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Novel patterns for the growing main bronchi in the human fetus: an anatomical, digital and statistical study

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Abstract

Purpose Intensive progress in prenatal medicine results in performing airway management in the fetus affected by life-threatening congenital malformations. This study aimed to examine age-specific reference intervals and growth dynamics for length, proximal and distal external transverse diameters, and projection surface areas of the two main bronchi at varying gestational ages, including their relative growth in length and projection surface area.

Materials and methods Using anatomical dissection, digital image analysis and statistics, length, proximal and distal external transverse diameters, and projection surface areas of the right and left main bronchi were examined in 73 human fetuses (39 males, 34 females) aged 14–25 weeks, derived from spontaneous abortions and stillbirths.

Results Statistical analysis showed no sex differences. Between the 14 and 25th week of gestation, the lengths of the right and left main bronchi increased from 1.43 ± 0.18 to 3.18 ± 0.39 mm, and from 2.97 ± 0.16 to 7.58 ± 1.95 mm, in accordance with the functions: $y = -4.850 + 2.452x \ln(\text{Age}) \pm 0.400$ and $y = -15.005 + 7.093x \ln(\text{Age}) \pm 0.579$, respectively. The proximal external transverse diameters of the right and left main bronchi varied from 2.13 ± 0.41 to 4.24 ± 0.20 mm, and from 1.84 ± 0.06 to 3.67 ± 0.66 mm, following the logarithmic models: $y = -8.666 + 4.018x \ln(\text{Age}) \pm 0.367$ and $y = -6.938 + 3.305x \ln(\text{Age}) \pm 0.323$, respectively. The distal external transverse diameter rose from 2.09 ± 0.47 to 4.24 ± 0.20 mm, as $y = -8.723 + 4.021x \ln(\text{Age}) \pm 0.392$ for the right main bronchus, and from 1.85 ± 0.04 to 3.67 ± 0.66 mm, like $y = -6.924 + 3.280x \ln(\text{Age}) \pm 0.348$ for the left one. On either side, there were no statistically significant differences between values of the proximal and distal transverse diameters of the main bronchus. The projection surface areas of the right and left main bronchi ranged from 2.95 ± 0.19 to 13.34 ± 2.12 mm^2, and from 5.57 ± 0.21 to 28.52 ± 5.24 mm^2, as $y = -10.212 + 0.943x \text{ Age} \pm 1.739$ and $y = -19.119 + 1.875x \text{ Age} \pm 3.054$. The two main bronchi revealed a proportionate increase in both length and projection surface area, since the right-to-left bronchial length ratio and the right-to-left bronchial projection surface area ratio were stable, 0.41 ± 0.07 and 0.47 ± 0.08, respectively, throughout the analyzed period.

Conclusions The main bronchi show no sex differences. The right and left main bronchi grow logarithmically in length and external transverse diameter, and linearly in projection surface area. The right and left main bronchi evolve proportionately, with the right-to-left bronchial ratios of 0.41 ± 0.07 for length, and 0.47 ± 0.08 for projection surface area.

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Introduction

The advancement of perinatal medicine has contributed to the early diagnosis and treatment of respiratory diseases, including in utero fetal tracheobronchial surgery [1, 3, 5, 14, 17, 21–24, 26]. Some of the life-threatening congenital tracheobronchial malformations are correctable if promptly recognized and corrective procedures implemented [26]. This necessitates an extensive knowledge of fetal airway biometric parameters for particular gestational weeks to further determine pathological criteria adapted to fetal and neonatal tracheobronchial anatomy [19, 24]. Furthermore, the appropriate size of a double-lumen tube for one-lung anesthesia depends on the internal diameter of the main-stem bronchus, in which the bronchial segment of the tube is to be inserted [2, 4, 7, 8, 10, 11].

To date, however, few studies have been published on bronchial measurements in fetal [16, 19] and neonatal [15] populations. According to Porwolik [19], the relationship between bronchial variables (length, external diameter) and gestational age were expressed only by linear functions. In the material of 27 newborns presented by Jit and Jit [15], the lengths of the right and left main bronchi averaged 9.92 ± 1.67 mm and 20.06 ± 1.64 mm, respectively, with a general tendency to increase up to 31–35 years in males and 26–30 years in females, but without any growth curves.

In order to considerably supplement fragmentary information on external dimensions of the two main bronchi in the human fetus, our objectives were set to examine:

– age-specific reference intervals for length, proximal and distal external transverse diameters, and projection surface areas of the right and left main bronchi at varying gestational ages,

– the best-fit growth curves for the parameters studied, and
– the relative growth in length and projection surface area of the two main bronchi.

