individuals were excluded due to imaging peculiarities (patient movement) that were expected to cause higher uncertainty in anatomical size measurements. The final sample consisted of 185 healthy individuals (95 males and 90 females) spanning the same age range as the original sample. For the purpose of the analysis that follows, we find it useful to define three nominal age-groups, namely, adolescents (10–25 yr), adults (25–65 yr), and elderly (above 65 yr), with corresponding sample sizes of seven (2 female), 130 (64 female), and 48 (24 female) subjects, respectively. Subject characteristics are summarized in Table 1. Unfortunately, we have no information on the height and body mass index (BMI) of the subjects, since the CT data were obtained retrospectively from the library of the Diagnostic Center. For the analysis that follows, a subset of subjects (24 males, 25 females) was identified with CT-based lung volume in the range of 4,140–5,140 mL (i.e., subset matched for lung volume, hereafter volume-matched subset). As a result of the retrospective character of this study, lobar volumes were not available from pulmonary function tests. For this reason, we have obtained lung volume estimates from the CT scans as described in the following section. For comparison purposes, Table 1 includes subject characteristics from the recent work of Dominelli et al. (17) who have addressed healthy subjects and provided clear evidence of sex-based differences in the size of the larger airways.

Methods: Segmentation and Feature Extraction

The airways of each subject were segmented via a protocol for semi-automatic segmentation of DICOM images using the Simpleware ScanIP software package (Version N-2018.03-SP1; Synopsys, Inc., Mountain View). Statistical analysis was performed with the aid of JMP Pro 14.3.0 (SAS Institute Inc., Cary, NC, 1989–2019). A repeated-measures mixed model with a Toeplitz unequal variances structure was used to compare mean values of measured anatomical features between men and women. When significant $F$ ratios were detected, subsequent pairwise Tukey–Kramer Honest Significant Difference (HSD) post hoc tests were adopted to identify the significant difference between the mean values of women to men ($P < 0.05$).

The 3-D airway reconstruction was completed by two trained software operators (S.C. and T.C.), each with prior experience of at least 1 year. The segmented airways were further analyzed within ScanIP to obtain anatomic measures for the trachea and upper bronchial tree, as described next. The 3-D reconstruction of the airways was done in three stages. In stage 1, a series of painting iterations using three different views was carried out, as shown in Fig. 2A. The airways are shown in blue color, whereas the lobar volumes are shown in light red. For the extraction of the lobar volumes, a flood fill approach was used with a fixed grayscale threshold value, followed by a Boolean operation to subtract the volume of segmented airways. In this study, we consider the sum of the derived lobar volumes as the CT-based lung volume. In stage 2, the results of the painting operations were used to construct three airway masks, as shown in Fig. 2B. Mask 1 on the left corresponds to the raw 3-D-reconstructed tracheobronchial tract and involves the intrathoracic part of the human airways. Mask 2 in the middle is a smoothed version of mask 1. Finally, mask 3 on the far right was enhanced further by correcting outlet imperfections as needed for subsequent use in computational fluid-particle dynamics (CFPD) mesh construction. Mask 2 was used in stage 3, where the centerline tree was created (Fig. 2C), which is the last step needed for the extraction of anatomical measures. Three types of anatomical measures were extracted, namely, lumen cross-sectional areas (abbreviated as cross-sectional areas, CSAs), segmental lengths, and bifurcation angles.

The airway nomenclature adopted and the anatomical features considered are summarized in Table 2. Furthermore, the diagram of Fig. 3 can be used for the identification of the measured features. Although extracted, the length of the trachea is not being reported because of the uncertainty associated with the location of the upper edge of the scan in the glottis area.

These anatomical measures were chosen because they are expected to have a direct effect on the airflow and regional aerosol deposition characteristics of the upper tracheobronchial airways. Furthermore, because they fall well within the CT resolution, they are simple to obtain and involve as little ambiguity as possible, a feature that is essential in minimizing uncertainty.

### Table 1. Demographics for subjects involved in the present study and the one of Dominelli et al. (17)

| Study | Subjects | Sex | Sample, n | Age, yr | Lung Volume, mL |
|-------|----------|-----|-----------|---------|----------------|
| Present | All | Men | 95 | 54 ± 17 | 5,276 ± 1,140 |
| | | Women | 90 | 55 ± 15 | 3,734 ± 1,039 |
| Dominelli et al. | Volume-matched | Men | 24 | 57 ± 13 | 4,690 ± 338 |
| | | Women | 25 | 52 ± 13 | 4,489 ± 228 |
| | All | Men | 51 | 52 ± 18 | 4,117 ± 1,582 |
| | | Women | 73 | 49 ± 18 | 2,927 ± 775 |
| | Height-matched | Men | 20 | 56 ± 20 | 3,956 ± 1,310 |
| | | Women | 20 | 47 ± 19 | 3,228 ± 882 |

Values are means ± SD. The present study includes analysis on all subjects and on a volume-matched subset. The work of Dominelli et al. involves analysis on all subjects and on a height-matched subset.
The mean values of the lumen cross-sectional areas (CSAs) were obtained through a semi-automated approach. The CSA tool in Simpleware ScanIP creates a predetermined number of CSAs onto the chosen line branch. The number of CSAs is controlled by the user by setting the distance from measurement point to measurement point on the chosen line. An example of the CSA measurement process is shown in Fig. 4A.

Airway lengths are provided by the software automatically, and they represent the length of each segment following its curvature (not its node-to-node vector). In Fig. 4B, the segments used for length measurements are identified in red, orange, and green color.

The angles are obtained through a dot-product algebraic operation. The user chooses a line (segment centerline) and for each of the bifurcation angles, P and D denote the parent and two daughter branches forming the angle, respectively. CSA, cross-sectional area.

### Table 2. Airway nomenclature and corresponding anatomic features

| Airway                      | Lumen Area | Length | Angle Main Bifurcation (AMB) | Angle First Right Bifurcation (AFR) | Angle First Left Bifurcation (AFL) |
|-----------------------------|------------|--------|-----------------------------|-------------------------------------|-----------------------------------|
| Trachea (TRA)               | CSA<sub>TRA</sub> | —      | P                           | —                                   | —                                 |
| Right main bronchus (RMB)   | CSA<sub>RMB</sub> | L<sub>RMB</sub> | D                           | P                                   | P                                 |
| Left main bronchus (LMB)    | CSA<sub>LMB</sub> | L<sub>LMB</sub> | D                           | —                                   | P                                 |
| Right intermediate bronchus (RIB) | CSA<sub>RIB</sub> | L<sub>RIB</sub> | —                           | D                                   | P                                 |
| Left lower lobar bronchus (LLB) | CSA<sub>LLB</sub> | L<sub>LLB</sub> | —                           | —                                   | D                                 |
| Right upper lobar bronchus (RUB) | CSA<sub>RUB</sub> | L<sub>RUB</sub> | —                           | D                                   | —                                 |
| Left upper lobar bronchus (LUB) | CSA<sub>LUB</sub> | L<sub>LUB</sub> | —                           | D                                   | —                                 |

For each of the bifurcation angles, P and D denote the parent and two daughter branches forming the angle, respectively. CSA, cross-sectional area.
a node connected to that line. The angle measured is the angle between the two nonselected lines that reach the selected node (Fig. 4C).

To assess the level of uncertainty introduced by operator bias when measuring the anatomical features, the following procedure was used. The CT scan DICOM datasets of 10 randomly selected subjects were independently processed by both operators. Thus, each data set was subjected to the steps of 3-D reconstruction and anatomical feature extraction twice (Figs. 2 and 4), once by each operator, and then, the results were compared. Because most of the steps involved are automated, differences in the final anatomical measures (mean cross-sectional areas, segmental lengths, and bifurcation angles) were essentially undetectable (within 1.0%).

## RESULTS

For the purpose of this study, we focus on the upper tracheobronchial tree including only the airway segments shown in the diagram of Fig. 3, namely, the trachea (TRA), the left main bronchus (LMB), the right main bronchus (RMB), the left upper lobar bronchus (LUB), the left lower lobar bronchus (LLB), the right upper lobar bronchus (RUB), and the right intermediate bronchus (RIB) (or “bronchus intermedius”). For each of the segments, we report the length and mean cross-sectional area measurements. In the case of the trachea, reliable extraction of the length was impossible since chest CT typically does not extend above the level of the supraclavicular extrathoracic trachea. In addition to segmental lengths and cross-sectional areas, we report three airway bifurcation angles, namely, the angle of the main bifurcation (AMB), the angle of the first right bifurcation (AFR), and the angle of the first left bifurcation (AFL).