Materials and methods

The present study included 73 human fetuses of both sexes (39 males and 34 females) aged 14–25 weeks (Table 1), which derived from spontaneous abortions or stillbirths, and had never been intubated. The fetal ages were precisely estimated, taking into account the following three criteria: (1) gestational age based on measurements of the crown-rump length [13], (2) known date of the beginning of the last maternal menstrual period, and (3) a combination of abdominal circumference, femur length and biparietal diameter obtained by early second-trimester ultrasound scan. The correlation between the gestational age based on the crown-rump length and those calculated by the two remaining criteria attained the value $r = 0.97$ ($P < 0.001$) for the whole sample. For statistical analysis, the fetuses were separated into six monthly groups, related to the 4–9th month of gestation. To the best of our knowledge, in no case the cause of fetal death resulted from congenital laryngo-tracheal or cardiovascular abnormalities. The sample consisted of fetuses, which were only the outcome of placental insufficiency. Ethical approval for this project was given by the Research Ethics Committee of the Ludwik Rydygier Collegium Medicum in Bydgoszcz (KB 189/2011).

After opening the thoracic cavity by sternotomy, both the pericardial sac with the heart and its great vascular trunks were dissected and removed out of the mediastinum.

Table 1 Distribution of fetuses examined

Fetal age[a]		Crown-rump length (mm)				Number of fetuses	Sex	
Months	Weeks (Hbd-life)	Mean	SD	Min	Max		Male	Female
4	14	78.5	2.5	76.0	81.0	2	1	1
	15	89.3	0.0	89.3	89.3	1	1	0
	16	102	6.0	96.0	108.0	2	1	1
5	17	114.0	7.3	110.0	123.0	9	5	4
	18	129.5	6.8	124.0	136.0	10	5	5
	19	141.9	5.9	138.0	149.0	7	4	3
	20	155.0	5.2	152.0	162.0	13	7	6
6	21	166.4	4.9	165.0	174.0	11	6	5
	22	178.9	7.2	175.0	185.0	5	2	3
	23	192.9	7.2	187.0	195.0	6	3	3
	24	201.4	4.2	199.0	204.0	5	3	2
7	25	214.5	2.5	212.0	217.0	2	1	1
Total						73	39	34

[a] The fetal age established by the crown-rump length is highly correlated with those calculated from the known data of the beginning of the last maternal menstrual period or a combination of abdominal circumference, femur length and biparietal diameter ($r = 0.97$, $P < 0.001$)

Afterward, using microsurgical instruments, the trachea and two main bronchi, with no conspicuous anomalies were dissected in the posterior mediastinum. In every individual, the trachea and two main bronchi in situ with a millimeter scale were positioned in a vertical manner to the optical lens axis, photographed with the use of Nikon D200 camera, and digitalized to TIFF images. Next, native pictures of every tracheobronchial segment were subjected to digital image analysis (NIS-Elements BR 3.0, Nikon), so as to evaluate semi-automatically the following eight independent variables for the right and left main bronchi (Fig. 1):

1, 2. lengths,
3, 4. proximal external transverse diameters,
5, 6. distal external transverse diameters, and
7, 8. projection surface areas.

Furthermore, since the fetuses varied in size, the two indexes of the two main bronchi were calculated, as follows:

9. right-to-left bronchial length ratio, and
10. right-to-left bronchial projection surface area ratio.

In a continuous effort to minimize measurement and observer bias, all measurements were conducted by one researcher (M.D.). Each measurement was done three times under the same conditions but at different times, and averaged. The differences between repeated bronchial

measurements, as the intra-observer variation, were evaluated by the one-way ANOVA test for paired data. Since the growing fetuses were separated into 12 intervals not equally distributed with relation to gestational age, in order to deal with that problem, the first three intervals (14–16 weeks), and the last two intervals (24–25 weeks) were separately grouped. As a prerequisite, the data obtained for the whole sample were checked for normality of distribution using the Kolmogorov–Smirnov test and for homogeneity of variance with the use of Levene's test. Obviously, this might not exclude any deviations within the examined subgroups. As the first step in the statistical analysis, t Student test was used to examine how sex influenced values of the bronchial parameters. Therefore, so as to examine sex differences, firstly we checked possible differences between the following nine age-groups: 14–16, 17, 18, 19, 20, 21, 22, 23 and 24–25 weeks, and secondly we tested possible sex differences for the whole group, without taking into account fetal ages. In order to check whether or not different variables significantly changed with age the one-way ANOVA test and post hoc Bonferroni test were used for the nine aforementioned groups (Table 2). After plotting values of every parameter against gestational age, linear and non-linear regression analysis was used to compute the best-fit curves with their standard errors of the estimate ($\pm$ SEE). Coefficients of

Fig. 1 Measurements of the right and left main bronchi in situ in a male fetus aged 19 weeks: *A* trachea, *B* right main bronchus, *C* left main bronchus, *1* length of right main bronchus, *2* length of left main bronchus, *3* proximal external diameter of right main bronchus, *4* proximal external diameter of left main bronchus, *5* distal external diameter of right main bronchus, *6* distal external diameter of left main bronchus, *7* projection surface area of right main bronchus, *8* projection surface area of left main bronchus
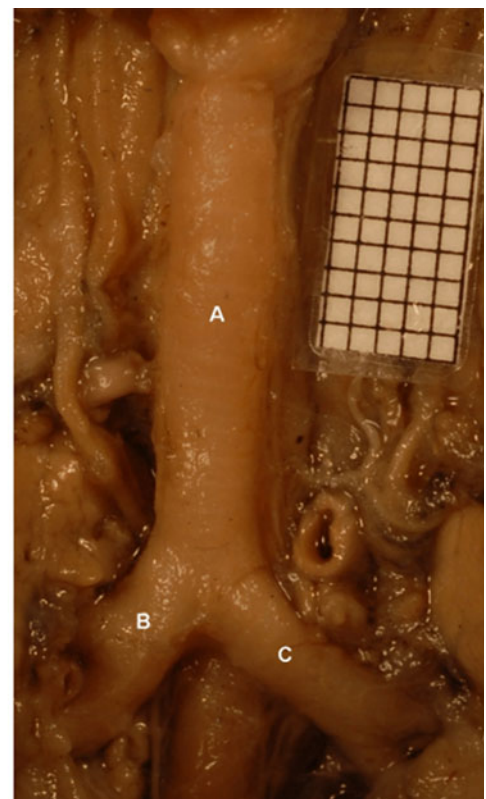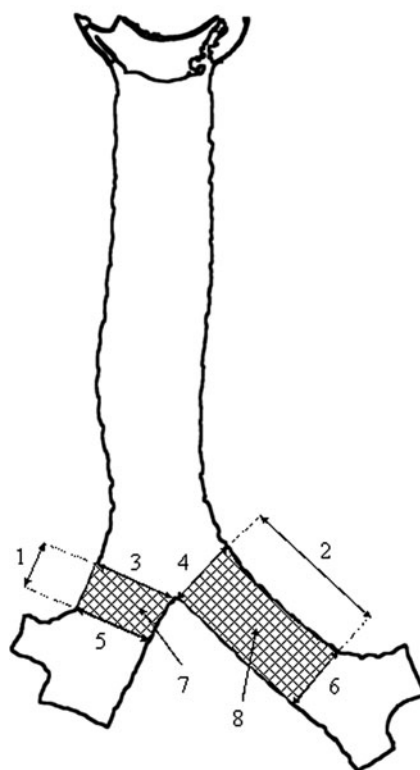
Table 2 Morphometric analysis of the right and left main bronchi in human fetuses