### Airway Cross-Sectional Areas

The distributions of the mean cross-sectional areas (CSAs) of the upper tracheobronchial airways, measured in units of $\text{mm}^2$, are shown in Fig. 5. For each airway, the left panel shows the count histogram of cross-sectional areas along with the fitted normal (red line) and log-normal (green line) distributions. The two middle panels show the corresponding quantile plot, where the $0, 2.5, 10, 25, 50, 75, 90, 97.5$, and 100 quantiles are shown, and an outlier box plot, where the 25, 50, and 75 quantiles are shown. The red bracket outside

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Figure 3. Schematic of the upper tracheobronchial tree geometry considered in the present study, including the adopted nomenclature and measured quantities.

Figure 4. Extraction of mean cross-sectional areas (A), segmental lengths (B), and bifurcation angles (C).
of the box identifies the shortest half, which is the most dense 50% of the observations (19). Included in the outlier box plot are the max and min values when outliers are excluded. The rightmost panel shows the normal quantile plot, where the red dashed lines represent the Lilliefors confidence bounds. Red and blue symbols are used to indicate female and male subjects, respectively. The data are strongly stratified by sex, with female subjects in general having smaller cross-sectional areas than males. The sex-based stratification is stronger in the trachea (TRA), the two main bronchi (RMB and LMB), and the right intermediate bronchus (RIB). Some degree of sex-based stratification is still present in the case of the upper left and right (LUB and RUB) bronchi, but it is significantly less pronounced. The RIB is a major conduit feeding both the middle and lower right lung lobes and thus has the largest lumen

Figure 5. Distribution plots for the average cross-sectional areas (CSAs). A: trachea (TRA). B and C: right (RMB) and left (LMB) main bronchi. D and E: right upper (RUB) and left upper (LUB) bronchi. F and G: right intermediate (RIB) and left lower (LLB) bronchi. Red and green lines in histograms show the normal and log-normal fits, respectively. The second panel shows the quantile box plot indicating the 0, 2.5, 10, 25, 50, 75, 90, 97.5, and 100 quantiles and the 95% confidence diamond of the mean. In the third panel, the outlier box plots show the 25, 50, and 75 quantiles and the min and max values when outliers are excluded. Red and blue symbols shown in the normal quantile plot indicate female and male subjects, respectively.
CSA among the four second-generation bronchi. In general, all CSA distributions are close to being normal, having only a few outliers departing from the expected normal distribution. In this regard, the RMB and LLB stand out as the ones with the largest number of departures from a normal distribution. In general, all CSA distributions are close to being normal, having only a few outliers departing from the expected normal distribution.

The trends shown in Fig. 5 are quantified in summary form in Table 3, which provides the key statistics for all cross-sectional area distributions. For each data entry, the columns T, M, and F stand for total, male, and female values. The data in Table 3 allow one to draw some interesting comparisons between men and women. For example, in the case of the four larger airways, namely, TRA, RMB, LMB, and RIB, the ratio of the mean of CSA for men to that for women is close to 1.5 (1.50, 1.46, 1.49, and 1.47, respectively). It is also instructive to look at the ratio of the maximum CSA for males to the minimum CSA among the four CSA values.

Cross-sectional areas are reported in units of mm$^2$. F, female values; LLB, left lower lobar bronchus; LMB, left main bronchus; LUB, left upper lobar bronchus; M, male values; RUB, right upper lobar bronchus; T, total values; TRA, trachea; VM, volume-matched subjects. *Significantly different from men with $P < 0.001$. ‡Significantly different from men with $P < 0.05$.

### Table 3. Statistics for airway cross-sectional areas

| Statistic | RMB (T/M/F) | LMB (T/M/F) | TRA (T/M/F) |
|-----------|-------------|-------------|-------------|
| Mean      | 242.91/289.72/193.50* | 174.36/205.96/141.00* | 118.30/140.71/94.65* |
| SD        | 68.54/54.25/42.37 | 49.71/43.87/29.74 | 35.71/31.18/22.54 |
| SE        | 5.04/5.57/4.47 | 3.65/4.50/3.13 | 2.62/3.20/2.38 |
| Median    | 233.00/282.93/215.50 | 171.00/198.00/143.00 | 115.00/137.00/93.00 |
| 75% quartile | 292.00/330.00/215.00 | 200.00/232.00/160.50 | 141.00/159.60/106.00 |
| 25% quartile | 191/259.00/162.00 | 140.60/181.00/118.00 | 91.80/117.00/78.20 |
| Maximum   | 463.00/463.00/310.00 | 318.00/318.00/220.00 | 232.00/232.00/165.00 |
| Minimum   | 104.00/171.00/104.00 | 74.50/114.00/74.50 | 46.60/81.60/46.60 |
| Mean Men  | 1.50   | 1.46   | 1.49 |
| Mean Women| 239.35/280.13/200.20* | 171.92/197.43/147.44* | 117.23/135.94/99.26* |

Cross-sectional areas are reported in units of mm$^2$. F, female values; LLB, left lower lobar bronchus; LMB, left main bronchus; LUB, left upper lobar bronchus; M, male values; RUB, right upper lobar bronchus; T, total values; TRA, trachea; VM, volume-matched subjects. *Significantly different from men with $P < 0.001$. ‡Significantly different from men with $P < 0.05$.

For the subset of volume-matched subjects, the relationship between airway CSA and age is shown in Appendix, where airway anatomical features are explored in further detail. As shown in Fig. A2, while a clear trend of CSAs with age is

$$\frac{CSA_{\text{max}} - \text{men}}{CSA_{\text{min}} - \text{wom}} = 4.45, \ 4.27, \ 4.98,$$

respectively, for each of the smaller RUB, LUB, and LLB airways, respectively, and

$$\frac{CSA_{\text{max}} - \text{men}}{CSA_{\text{min}} - \text{wom}} = 6.19, \ 8.57, \ 6.51,$$

for the larger TRA, RMB, and LMB airways, respectively.
lacking, sex emerges again as a strong determinant, with men having in general significantly larger cross-sectional areas than women. Stratification of CSA by sex is found to be strongest in the case of the trachea (TRA), the right main (RMB), and right intermediate (RIB) bronchi, while sex stratification is the smallest in the case of the right upper bronchus (RUB).

Cross-Sectional Area Ratios

Further insights into the morphometry of the upper bronchial tree can be obtained by examining ratios of airway cross-sectional area measures. Figure 6 summarizes the distributions of cross-sectional area ratios (hereafter CSA-ratios) for the airway

Figure 6. Distribution plots for cross-sectional area (CSA) ratios of segments branching off each bifurcation. Main bifurcation, $\frac{\text{CSA}_{\text{RMB}}}{\text{CSA}_{\text{TRA}}}$ (A), $\frac{\text{CSA}_{\text{RMB}} + \text{CSA}_{\text{LMB}}}{\text{CSA}_{\text{RMB}}}$ (B), and $\frac{\text{CSA}_{\text{RIB}}}{\text{CSA}_{\text{RMB}}}$ (C). First right bifurcation, $\frac{\text{CSA}_{\text{RIB}}}{\text{CSA}_{\text{RMB}}}$ (D), $\frac{\text{CSA}_{\text{RIB}} + \text{CSA}_{\text{RUB}}}{\text{CSA}_{\text{RIB}}}$ (E), and $\frac{\text{CSA}_{\text{RIB}} + \text{CSA}_{\text{RUB}}}{\text{CSA}_{\text{RMB}}}$ (F). First left bifurcation, $\frac{\text{CSA}_{\text{LUB}}}{\text{CSA}_{\text{LMB}}}$ (G), $\frac{\text{CSA}_{\text{LUB}} + \text{CSA}_{\text{LUB}}}{\text{CSA}_{\text{LMB}}}$ (H), and $\frac{\text{CSA}_{\text{LUB}} + \text{CSA}_{\text{LUB}}}{\text{CSA}_{\text{LMB}}}$ (I). The CSA-ratios reported are of the largest daughter branch to the parent (A, D, G) of the largest daughter branch to the sum of both daughter branches (B, E, H) and of the sum of the daughter branches to the parent (C, F, I). Symbols and lines as in Fig. 5. LLB, left lower lobar bronchus; LMB, left main bronchus; LUB, left upper lobar bronchus; RIB, right immediate bronchus; RMB, right main bronchus; RUB, right upper lobar bronchus.
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segments that branch off from each of the first three bifurcations, namely, the main bifurcation and the first right and first left bifurcations. To avoid presenting superfluous information, at each bifurcation, the CSA-ratios reported are of the larger daughter branch to the parent, of the larger daughter branch to the sum of the CSAs of both daughter branches, and finally of the sum of the CSAs of the two daughter branches to that of the parent. Information is presented in the same format as used in Fig. 5. A quick comparison of Fig. 5 with Fig. 6 shows that CSA-ratios fall more closely to normal distributions than CSAs themselves. Furthermore, the strong sex-based stratification that is evident in the distributions of Fig. 5 is largely absent in Fig. 6.