Fetal age (weeks)	Number of fetuses	Right main bronchus				Left main bronchus			
		Length (mm)	External diameter (mm)		Projection surface area (mm^2)	Length (mm)	External diameter (mm)		Projection surface area (mm^2)
			Proximal	Distal			Proximal	Distal	
14	2	1.43 ± 0.18	2.13 ± 0.41	2.09 ± 0.47	2.95 ± 0.19	2.97 ± 0.16	1.84 ± 0.06	1.85 ± 0.04	5.57 ± 0.21
15	1	1.38	2.14	2.14	2.88	3.88	1.77	1.68	6.99
16	2	2.37 ± 0.07	2.24 ± 0.17	2.06 ± 0.15	5.29 ± 0.58	4.99 ± 0.50	2.34 ± 0.38	2.01 ± 0.21	11.08 ± 0.13
		↓ ($P < 0.05$)	↓ ($P < 0.01$)	↓ ($P < 0.01$)	↓ ($P < 0.01$)	↓ ($P < 0.01$)	↓ ($P < 0.05$)	↓ ($P < 0.01$)	↓ ($P < 0.01$)
17	9	2.11 ± 0.31	2.80 ± 0.35	2.73 ± 0.36	6.01 ± 1.21	5.37 ± 0.63	2.38 ± 0.22	2.41 ± 0.29	13.07 ± 2.76
		↓ ($P > 0.05$)	↓ ($P < 0.05$)	↓ ($P < 0.01$)	↓ ($P < 0.05$)	↓ ($P < 0.05$)	↓ ($P < 0.01$)	↓ ($P < 0.05$)	↓ ($P < 0.05$)
18	10	2.12 ± 0.45	2.86 ± 0.36	2.90 ± 0.40	6.23 ± 1.41	5.50 ± 0.71	2.62 ± 0.26	2.52 ± 0.31	14.30 ± 2.49
		↓ ($P < 0.01$)	↓ ($P < 0.01$)	↓ ($P < 0.01$)	↓ ($P < 0.01$)	↓ ($P < 0.01$)	↓ ($P < 0.01$)	↓ ($P < 0.01$)	↓ ($P < 0.01$)
19	7	2.55 ± 0.48	3.47 ± 0.37	3.41 ± 0.35	9.08 ± 2.08	6.01 ± 0.55	2.92 ± 0.32	2.87 ± 0.18	17.80 ± 2.86
		↓ ($P > 0.05$)	↓ ($P < 0.05$)	↓ ($P > 0.05$)	↓ ($P > 0.05$)	↓ ($P < 0.05$)	↓ ($P < 0.05$)	↓ ($P < 0.05$)	↓ ($P < 0.05$)
20	13	2.55 ± 0.43	3.42 ± 0.48	3.38 ± 0.51	8.92 ± 2.39	6.28 ± 0.65	3.01 ± 0.32	2.97 ± 0.42	18.95 ± 3.34
		↓ ($P < 0.01$)	↓ ($P < 0.05$)	↓ ($P < 0.05$)	↓ ($P < 0.05$)	↓ ($P < 0.05$)	↓ ($P < 0.05$)	↓ ($P < 0.05$)	↓ ($P < 0.05$)
21	11	2.76 ± 0.60	3.31 ± 0.37	3.25 ± 0.36	9.15 ± 2.22	6.48 ± 0.77	2.88 ± 0.40	2.72 ± 0.38	18.40 ± 3.05
		↓ ($P < 0.05$)	↓ ($P < 0.01$)	↓ ($P < 0.01$)	↓ ($P < 0.01$)	↓ ($P < 0.01$)	↓ ($P < 0.01$)	↓ ($P < 0.01$)	↓ ($P < 0.01$)
22	5	2.50 ± 0.45	3.63 ± 0.67	3.71 ± 0.70	9.36 ± 1.38	6.78 ± 0.83	3.24 ± 0.43	3.22 ± 0.30	22.04 ± 3.86
		↓ ($P < 0.01$)	↓ ($P < 0.01$)	↓ ($P < 0.01$)	↓ ($P < 0.01$)	↓ ($P < 0.01$)	↓ ($P < 0.01$)	↓ ($P < 0.01$)	↓ ($P < 0.01$)
23	6	3.10 ± 0.52	4.05 ± 0.30	3.99 ± 0.33	12.64 ± 1.69	7.57 ± 0.49	3.63 ± 0.65	3.46 ± 0.55	26.99 ± 5.35
		↓ ($P < 0.05$)	↓ ($P < 0.01$)	↓ ($P < 0.01$)	↓ ($P < 0.05$)	↓ ($P < 0.05$)	↓ ($P < 0.01$)	↓ ($P < 0.01$)	↓ ($P < 0.01$)
24	5	2.80 ± 0.26	4.34 ± 0.29	4.33 ± 0.25	12.32 ± 1.36	7.29 ± 0.65	3.86 ± 0.21	3.73 ± 0.24	27.59 ± 2.45
25	2	3.18 ± 0.39	4.24 ± 0.20	4.24 ± 0.20	13.34 ± 2.12	7.58 ± 1.95	3.67 ± 0.66	3.67 ± 0.66	28.52 ± 5.24

Means for all examined parameters between the nine neighboring age ranges in columns differ (if $P < 0.05$) or do not differ (if $P > 0.05$) significantly

determination (R^2) between each parameter and fetal age were estimated. Differences were considered significant at $P < 0.05$.

Results

Insignificant differences were observed in the evaluation of intra-observer reproducibility of the bronchial measurements ($P > 0.05$). Since the statistical analysis of bronchial parameters revealed no sex differences ($P > 0.05$), the numerical data without regard to sex have been given in Table 2. Because of this, both the morphometric analysis and growth dynamics could be applied to the whole group. The morphometric values obtained were characterized by normality of distribution (the Kolmogorov–Smirnov test) and homogeneity of variance (Levene's test). As a consequence, quantitative variables have been expressed as the mean ± standard deviation. On the contrary to sex, the growth curves of best fit for every parameter studied against gestational age were statistically significant ($P = 0.0000$).
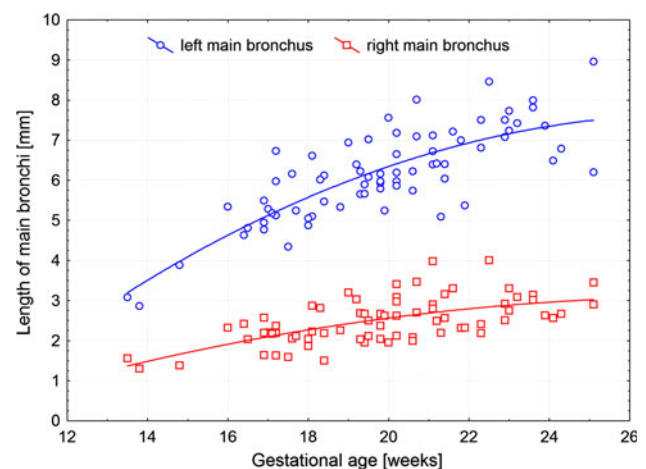
The length of the right main bronchus (Fig. 2a) increased from 1.43 ± 0.18 mm in the 14th week to 3.18 ± 0.39 mm in the 25th week of gestation, in accordance with the function $y = -4.850 + 2.452 x \ln(\text{Age}) \pm 0.400$ ($R^2 = 0.41$). During that time, the length of the left main bronchus (Fig. 2b) ranged between 2.97 ± 0.16 and 7.58 ± 1.95 mm, and as with the right side, increased logarithmically following the function $y = -15.005 + 7.093 x \ln(\text{Age}) \pm 0.579$ ($R^2 = 0.73$). In any age range, the left main bronchus was always longer than the right one (Fig. 3). In addition to that, the two main bronchi revealed a proportionate increase in length, since the right-to-left bronchial length ratio was relatively stable (Fig. 4) throughout the analyzed period, according to the linear function $y = 0.444 - 0.002 x$, and averaged 0.41 ± 0.07.

On either side, for the whole group there were no statistically significant differences ($P > 0.05$) between values of the proximal and distal transverse diameters of the main bronchus. However, because of their great inter-individual variability in particular age ranges, the growth dynamics for proximal and distal external diameters were presented separately.

Between the 14th and 25th week of gestation, the proximal external transverse diameter of the right main bronchus (Fig. 5a) varied from 2.13 ± 0.41 to 4.24 ± 0.20 mm, and grew according to the logarithmic fashion $y = -8.666 + 4.018 x \ln(\text{Age}) \pm 0.367$ ($R^2 = 0.69$). The proximal external transverse diameter of the left main bronchus (Fig. 5b) rose from 1.84 ± 0.06 mm in fetuses aged 14 weeks to 3.67 ± 0.66 mm in fetuses aged 25 weeks, as the function $y = -6.938 + 3.305 x \ln(\text{Age}) \pm 0.323$ ($R^2 = 0.65$).
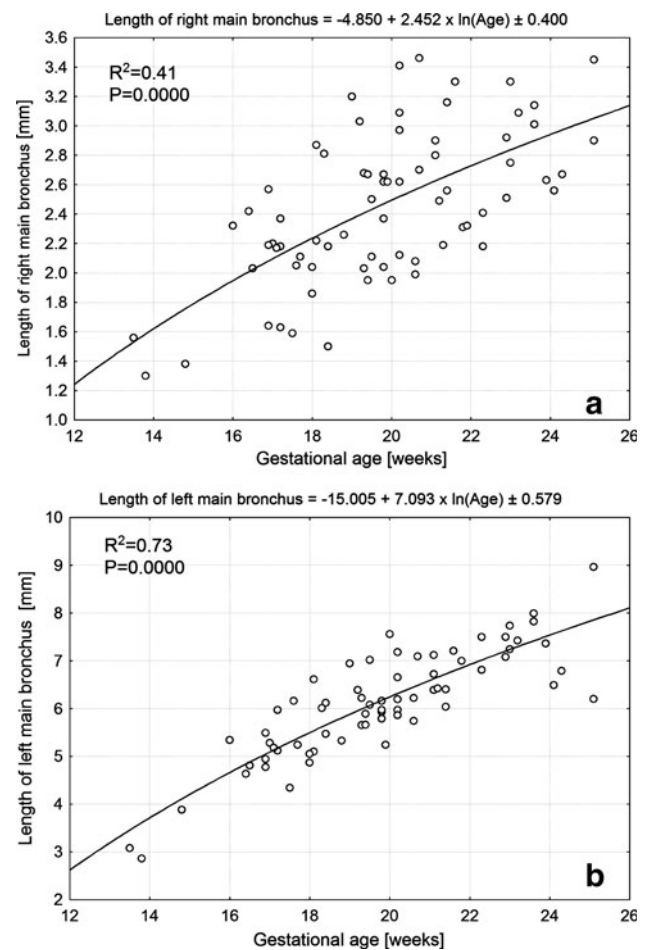
Fig. 2 Growth dynamics of the lengths of the right (**a**) and left (**b**) main bronchi *versus* gestational age in human fetuses