The main statistical features of the information shown in Fig. 6 are summarized in Table 4. The lack of significant sex-based differences is reflected in the proximity of the mean and median values in the data for the two sexes but also in the similarity of the scatter. For example, in most cases, standard deviation and error of the mean values are equal for men and women or otherwise very close to each other. Statistical analysis reveals fewer significant differences between women and men for the CSA-ratios compared with the absolute CSAs. For the subset of volumematched subjects, the significant differences are even fewer.

One can also compare the means of the CSA-ratios given in Table 4 with the corresponding ratios of mean CSA values given in Table 3. For example, at the main bifurcation (MB), the corresponding values are

\[
\frac{\text{CSARMB}}{\text{CSATRA}} = 0.73, \quad \frac{\text{CSATRA}}{\text{CSARMB}} = 0.72
\]

\[
\frac{\text{CSARMB}}{\text{CSALMB}} = 0.61, \quad \frac{\text{CSALMB}}{\text{CSARMB}} = 0.60
\]

\[
\frac{\text{CSARMB}}{\text{CSATRA} + \text{CSALMB}} = 1.22, \quad \frac{\text{CSATRA} + \text{CSALMB}}{\text{CSARMB}} = 1.20
\]

(1)

Similarly, for the first right (FRB) and first left (FLB) bifurcations, the comparisons yield

\[
\frac{\text{CSARIB}}{\text{CSATRA}} = 0.60, \quad \frac{\text{CSATRA}}{\text{CSARIB}} = 0.60
\]

\[
\frac{\text{CSARIB}}{\text{CSALIB} + \text{CSALUB}} = 0.61, \quad \frac{\text{CSALIB} + \text{CSALUB}}{\text{CSARIB}} = 0.61
\]

\[
\frac{\text{CSARIB}}{\text{CSATRA} + \text{CSALIB} + \text{CSALUB}} = 0.99, \quad \frac{\text{CSATRA} + \text{CSALIB} + \text{CSALUB}}{\text{CSARIB}} = 0.98
\]

(2)

\[
\frac{\text{CSALUB}}{\text{CSATRA}} = 0.63, \quad \frac{\text{CSATRA}}{\text{CSALUB}} = 0.62
\]

\[
\frac{\text{CSALUB}}{\text{CSALLB}} = 0.51, \quad \frac{\text{CSALLB}}{\text{CSALUB}} = 0.51
\]

\[
\frac{\text{CSALUB}}{\text{CSATRA} + \text{CSALLB}} = 1.23, \quad \frac{\text{CSATRA} + \text{CSALLB}}{\text{CSALUB}} = 1.21
\]

(3)

The very good agreement between the means of the ratios and the corresponding ratios of the means provides support for the robustness of the statistical measures presented in Table 3 and Table 4.

The effect of age on the CSA-ratios is shown in Fig. A3. In most cases, age appears to have no appreciable effect on CSA-ratios, the only exception being \(\text{CSALUB} + \text{CSALMB}\), where a moderate decrease with age is noted. Though mild, the trend seems to hold equally for both women and men. The lack of systematic sex-based bias in CSA-ratios comes in sharp contrast to the strong bias present in the case of CSAs that was noted in Fig. A2.

Taken together, the results of this section paint the picture of the upper tracheobronchial tree shown in Fig. 7. At each bifurcation, we note the ratios of the means of the cross-sectional areas of the corresponding branches. The values shown are based on the entire sample size of 185 subjects, but as
discussed earlier, for ratios, as opposed to absolute CSA values, sex-based variability is quite small. Also, next to each bronchial segment we denote the ratio of that segment’s mean CSA to the mean cross-sectional area of the trachea (CSA_{TRA}). For example, note that in a mean sense, three of the four second-generation bronchi have cross-sectional areas that range from 27% to 30% of the tracheal cross-sectional area, whereas the cross-sectional area of the larger RIB bronchi amounts to 43% of the tracheal cross-sectional area.

### Airway Lengths

Figure 8 shows the distributions for the lengths of the six bronchial segments. It is worth noting that airway lengths follow normal distributions much more closely than do the cross-sectional areas shown in Fig. 5. Furthermore, sex-based stratification of the data is much weaker for segmental lengths compared with segmental cross-sectional areas, as evidenced by the intermingling of red and blue symbols.

Table 5 provides the summary statistics of these distributions following the format used previously in Table 3. In general, females appear to have segmental lengths that (based on mean values) are around 5%–20% shorter than those of males. The largest difference is found in the upper lobar airways (RUB and LUB). Also, on average, RMB is almost half as long as the LMB, the ratio of the corresponding means being $\frac{LMB_{men}}{LMB_{wom}} \approx 0.48$ for both sexes. The shortness of the RMB is of course not surprising due to the early branching off of the RUB, while the RIB continues as a conduit into the two lower right lobes. For all lengths except LLB, there is a significant difference between the mean values of women to men ($P < 0.05$). Interestingly, for the subset of volume-matched subjects the branches that supply the lower lobes (i.e., RIB and LUB) exhibit no significant difference between women and men.

The rather weak effect of sex on airway lengths is also evident in Fig. A4, where scatterplots of airway lengths versus age are shown separately for women and men. The same figure establishes that age has no systematic effect on airway lengths.

### Airway Angles

In this section, we consider the first three airway bifurcations, namely, the angle of the main bifurcation (AMB) and the angles of the first right and first left bifurcations, denoted as AFR and AFL, respectively (Fig. 3). The corresponding count histograms and normal quantile plots are given in Fig. 9.

It is evident that bifurcation angles follow very closely a normal distribution and that sex does not appear to have any clear direct effect on bifurcation angles. Thus, moving from airway cross-sectional areas to lengths, we saw the influence of sex to decrease, and now turning our focus to airway angles, the direct effect of sex seems to disappear altogether. These qualitative observations are further quantified in terms of key statistical measures in Table 6. Interestingly, even though the direct effect of sex on bifurcation angles is almost negligible, on average, the main bifurcation angle is marginally larger for men than women, but this trend is reversed in the case of the first right (AFR) and first left (AFL). For all three bifurcation angles, there is no significant difference between the mean values of women and men (i.e., $P = 0.16$, $P = 0.43$, and $P = 0.13$ for AMB, AFR, and AFL respectively). This also holds true for the subset of volume-matched subjects. Figure A5 provides the corresponding scatterplots against age, establishing the absence of a systematic age bias.

It should be noted that the range of bifurcation angles is in fact quite impressive. For example, the ratio of the maximum to the minimum for the main bifurcation is

$$\frac{\text{AMP}_{\text{max}}}{\text{AMP}_{\text{min}}} = \left(0.87, 1.64\right),$$

where the values in the parentheses correspond to the ratios for men and women, respectively. The corresponding values for the other two angles are...
As we have seen earlier, men tend to have wider and longer tracheobronchial airways, but the difference in diameters is in general more pronounced. Thus, on average, one would expect women to have airways that tend to be more slender than those of men. In this section, we quantify this and show that women have airways that are more slender in men than in women, but in this case, the difference is not statistically significant. The trend is reversed in the case of the upper bronchi, RUB and LUB, which, on average, are more slender in men than in women, but in this case, the difference is not statistically significant. Furthermore, as shown in the scatterplots of Fig. A6, there is no systematic variation of segmental aspect ratios with age. The scatter in AR values appears to be comparable in men and women, which is consistent with the error measures indicated in Table 7.

Airway Aspect Ratios

As we have seen earlier, men tend to have wider and longer tracheobronchial airways, but the difference in diameters is in general more pronounced. Thus, on average, one would expect women to have airways that tend to be more slender than those of men. In this section, we quantify this observation by examining in greater detail the distributions of the segmental aspect ratios (ARs), defined by

$$\frac{\text{AR}_{\text{seg}}}{\text{D}_{\text{seg}}} = \frac{\text{L}_{\text{seg}}}{\text{D}_{\text{seg}}}$$

where $\text{L}_{\text{seg}}$ and $\text{D}_{\text{seg}}$ are the length and diameter of any particular airway segment, respectively. As shown on Fig. 10, the AR follows closely normal distributions. It is worth noting the relatively larger number of outliers in the case of AR_{RUB}, which might be related to variability in the location where RUB branches off the RMB.

The key statistics of the distributions are summarized in Table 7 and confirm the expectation that, in general, women tend to have more slender tracheobronchial airways. Thus, the ARs for RMB, LMB, RIB, and LLB are roughly 10% larger in women than in men. Statistical analysis reveals that for these ARs, there is significant difference between the mean values of women to men ($P < 0.05$). The trend is reversed in the case of the upper bronchi, RUB and LUB, which, on average, are more slender in men than in women, but in this case, the difference is not statistically significant ($P < 0.05$). Furthermore, as shown in the scatterplots of Fig. A6, there is no systematic variation of segmental aspect ratios with age. The scatter in AR values appears to be comparable in men and women, which is consistent with the error measures indicated in Table 7.