Fig. 3 The lengths of the right and left main bronchi in human fetuses

On the other hand, an increase of the right main bronchus in distal external transverse diameter (Fig. 6a) rose from 2.09 ± 0.47 mm in the 14th week to 4.24 ± 0.20 mm in the

25th week, in keeping with the function $y = -8.723 + 4.021x \ln(\text{Age}) \pm 0.392$ $(R^2 = 0.66)$. At that time, the distal external transverse diameter of the left main bronchus (Fig. 6b) fluctuated from 1.85 ± 0.04 to 3.67 ± 0.66 mm, following the logarithmic function $y = -6.924 + 3.280x \ln(\text{Age}) \pm 0.348$ $(R^2 = 0.62)$.

According to the aforementioned logarithmic models, the growth velocities for both length and two external transverse diameters of the right and left main bronchi (Table 3) gradually declined with advanced fetal age ($P < 0.05$).

During the study period, the projection surface area of the right main bronchus (Fig. 7a) ranged from 2.95 ± 0.19 to 13.34 ± 2.12 mm^2, increasing logarithmically as $y = -10.212 + 0.943x$ Age ± 1.739 $(R^2 = 0.67)$. At the same time, an increase in projection surface area of the left main bronchus (Fig. 7b) from 5.57 ± 0.21 to 28.52 ± 5.24 mm^2 followed linearly as $y = -19.119 + 1.875x$ Age ± 3.054 $(R^2 = 0.70)$. In any age range, the projection surface area of the left main bronchus was significantly larger than that of the right main bronchus ($P = 0.0000$). The right and left main bronchi showed a proportionate increase in projection surface area, since the right-to-left bronchial projection surface area ratio was relatively stable (Fig. 8) throughout the analyzed period, according to the linear function $y = 0.472 - 0.00005 \, x$, and averaged 0.47 ± 0.08.

Discussion

The present study describes the external size of the right and left main bronchi in the human fetus, providing the existing literature with completely novel quantitative data. Our findings have been presented as if describing a developmental sequence in one fetus, even though the numerical data have truly been cross-sectional, derived from 73 autopsied fetuses aged 14–25 weeks. For anatomists dealing with aborted fetuses the most important information for determining fetal ages is included in a very objective crown-rump length, when compared to the known data of the beginning of the last maternal menstrual period or to a combination of abdominal circumference, femur length and biparietal diameter [20]. However, ultrasonographic estimation of gestational age is based on the crown-rump length up to 14 weeks only, and beyond due to a combination of abdominal circumference, femur length and biparietal diameter [21]. In our opinion, this examination is characterized by the following four advantages. Firstly, the unique examined material consisted of a considerably numerous sample size ($n = 73$), without any conspicuous malformations. In fact, the subjects might potentially have smaller bronchial size due to placental
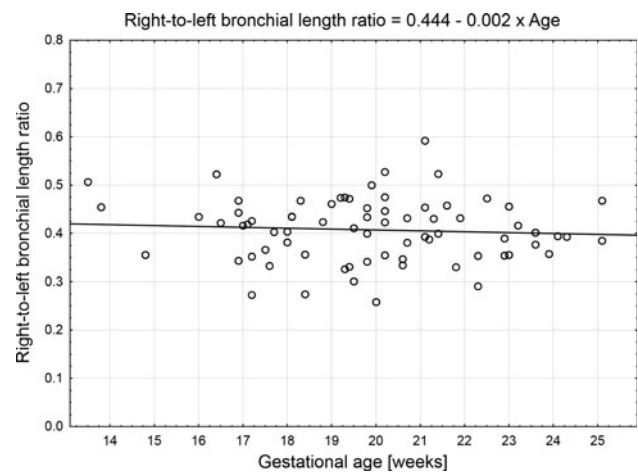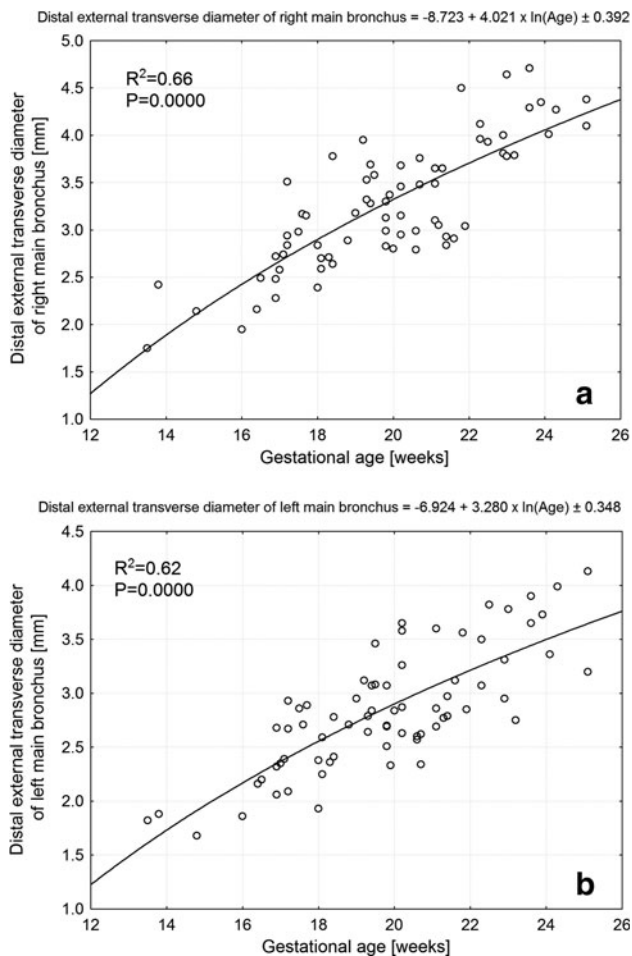