**DISCUSSION**

Interpretation and Further Insights

As seen in section Airway Cross-Sectional Areas, CSAs vary strongly between the two sexes, with men having significantly wider airways. On the other hand, the results of the last three sections show that sex is not as a strong determinant of bronchial lengths, bifurcation angles and bronchial aspect ratios. Yet, one should not assume a complete lack of sexual dimorphism when it comes to the latter three morphometric characteristics because the possibility remains that associations between these measures could differ between the sexes. To gain further insights, we have used false discovery rate analysis to explore associations among different types of morphometric measures. We carried the analysis separately for women and men and found no associations of statistical significance in men or in the left lung of women. However, in the right lung of women, a strong association was found between the angle of the first right (AFR) bifurcation and the lengths of the right main bronchus ($L_{RMB}$) and the right upper bronchus ($L_{RUB}$) (FDR $P < 0.001$ and FDR $P < 0.01$, respectively). In an effort to gain further insights, we visualize the association in women between AFR and the lengths $L_{RMB}$ and $L_{RUB}$ via the bubble scatter-plots of Fig. 11.

In these plots, the solid vertical and horizontal lines indicate the population means for $L_{RMB}$ and $L_{RUB}$, respectively, while the size of the bubbles indicates the value of AFR. Furthermore, women were assigned to three groups based on AFR values. Women whose AFR falls in the lower 25th percentile are referred to the “lower” group and indicated with green bubbles. Women whose AFR falls between the 25th and 75th percentiles are designated as the “middle” group and shown with orange bubbles, and finally, women whose AFR falls above the 75th percentile are referred to as the “upper” group and shown with purple bubbles. When the entire population of women is considered (Fig. 11A), there seems to be a weak tendency to have large AFR values preferentially associated with long RMB (large $L_{RMB}$) and short RUB (small $L_{RUB}$), as evidenced by the distribution of bubbles of different colors and sizes. A clearer picture emerges...
when only the “lower” and “upper” groups are considered (Fig. 11B). Women who have large AFR (“upper” group shown with purple bubbles) also tend to have L_RUB values that fall above and below the corresponding population means, respectively. Thus, when RUB branches off late, it tends to be shorter and positioned at a larger angle relative to RMB. On the other hand, in women with longer RUB, the first right bifurcation tends to occur early (short RMB) and at a small branching angle (“lower” group green bubbles).

Figure 11 suggests that the means of L_LRMB and L_LRUB differ significantly between the “lower” and “upper” groups of women. Indeed, when a repeated-measures mixed model with a Toeplitz unequal variances structure was used to compare the means, significant F ratios were detected. A Tukey–Kramer HSD post hoc test showed the difference between (L_LRMB)_lower = 21.95 mm and (L_LRMB)_upper = 27.18 mm, as well as between (L_LRUB)_lower = 16.76 mm and (L_LRUB)_upper = 13.81 mm, to be statistically significant at P < 0.001. These effects are summarized in the schematic of Fig. 12. All morphometric measures shown in the diagram represent the corresponding group means, for example, (AFR)_lower = 75° and (AFR)_upper = 99°.

Interestingly, statistically significant associations have been detected only in the right lung and only for women. No equivalent associations have been found for men either on the right or left lung. The result is rather intriguing and is worth looking for plausible explanations. Here, we propose the following conjecture stemming from our observations and analysis of the data. The significant difference in thorax size between men and women means that bifurcation angles need to adjust differently in the two sexes to accommodate airways in subjects whose lung volume deviates significantly from the mean. Because women have, on average, significantly smaller thoracic cavities, bifurcation angles in women show stronger variation with other anatomical features of the airways than bifurcation angles in men. A larger population sample and further independent analysis would be needed to prove this hypothesis. Nevertheless, similar observations in the literature provide support to this hypothesis. For example, Bastir and co-workers (3, 5, 20) have noted that, on average, women have smaller thoracic volume than men, and furthermore, the barrel shape of the female thorax allows smaller expansion during inspiration than the pyramidal shape of men. They also found that men and women do

Figure 8. Distribution plots for the bronchial lengths. A and B: right (RMB) and left (LMB) main bronchi. C and D: right upper (RUB) and left upper (LUB) bronchi. E and F: right intermediate (RIB) and left lower (LLB) bronchi. Symbols and lines as in Fig. 5.
reflects a morphometric variation in response to the available thoracic volume or whether it points to more complex effects that could involve modified lung volumes, as for example is known to occur in overweight subjects. Unfortunately, the retrospective nature of this study and the unavailability of full medical profiles for the subjects precludes exploring this question further. An interesting strategy for a future study would be to look for statistical association between AFR with body mass index (BMI) or even better with upper body fat as quantified by dual-energy X-ray absorptiometry (21).

Comparison with Recent Studies

A number of previous studies provide some evidence of morphological variability in the tracheobronchial airways, but most of them are confined by a number of limitations. For example, some studies provided only indirect evidence in the form of dysanapsis ratios (22, 23), whereas others reported only the cross-sectional area of the trachea (24–26) or were addressing older subjects who had a smoking history (27). The recent study of Dominelli et al. (17) is, to the best of our knowledge, the only study that has addressed healthy adult subjects in the general population and provided clear evidence of large sex-based differences in the size (cross-sectional areas and lengths) of the larger airways. Since their work was driven primarily by an interest in airway resistance, they did not report bifurcation angles, which nevertheless can be significant determinants of regional deposition during drug delivery. For these reasons, in this section, we compare our main results for airways cross-sectional areas and lengths with their results.

In the bar chart of Fig. 13, the means of the airway cross-sectional areas are compared. The error bars denote the reported standard deviations (SDs). Lighter shades correspond to the results of Dominelli et al. (17) and darker shades to the present results. For most of the segments, the agreement is impressive, especially taking into account that the two studies addressed two different population pools (United States and Cyprus) and they have used different software to segment the airways and extract the morphometric data. The largest difference is found in the case of LBL, but even in this case, the discrepancy falls within the SD. We also note the good agreement between the results for the height-matched subset of Dominelli et al. with the results for the volume-matched subset in the present study.

Both studies document strong sex-based differences. For example, Table 8 shows the ratio \( \frac{CSA_{\text{min}}}{CSA_{\text{max}} - CSA_{\text{min}}} \) which provides a measure of the maximum sex-based difference in the size of each airway. Results are reported only for TRA, LMB, and RUB because these are the only airways for which the information was available in the study by Dominelli et al. (17). The results from the two studies are in good agreement and they follow the same trend, with the ratio increasing as one moves from TRA to LMB and then to RUB.

Dominelli et al. (17) reported that they had measured segment lengths for TRA, LMB, RMB, and RIB and that they have found women to have shorter airways by approximately 10%–14%. This result also agrees well with our own conclusion that the segment lengths of RMB, LMB, and RIB are approximately 9%–13% shorter in women than in men (Table 5). It should be

| Table 5. Statistics for the airway lengths |
|-----------------------------------------|
| **Statistics for the segment lengths of bronchi RMB and LMB** |
| Statistic | RMB (T/M/F) | LMB (T/M/F) |
| Mean | 26.08/27.28/24.80* | 53.95/56.36/51.40* |
| SD | 4.86/3.90/5.44 | 5.44/5.05/4.63 |
| SE | 0.36/0.40/0.57 | 0.40/0.52/0.49 |
| Median | 25.80/27.10/24.15 | 54.30/56.70/51.55 |
| 75% quartile | 29.30/30.00/26.82 | 58.00/59.40/54.22 |
| 25% quartile | 23.15/24.50/21.75 | 50.25/54.40/48.12 |
| Maximum | 49.40/37.80/49.40 | 71.20/71.20/63.60 |
| Minimum | 12.00/15.00/12.00 | 38.60/38.60/41.30 |
| Main Men | 110 | 110 |
| Mean Men | 26.77/28.34/25.27* | 54.50/56.98/52.11* |
| **Statistics for the segment lengths of bronchi RUB and LUB** |
| Statistic | RUB (T/M/F) | LUB (T/M/F) |
| Mean | 16.24/17.48/14.93* | 14.35/15.83/12.78* |
| SD | 3.15/2.81/2.97 | 3.20/2.84/2.79 |
| SE | 0.23/0.29/0.31 | 0.23/0.29/0.29 |
| Median | 16.28/17.44/14.99 | 14.65/15.12/12.86 |
| 75% quartile | 18.27/19.23/16.77 | 16.44/17.64/14.72 |
| 25% quartile | 14.26/15.73/14.31 | 12.24/14.31/11.32 |
| Maximum | 23.79/23.79/21.26 | 21.59/21.59/18.95 |
| Minimum | 5.09/10.68/5.09 | 5.14/8.34/5.14 |
| Main Men | 1.17 | 1.24 |
| Mean Men | 15.88/17.21/14.61† | 14.03/15.28/12.82† |
| **Statistics for the segment lengths of bronchi RIB and LIB** |
| Statistic | RIB (T/M/F) | LIB (T/M/F) |
| Mean | 26.58/28.16/24.93* | 12.73/13.05/12.39 |
| SD | 4.12/3.68/3.94 | 2.38/2.44/2.28 |
| SE | 0.30/0.38/0.41 | 0.17/0.25/0.24 |
| Median | 26.63/28.21/25.22 | 12.78/13.02/12.64 |
| 75% quartile | 29.28/30.51/27.78 | 14.41/14.50/13.91 |
| 25% quartile | 24.06/23.41/22.16 | 11.91/11.22/10.51 |
| Maximum | 40.30/40.30/33.64 | 20.71/20.71/18.29 |
| Minimum | 11.64/19.81/11.64 | 6.29/8.21/6.29 |
| Main Men | 1.13 | 1.05 |
| Mean Men | 26.96/27.73/26.21 | 12.89/12.54/12.31 |

Airway lengths are reported in units of mm. F, female values; LUB, left lower lobar bronchus; LMB, left main bronchus; LUB, left upper lobar bronchus; M, male values; RIB, right immediate bronchus; RMB, right main bronchus; T, total values; VM, volume-matched subjects. *Significantly different from men with \( P < 0.001 \). †Significantly different from men with \( P < 0.01 \).
noted that we have not measured the length of the trachea \( L_{\text{TRA}} \) and that we have also measured the segment lengths for RUB and LUB, which we have found to be, on average, 15% and 19% shorter in women than in men.

**Ramifications for Personalized Inhalation Therapies**

In the preceding sections, we have seen the impressive intersubject variability that characterizes the morphometric data of the upper tracheobronchial tree, especially in terms of cross-sectional areas and bifurcation angles. The data also established significant differences between men and women, both in terms of the range of the various morphometric values but also in terms of the trends by which pairs of morphometric parameters relate to each other. In women but not in men, we have found that different morphometric features (e.g., lengths and angles) are related to each other by statistically significant associations.

Here, it is worth taking a moment to appreciate what these differences mean in terms of the aerodynamics of inspiration in men and women. One can estimate a Reynolds number in each airway segment as,

\[
\text{Re}_{\text{seg}} = \frac{U_{\text{seg}} D_{\text{seg}}}{\nu_{\text{air}}} = \frac{2 Q_{\text{bulk}}}{\pi A_{\text{seg}} \nu_{\text{air}}},
\]

where the mean segment diameter is

\[
D_{\text{seg}} = \sqrt{\frac{4 A_{\text{seg}}}{\pi}}
\]

and the bulk velocity in the segment is simply

\[
U_{\text{seg}} = \frac{Q_{\text{bulk}}}{A_{\text{seg}}}
\]

**Figure 9.** Distribution plots for the bifurcation angles. A: angle of the main bifurcation (AMB). B: angle of the first right bifurcation (AFR). C: angle of the first left bifurcation (AFL). Symbols and lines as in Fig. 5.

**Table 6.** Statistics for the first three bifurcation angles, angle of main bifurcation (AMB), angle of first right (AFR), and angle of first left (AFL) bifurcations

| Statistic        | AMB (T/M/F)       | AFR (T/M/F)     | AFL (T/M/F)     |
|------------------|-------------------|-----------------|-----------------|
| Mean             | 92.06/93.04/91.03 | 86.41/85.94/86.91 | 83.67/82.65/84.74 |
| SD               | 9.72/9.58/9.81    | 8.43/7.47/9.36  | 9.38/8.31/10.33  |
| SE               | 0.71/0.98/1.03    | 0.62/0.77/0.99  | 0.70/0.85/1.035  |
| Median           | 92.58/92.92/92.18| 86.69/86.56/88.87 | 84.18/84.18/84.15 |
| 75% quartile     | 99.12/99.38/98.82 | 92.24/92.12/93.04 | 89.26/88.91/91.74 |
| 25% quartile     | 86.20/87.02/83.89 | 81.00/80.51/82.56 | 76.97/76.99/76.53 |
| Maximum          | 122.01/122.01/113.94 | 106.25/105.43/106.25 | 117.10/110.94/111.70 |
| Minimum          | 65.04/65.04/69.46 | 60.89/72.23/60.89 | 60.17/60.17/62.87 |
| Mean Mat.        | 1.02              | 0.99            | 0.98            |
| MeanVM           | 91.32/93.44/89.27 | 86.17/83.90/88.34 | 83.30/80.99/85.52 |

Bifurcation angles are reported in degrees. F, female values; M, male values; T, total values; VM, volume-matched subjects.
Thus, the ratio of Reynolds numbers for two subjects with cross-sectional areas $A_{seg}^{1}$ and $A_{seg}^{2}$ scales like
\[
\frac{Re_{seg}^{2}}{Re_{seg}^{1}} \sim \sqrt{\frac{A_{seg}^{1}}{A_{seg}^{2}}}.
\]

Finally, from the point of view of aerosol deposition, one needs to consider the local particle Stokes number
\[
St_{seg} = \frac{\tau_p}{D_{seg}} \frac{U_{seg}}{D_{seg}}
\]
where
\[
\tau_p = \frac{\rho_p \cdot D_p^2}{18 \cdot \nu \cdot \rho_{air}}
\]
is the particle relaxation time. Hence, the corresponding ratio of local Stokes numbers is given by
\[
\frac{St_{seg}^{2}}{St_{seg}^{1}} \sim \frac{A_{seg}^{1}}{A_{seg}^{2}} \frac{Re_{seg}^{1}}{Re_{seg}^{2}} \left(\frac{A_{seg}^{1}}{A_{seg}^{2}}\right)^{\frac{1}{2}}.
\]

Thus, for a given nominal inhalation rate, one can expect bulk velocities in the upper tracheobronchial segments of women to reach values that range from 1.5 to 5.5 times higher than the velocities of men in the same segments. Clearly, deposition characteristics are likely to differ appreciably, as the corresponding Stokes numbers will differ by factors ranging from 1.8 to ~13 times. In terms of bulk Reynolds numbers, the values in women are from 1.2 to 2.4 times higher than in men. Depending on the nominal inhalation flow rate, these differences can be sufficient to induce changes in the flow character (laminar or transitional vs. turbulent). Under conditions of relaxed breathing, these differences are partly mediated by the fact that women tend to have lower mean values of minute-ventilation than men by about 10%–20%. However, during the use of medical devices, such as dry-powder inhalers and pressurized metered dose inhalers, the peak inspiratory flow rate values reached by women are, on average, only about 10% lower than those achieved by men. In each case, these inspiratory flow rate differences are too small to compensate for the differences in cross-sectional areas described earlier (18, 28, 29).

The results of the last section indicate that particular attention is warranted in the case of female patients, where

**Figure 10.** Distribution plots for segmental aspect ratios (ARs). A and B: right (RMB) and left (LMB) main bronchi. C and D: right upper (RUB) and left upper (LUB) bronchi. E and F: right intermediate (RIB) and left lower (LLB) bronchi. Symbols and lines as in Fig. 5.
ular phenotypes. The first one corresponds to women with very large angle of the first right bifurcation (AFR) (above the 75th percentile) who also tend to have longer than average right main bronchus (RMB). In these women, the RMB tends to branch off earlier than average and be more slender than average. For women who fall in the second phenotype, one would expect higher than average filtration in the RMB, followed by lower-than-average deposition in lobar RIB and RUB bronchi, owing to their larger-than-average luminal areas (and thus lower-than-average local Reynolds and Stokes numbers). The opposite trend would be expected for women belonging in the second phenotype.

Of course, all these arguments are qualitative in nature and they can only be made precise for specific combinations of inhalation flowrates and particles sizes. Nevertheless, these observations are worth noting since they raise a direction for further investigations aiming at a more systematic understanding of some of the root causes behind the significant intersubject variability in regional deposition patterns that is known to exist among individuals. In silico populations studies can be a valuable tool in helping us quantify the significance of these observations, and this is a direction that we are currently pursuing.

To showcase the value of in silico studies, here we present results from computational fluid-particle dynamics (CFPD) simulations that quantify the regional deposition in two subjects with significant differences in airway cross-sectional areas. The simulated airways are shown in Fig. 14, and the respective airway characteristics are summarized in Table 9. To complete the airway geometries, we have merged the segmented tracheobronchial airways with the extrathoracic mouth-throat model of Stylianou et al. (30).