Fig. 4 Right-to-left bronchial length ratio *versus* gestational age in human fetuses
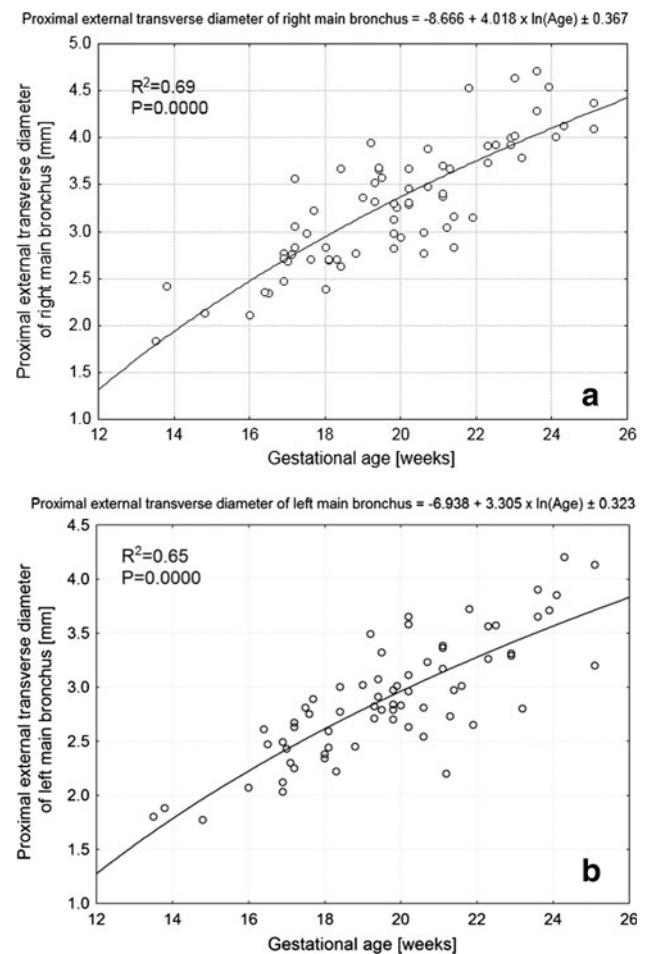
Fig. 5 Growth dynamics of the proximal external transverse diameters of the right (a) and left (b) main bronchi *versus* gestational age in human fetuses

insufficiency. However, as it turned out they could not suffer from intrauterine growth retardation, because the correlation between the gestational age based on the

Distal external transverse diameter of right main bronchus = -8.723 + 4.021 x ln(Age) ± 0.392

Distal external transverse diameter of left main bronchus = -6.924 + 3.280 x ln(Age) ± 0.348