Table 7. Statistics for airway aspect ratios (ARs)

| Statistic             | RMB (T/M/F)       | LMB (T/M/F)       |
|-----------------------|-------------------|-------------------|
| Mean                  | 1.80/1.72/1.87†   | 4.52/4.28/4.77‡   |
| SD                    | 0.42/0.32/0.50    | 0.64/0.60/0.61‡   |
| SE                    | 0.03/0.03/0.05    | 0.05/0.06/0.06‡   |
| Median                | 1.76/1.70/1.84    | 4.56/4.29/4.73‡   |
| 75% quartile          | 2.02/1.94/2.14    | 4.95/4.71/5.20‡   |
| 25% quartile          | 1.52/1.47/1.59    | 4.07/3.87/4.28‡   |
| Maximum               | 4.53/2.54/4.53    | 6.56/5.47/6.56‡   |
| Minimum               | 0.92/0.92/0.99    | 2.65/2.65/3.40‡   |
| Mean_Wom              | 1.09              | 1.11              |
| Mean_Men             | 1.84/1.81/1.87    | 4.55/4.41/4.68‡   |

F, female values; LLB, left lower lobar bronchus; LMB, left main bronchus; LRMB, length of the right main bronchus; LRUB, length of the right upper bronchus; M, male values; RIB, right immediate bronchus; RMB, right main bronchus; RUB, right upper lobar bronchus; T, total values; VM, volume-matched subjects. *Significantly different from men with \( P < 0.001 \); †significantly different from women with \( P < 0.01 \); ‡significantly different from men with \( P < 0.05 \).

Figure 11. Bubble scatterplots of the length of the right main bronchus (LRMB) versus the length of the right upper bronchus (LRUB). Vertical and horizontal lines indicate the corresponding population means for all women. Bubble size indicates the value of the angle of the first right (AFR) bifurcation. Green, orange, and purple bubbles correspond to women belonging in the “lower” (AFR below 25th percentile), “middle” (AFR between 25th and 75th percentile), and “upper” (AFR above 75th percentile) groups, respectively. A: all women. B: only women in the “lower” and “upper” groups.

F, female values; LLB, left lower lobar bronchus; LMB, left main bronchus; LRMB, length of the right main bronchus; LRUB, length of the right upper bronchus; M, male values; RIB, right immediate bronchus; RMB, right main bronchus; RUB, right upper lobar bronchus; T, total values; VM, volume-matched subjects. *Significantly different from men with \( P < 0.001 \); †significantly different from women with \( P < 0.01 \); ‡significantly different from men with \( P < 0.05 \).
region, where the model is smoothly transformed to merge seamlessly with the tracheas. Furthermore, using the same mouth-throat model allows for a direct comparison between particle deposition in the two different tracheobronchial trees. It should be mentioned that the actual anatomical dimensions of the upper airways (in particular the glottic region) can be a significant contributor to intersubject deposition variability.

Accurate in silico predictions on particle deposition require high-fidelity numerical simulations of turbulent airflow and particle transport in the human airways. For this reason, we have used large eddy simulations using the dynamic Smagorinsky model and in conjunction with high-quality unstructured grids of 10–15 million cells with five prismatic layers in the near wall regions of the airways. Constant inhalation conditions have been considered at 30

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**Figure 12.** Schematic diagram summarizing the key morphometric features of the phenotypes associated with the “lower” (A) and “upper” (B) groups in women. Mean values are based on each group sample.

**Figure 13.** Comparison of the means of the airway cross-sectional areas reported in the present study (Table 3) and in the work of Dominelli et al. (17). Blueish and reddish columns correspond the means for men and women. For each airway branch and sex, first column corresponds to data from Dominelli et al. marked with “D,” second column corresponds to data from present study marked with “P,” third column corresponds to height-matched data from Dominelli et al. marked with “H,” and forth column corresponds to volume matched data from present study marked with “V.” Whiskers denote the SD. For both studies the number of subjects in each group can be found in Table 1.
At the mouth inlet, turbulent inlet conditions have been generated, while at the bronchial outlets, the convective outlet condition is prescribed with the lobar ventilation distributed as: RUL = 15.4%, RML = 7.7%, RLL = 30.77%, LUL = 15.4%, and LLL = 30.77%. For particle transport, the Lagrangian approach has been used accounting for impact, sedimentation, and diffusion mechanisms. Various particle sizes have been simulated with fixed density $\rho_p = 1000 \text{ kg/m}^3$ and particle diameters $d_p$ in the range of 0.25–15 μm.

Qualitative tracheobronchial deposition for particles with size $d_p = 6 \mu m$ is shown in Fig. 15 with black dots marked on the airways. Evidently, deposition sites are notably different, with the small geometry having substantially more deposition in the central and lobar bronchi. For this specific particle size, the deposition fraction in the tracheobronchial tree is ∼9% for the large geometry and ∼18% for the small geometry.

Quantitative particle fractions at three airway locations are provided by Fig. 16, for typical inhaled particle sizes, with aerodynamic diameters in the range of $d_p = 0.25–15 \mu m$. Particle fractions are divided into mouth-throat (MT) deposition, tracheobronchial (TB) deposition, and deep-lung (DL) penetrations. Since both airways share virtually the same mouth-throat model, the deposition in this location is practically the same. For particles larger than the fine particle dose (FPD; $d_p < 5 \mu m$), MT deposition is substantial, as it is well known in the literature. For the tracheobronchial region, it is evident that particles with intermediate sizes ($d_p$ in the range of 4–10 μm) have higher deposition in the case of the small airway geometry. Note that the TB deposition is not corrected for the fact that the large geometry involves more airway branches that reach to deeper airway generations. If we were to account for this fact, the relative difference in TB deposition would have been even higher between the two

**Table 8. Maximum sex-based difference in airway CSA as indicated by the ratio CSA\text{max–men}/CSA\text{min–wom}**

| Study          | TRA | LMB | RUB |
|---------------|-----|-----|-----|
| Dominelli et al. | 3.06 | 4.08 | 5.22 |
| Present       | 4.45 | 4.98 | 6.19 |

CSA, cross-sectional area; LMB, left main bronchus; RUB, right upper lobar bronchus; TRA, trachea.

**Table 9. Airway characteristics of the two subjects simulated**

| Characteristic | Large Airway | Small Airway |
|---------------|--------------|--------------|
| Sex           | Male         | Female       |
| Age, yr       | 45           | 50           |
| CSA\text{TRA}, mm$^2$ | 382          | 167          |
| CSA\text{RMB}, mm$^2$ | 267          | 116          |
| CSA\text{LMB}, mm$^2$ | 185          | 88.6         |
| CSA\text{RUB}, mm$^2$ | 97.8         | 40.9         |
| CSA\text{LUB}, mm$^2$ | 117.2        | 80.6         |
| CSA\text{RIB}, mm$^2$ | 128.9        | 71.0         |
| CSA\text{LLB}, mm$^2$ | 105.7        | 46.7         |
| AMB, °         | 95           | 95           |
| AFR, °         | 77           | 90           |
| AFL, °         | 87           | 102          |
| L\text{RMB}, mm | 30.0         | 28.6         |
| L\text{LMB}, mm | 59.7         | 57.3         |
| L\text{RUB}, mm | 21.1         | 17.2         |
| L\text{LUB}, mm | 13.3         | 7.6          |
| L\text{RIB}, mm | 32.2         | 28.0         |
| L\text{LLB}, mm | 13.9         | 12.0         |
| V\text{RL}, mL  | 4,103        | 2,586        |
| V\text{RL}, mL  | 3,610        | 2,192        |

AMB, angle of main bifurcation; AFR, angle of first right bifurcation; AFL, angle of first left bifurcation; CSA, cross-sectional area; LLB, left lower lobar bronchus; LMB, left main bronchus; LUB, left upper lobar bronchus; RIB, right immediate bronchus; RMB, right main bronchus; RUB, right upper lobar bronchus; TRA, trachea; V\text{RL}, lung volume of right lobe; V\text{LL}, lung volume of left lobe.

**Figure 14.** Airway geometries of two subjects, one with large (A) and the other with small (B) cross-sectional areas. To allow for realistic computational fluid-particle dynamics simulations, the segmented tracheobronchial airways where completed with the extrathoracic mouth-throat model of Stylianou et al. (30).

**Figure 15.** Tracheobronchial deposition sites for inhaled particles with diameter 6 μm. For this specific particle size, the deposition fraction in the tracheobronchial tree is ∼9% for the geometry with large cross-sectional areas (A) and ∼18% for the geometry with small cross-sectional areas (B).
the airway diameter, and where the ICRP model assumes a constant length of the trachea. To answer this question, we need to recall that subject-specific variability in deposition that has been documented in the pre-existing literature.

In this section, we examine the limitations of simple 1-D models by comparing their deposition predictions with the results of 3-D CFD simulations described in the previous section. As stated, the ICRP model applies no subject-specific scaling for the bronchial lengths, whereas simple models utilizing average man type of morphometrics, such as the ICRP, will be challenging to capture the expected deposition variability. To assess the ability of simple 1-D models to deal with this challenge, we compare their deposition predictions with the results of 3-D CFD simulations on the two airways described in the previous section. It is worth noting at this point that 3-D CFD simulations, although much more computationally demanding than 1-D models, can capture 3-D flow effects and, as a result, can account much more precisely for subject-specific heterogeneities of airway anatomy on aerosol filtering. The extent of variability in deposition predictions from different models is shown in Fig. 19, which plots deposition efficiency (DE) in the tracheobronchial (TB) airways as a function of aerodynamic particle size dₚ. For this figure, we have adopted the DE concept, which excludes prior deposition in the mouth-throat region and emphasizes the regional deposition in the TB tree. Deposition is predicted using: 1) the ICRP model with a lung volume of 3 L at functional residual capacity (FRC), 2) the NCRP model with the morphometries of Weibel or Yeh and Schum scaled at FRC volumes corresponding to the small or large geometry of Fig. 14, and 3) the CFD simulations described in the previous section.

Before discussing the deposition curves, a few comments on how we have obtained the 1-D predictions are necessary. The Mimetikos Preludium software (Emmace Consulting...
AB, Lund, Sweden) was used to generate the raw data. As inputs to the software, we have used settings that matched the CFPD simulations, to enable a fair comparison. Since the software takes as input the FRC instead of the TLC, we have translated the lung volumes given in Table 9 for the two simulated geometries. For this translation, we have used the scale factors 0.4728 and 0.5391 for the large and small geometries, respectively, deduced from the ICRP-physiological-parameters document (dividing FRC with TLC for male and female). Finally, the per generation raw deposition data produced by the software were weighted accordingly to account for the incomplete number of branches per generation for the simulated geometries.

It is clear that predictions from 1-D model show large variations, which depend both on the deposition model itself as well as the employed airway morphometry. For example, NCRP predictions with the Yeh and Schum morphometry show a better match with the CFPD results for the smaller particle sizes ($d_p < 4 \mu m$). For the larger particle sizes, NCRP with the Yeh and Schum morphometry fails to predict deposition, whereas NCRP predictions with the Weibel morphometry are better aligned with the CFPD results. ICRP deposition curve using a reference morphometry (3 L) lies in the middle of CFPD results for the larger particle sizes and overestimates deposition compared with CFPD for particles smaller than 5 $\mu m$. Differences in deposition predictions between ICRP and the subject-specific 3-D CFPD computations can be as much as 35% for 8-$\mu m$ particles (absolute difference), indicating the inability of ICRP model to accurately capture deposition for subjects that lie away from the average morphometry. Although deposition predictions from volume-matched 1-D models (NCRP) can capture the trends associated to anatomical characteristics, these are sensitive to the morphometry model chosen and still show large deviations from the more accurate calculations of 3-D models. In conclusion, deposition predictions from simple 1-D models
cannot account for the great anatomical variability found in different groups of patients.

**Limitations**

The sample size of 185 subjects considered is large enough to establish the statistics of most airway morphometric distributions with a satisfactory level of confidence. Yet, the sample size of the special subgroups such as those belonging to the two suggested phenotypes for the right lung in women is ~25 subjects each. A larger sample size would be desirable to be able to verify the observed trends in these subgroups with a higher degree of confidence. Furthermore, subjects were scanned only at maximal inspiration, but it would be preferable if multiple scans at different levels of inspiration were available because that would have allowed us to account for differences in airway response to inspiration across subjects. Another limitation of the present study is the lack of a complete medical history record for each subject. Although all subjects were cleared of chronic airway disease and no obvious airway remodeling could be identified by radiologists, the lack of complete medical history means that we cannot account for concomitant factors such as body mass index (BMI) and other chronic conditions such as cardiovascular disease and metabolic syndromes. Nevertheless, we do not expect that these factors would significantly change the conclusions reached in this study. Furthermore, from a drug delivery perspective, the results obtained herein reflect the general population who is free of chronic airway disease and who might at some point be prescribed short-term use of inhalers, e.g., for transient asthma symptoms.

Another aspect of the present study that deserves discussing is the fact that all subjects considered were Cyprus residents (nearly all with Greek-Cypriot ethnicity). Thus, one has to be careful in generalizing conclusions reached here to other populations due to the potential effect of ethnicity.

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**Figure 18.** Central airways of eight subjects highlighting the variability in the cross-sectional area of trachea (CSA_{TRA}). Four groups (A–D) are depicted in each of which the subjects have the same sex and are closely matched in age and lung volume.
on the results. On the other hand, the excellent agreement with the results of Dominelli et al. (17) and Sheel et al. (27), which were obtained for two entirely different population in the United States and Canada, respectively, provides reason to expect that our conclusions are of more general applicability.

Implications and Future Research Directions

In the present work, we have attempted to quantify the variability of airway anatomical features in the upper tracheobronchial tree for a sample of 185 healthy Cyprus residents. We also focused particularly on sex-based differences because we believe that is an important area that has been largely ignored in pulmonary medicine and drug delivery applications. Our primary motivation for performing the statistical analysis presented herein was to understand the structure of the sample to guide subsequent in silico population studies aiming to quantify variability in regional aerosol deposition in healthy adults. Clearly, of higher interest would be population studies focusing on specific patient groups, such as patients with chronic obstructive pulmonary disease or cystic fibrosis (CF). Nevertheless, we have opted to consider first a group of adults with healthy airways to set the baseline for future comparisons.

Although we expected to find significant variability among subjects and between men and women, we were surprised as to the level that this variability reaches. For example, the main bifurcation angle can vary from 60° to 122° and airway cross-sectional areas can vary between men and women by factors as high as eight times. Similarly, strong sex-based variability was reported recently by Dominelli et al. (17), providing further support to this astonishing conclusion. Such differences extend well beyond what simple morphometric models (such as the ICRP model) can capture and presumably cause significant differences in regional deposition of aerosols in the upper tracheobronchial tree. Armed with this understanding of the sample, we are now planning a series of computational fluid-particle dynamics (CFPD) simulations to quantify the differences in regional deposition. From the drug delivery perspective, these results suggest that one-size-fits-all type of 1-D modeling approaches, which are based on simple-minded average human morphometry, need to be replaced by more sophisticated models that can account for the strong variability in the population.

We also plan to focus on understanding regional deposition differences among women belonging to the two phenotypes of the right female lung. The right upper lobe (RUB) is known to be a hot spot of higher-than-average incidence for an array of airway ailments, ranging from CF to cancer. In this regard, it would be useful to attempt to quantify deposition rates of particulates in that part of the lung and to see if increased deposition for some groups of patients could be one of the factors contributing to the increased disease rates.
APPENDIX: FURTHER ANALYSIS

Population Characteristics

This study involves 185 individuals, 95 males and 90 females. Figure A1 shows the relationship between age and sex in the form of histogram plots. In the quantile plot panels, the horizontal line within the box represents the median sample value (50th quantile), whereas the bottom and top sides of the box correspond to the 25th and 75th quantiles, respectively. Moving away from the box, the horizontal lines indicate the 10th and 90th, followed by the 2.5th and 97.5th, and finally by the 0th and 100th quantiles, respectively. A line drawn through the middle of the 95% confidence diamond would correspond to the mean. The median age of males is 56, which is very close to the median age for females (55.5 yr), and overall, the male and female populations have similar statistics.

Relationship between Airway Anatomical Characteristics and Age

In this section, we provide a collection of figures illustrating the relationship between age and various airway anatomical characteristics (i.e., cross-sectional areas (CSAs), ratios of CSAs, lengths, angles, and AR). In summary, these figures reveal that for healthy adults, the age has no systematic effect on the airway anatomical characteristics. Nevertheless, the tendency of the group of adolescents/elderly to have increasing/decreasing CSAs with age is noted in Fig. A2. Although the increase in CSAs from youth to adult is expected due to normal growth, the decrease near the upper age limit might be associated with the kyphotic posture, which is more prevalent in the elderly. Unfortunately, the sample size at these advanced ages is insufficient to allow establishing the statistical significance of this trend.

Figure A2. Relationship between airway cross-sectional areas and age: trachea (TRA) (A), right (RMB) and left main (LMB) bronchi (B and C), right upper (RUB) and left upper (LUB) bronchi (D and E), and right intermediate (RIB) and left lower (LLB) bronchi (F and G). Female/male subjects are shown in red/blue symbols, whereas the lines show the corresponding loess smooth curves.
A Condensed View of CSAs in Terms of Contour Plots

The information on CSAs can be further understood with the help of contour plots, which enable the simultaneous presentation of many aspects of the data. Figures A7, A8, and A9 present the contour plots corresponding to the main bifurcation (MB), the first right (FRB), and first left (FLB) bifurcations, respectively.

In each figure, there are four rows of plots and three columns. Plots in the first row show data for the entire population sample of 185 individuals, whereas those in the second row include only subjects belonging to the “adolescents” group, i.e., younger than 25 yr old (sample size of 7). Plots in the third row include individuals in both the “adolescents” and “adults” groups, i.e., all subjects younger than 65 yr old (sample size of 137). Finally, the plots in the bottom row show the scatter of the data only for the group of “elderly,” i.e., subjects over the age of 65 (sample size of 48).

In each of the Figs. A7–A9, the leftmost column shows scatterplots of the ratio $\frac{CSALD_i}{\sum_{j=1}^{3} CSA_{D_j}}$ plotted against the ratio $\frac{CSAD_i}{CSAP}$, where subscripts P, D, and LD stand for parent, daughter, and larger daughter, respectively. Superimposed on the scatterplots are contours of the cross-sectional area of the parent branch CSAP, with blue shades indicating smaller CSAs and red shades indicating larger CSAs. Because CSA-ratios are largely free of sex-based bias, data points for both men (blue) and women (red) are shown in red/blue symbols, whereas the lines show the corresponding loess smooth curves.

**Figure A3.** Relationship between CSA-ratios and age. Main bifurcation: $\frac{CSA_{LMB}}{CSA_{TRA}}$ (A), $\frac{CSA_{LMB}}{CSA_{LMB} + CSA_{UBL}}$ (B), and $\frac{CSA_{LMB} + CSA_{UBL}}{CSA_{TRA}}$ (C). First right bifurcation: $\frac{CSA_{LMB}}{CSA_{DIB}}$ (D), $\frac{CSA_{LMB} + CSA_{DIB}}{CSA_{DIB} + CSA_{UBL}}$ (E), and $\frac{CSA_{LMB} + CSA_{DIB} + CSA_{UBL}}{CSA_{DIB}}$ (F). First left bifurcation: $\frac{CSA_{UBL}}{CSA_{LUB}}$ (G), $\frac{CSA_{UBL} + CSA_{LUB}}{CSA_{LUB} + CSA_{LLB}}$ (H), and $\frac{CSA_{UBL} + CSA_{LUB} + CSA_{LLB}}{CSA_{LUB}}$ (I). For each of the first three bifurcations, the CSA-ratios reported are of the largest daughter branch to the parent (A, D, G), of the largest daughter branch to the sum of both daughter branches (B, E, H), and of the sum of the daughter branches to the parent (C, F, I). Female/male subjects are shown in red/blue symbols, whereas the lines show the corresponding loess smooth curves. LLB, left lower lobar bronchus; LMB, left main bronchus; LUB, left upper lobar bronchus; RIB, right immediate bronchus; RMB, right main bronchus; RUB, right upper lobar bronchus; TRA, trachea.
closely packed about the mean values given in Eqs. 1–3 and indicated by green solid lines. Furthermore, as evidenced by the intermingled contour levels, nominal airway size (parent CSA) does not appear to have an effect on the CSA-ratios.

Plots in the middle row show scatterplots of CSA_{LD} plotted against CSA_{SD}, where subscripts LD and SD stand for larger daughter and smaller daughter, respectively. As in the first column, here again the superimposed contours indicate the size of the parent CSA. In each case, the solid green line corresponds to the linear fit suggested by the ratios in Eqs. 1–3, i.e.,

$$\frac{\text{CSA}_{RMB}}{\text{CSA}_{LMB}} = 1.50, \quad \frac{\text{CSA}_{RIB}}{\text{CSA}_{RUB}} = 1.56, \quad \frac{\text{CSA}_{LUB}}{\text{CSA}_{LLB}} = 1.00. \quad (4)$$

Figure A3.---Continued

Figure A4. Relationship between airway lengths and age for right (RMB) and left (LMB) main bronchi (A and B), right upper (RUB) and left upper (LUB) bronchi (C and D), and right intermediate (RIB) and left lower (LLB) bronchi (E and F). Female/male subjects are shown in red/blue symbols, while the lines show the corresponding loess smooth curves.
In contrast to the first column, here a strong sex-based stratification is evident, which is further modulated by the contour colors of the parent CSA. Here, dependence on sex is not surprising since the axes correspond to CSA values and not their ratios. As expected, data points for males are localized in regions of warm contour shares (larger CSAs) and females in cold shades (smaller CSAs). Despite the sex-based bias, the data for both men and women are clustered around the linear fit of Eq. 4, which is expected since, as we have seen, the ratio $(\text{CSA}_{LD}/\text{CSA}_{SD})$ is independent of sex bias.

Figure A5. Scatterplots for the bifurcation angles against age. A: angle of the main bifurcation (AMB). B: angle of the first right bifurcation (AFR). C: angle of the first left bifurcation (AFL). Female/male subjects are shown in red/blue symbols, whereas the lines show the corresponding loess smooth curves.

Figure A6. Scatterplots for the variation of segment aspect ratios (ARs) with age. A: right main bronchus (RMB). B: left main bronchus (LMB). C: right upper lobar bronchus (RUB). D: left upper lobar bronchus (LUB). E: right immediate bronchus (RIB). F: left lower lobar bronchus (LLB). Red/blue lines denote the means for women/men.
The last column shows scatterplots of CSALD plotted against CSAP, but in this case, the superimposed contours show age rather than the CSA size of the parent. Green contour shades indicate younger age. Not surprisingly, and as was the case in the second column, the data points exhibit strong sex-based stratification. As has been shown before, age does not appear to have any systematic effect on the data, and this is reflected in the lack of a clear organization of contour levels. Despite the sex-based stratification, the data points for both men and women cluster closely around the solid green line, which correspond to the CSA-ratios given in Eq. 4.

Finally, it is worth commenting on the effect of nominal age-group by comparing the plots in each of the four rows. While the sample size for adolescents is small, the plots in the second row suggest that adolescent ratios follow the

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**Figure A7.** Scatterplots of CSA-ratios across the main bifurcation with superimposed contour plots. Rows correspond to nominal age-groups: A–C: all subjects; D–F: adolescents; G–I: adolescents and adults together; and J–L: elderly. First and second columns: contours refer to values of CSA_{TRA}, with red/blue shades indicating wider/narrower tracheas. Third column: contours refer to age, with green/red shades indicating younger/older age. Red/blue symbols correspond to female/male subjects. CSA, cross-sectional area; LLB, left lower lobar bronchus; LMB, left main bronchus; LUB, left upper lobar bronchus; RIB, right immediate bronchus; RMB, right main bronchus; RUB, right upper lobar bronchus; TRA, trachea.
general trends of the entire population with no significant departure, as one might have supposed because of the anatomical maturation that takes place during puberty and early adulthood. This suggests the possibility that absolute anatomical measures might be more sensitive to airway maturation during adolescence than ratios. Clearly, a larger sample for this age-group would be valuable to establish this observation on a firm statistical ground, but the observation is intriguing because, if proven correct, it would mean that CSA-ratios are quite robust and free of both sex and age biases, even through the transitional period of adolescence and early adulthood.
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Figure A9. Scatterplots of CSA-ratios across the first left bifurcation with superimposed contour plots. Rows correspond to nominal age-groups: A–C: all subjects; D–F: adolescents; G–I: adolescents and adults together; and J–L: elderly. First and second columns: contours refer to values of CSA_LMB, with red/blue shades indicating wider/narrower tracheas. Third column: contours refer to age, with green/red shades indicating younger/older age. Red/blue symbols correspond to female/male subjects. CSA, cross-sectional area; LLB, left lower lobar bronchus; LMB, left main bronchus; LUB, left upper lobar bronchus; RIB, right immediate bronchus; RMB, right main bronchus; RUB, right upper lobar bronchus; TRA, trachea.
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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

F.S. and S.C.K. conceived and designed research; S.C., T.C., and S.A. performed experiments; S.C., T.C., S.A., P.K., F.S., and S.C.K. analyzed data; F.S., J.S., H.H.G., and S.C.K. interpreted results of experiments; S.C., T.C., F.S., and S.C.K. prepared figures; S.C.K. drafted manuscript; P.K., F.S., J.S., H.H.G., and S.C.K. edited and revised manuscript; S.A., F.S., J.S., H.H.G., and S.C.K. approved final version of manuscript.

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