Fig. 6 Growth dynamics of the distal external transverse diameters of the right (a) and left (b) main bronchi *versus* gestational age in human fetuses

crown-rump length and those calculated by the last menstruation and a combination of abdominal circumference, femur length and biparietal diameter reached the value $r = 0.97$ ($P < 0.001$) for the whole sample. Secondly, all measurements were taken in situ to minimize to 0.5–1.0 % tissue shrinkage related to formalin fixation, when compared to 10 % shrinkage in isolated tracheobronchial segments [22–24]. That is because we could focus only on external dimensions of the two main bronchi. Thirdly, the precise and clearly defined parameters studied were evaluated with the use of a valid objective software package (NIS-Elements BR 3.0, Nikon) in a direct manner, instead of deduced, extrapolated through a series of indirect measurements. Fourthly, the evidence material comprised 10 results for every fetus, resulting in 730 individual numerical data for the whole sample. On the other hand, the main limitation of the present study may result from a relatively narrow fetal age, varying from 14 to 25 weeks of gestation. Furthermore, all measurements were done by one observer in a blind fashion. Another partial limitation results in the

values of coefficients of determination (R^2), being less than 0.8 for the obtained formulae. This is mainly because of great inter-individual variability of the examined parameters in particular age ranges.

Some authors found sex differences concerning morphometric features of the two main bronchi in fetuses [19], children [25] and adults [10]. Porwolik [19] stated that the proximal transverse diameter of the left main bronchus was somewhat larger in female fetuses than in males. According to Tahir et al. [25], in children under 16 years, only the right main bronchus was significantly wider in boys than in girls, whereas the widths of the left main bronchus were statistically insignificant in both sexes. Hampton et al. [10], however, emphasized significantly greater widths of both main bronchi in men than in women. On the contrary, as in the present study there were no significant differences in the required measurements between males and females, our results were combined for two sexes.

Kher and Makhani [16] and Harjeet et al. [12], with the use of anatomical dissection and a caliper, examined the lengths of the mainstem bronchi in human fetuses of Indian origin. In the material of Kher and Makhani [16], consisting of 36 human fetuses without giving fetal ages, the length of the right main bronchus ranged from 0.4 to 1.5 cm, on average 0.50 cm, and that of the left main bronchus was nearly three times greater, varying from 0.9 to 2.7 cm, on average 1.44 cm. In a much more precise study performed by Harjeet et al. [12], in the following three fetal groups with the crown-rump length of 61–130 mm ($n = 16$), 131–200 mm ($n = 13$), and 201–270 mm ($n = 11$), the length of the right main bronchus increased steadily from 2.97 ± 0.69 mm, through 3.79 ± 0.66 mm up to 7.07 ± 0.97 mm ($P < 0.001$). The left main bronchus was significantly longer, attaining the following values of 5.40 ± 1.29, 7.17 ± 1.74, and 11.10 ± 1.52 mm, respectively. Similarly, a proportionate increase in length of both main bronchi was supported by Porwolik's findings [19] in fetuses of white racial origin. The length of the right main bronchus was found to increase with age in days according to the linear function $y = 0.025x$ Age ($r = 0.70$). As far as the left main bronchus was concerned, its length followed the function $y = -1.40 + 0.063x$ Age ($r = 0.92$). Surprisingly enough, in spite of a linear relationship between bronchial length and age, Porwolik [19] finally stated that the main bronchi up to the 6th gestational month lengthened intensively to slow down afterward. In contrast to previous claims, in the material under examination the main bronchi did not elongate in a straight fashion, because logarithmic functions turned out to be the best-fit curves. Therefore, the right and left main bronchi grew in length in accordance with the following functions, $y = -4.850 + 2.452x$ ln(Age) ± 0.400 and $y = -15.005 + 7.093x$ ln(Age) ± 0.579, respectively.

Table 3 Predicted weekly growth of the examined parameters of the main bronchi in human fetuses

Fetal age (weeks)	Number of fetuses	Growth (mm/week)					
		Right main bronchus			Left main bronchus		
		Length	Transverse diameter		Length	Transverse diameter	
			Proximal	Distal		Proximal	Distal
14	2	0.17	0.28	0.28	0.49	0.23	0.23
15	1	0.16	0.26	0.26	0.46	0.21	0.21
16	2	0.15	0.24	0.24	0.43	0.20	0.20
17	9	↓ ($P < 0.05$)	↓ ($P < 0.05$)	↓ ($P < 0.05$)	↓ ($P < 0.01$)	↓ ($P < 0.05$)	↓ ($P < 0.05$)
		0.14	0.23	0.23	0.41	0.19	0.19
		↓ ($P < 0.05$)	↓ ($P < 0.05$)	↓ ($P < 0.05$)	↓ ($P < 0.01$)	↓ ($P < 0.05$)	↓ ($P < 0.05$)
18	10	0.13	0.22	0.22	0.38	0.18	0.18
		↓ ($P < 0.05$)	↓ ($P < 0.05$)	↓ ($P < 0.05$)	↓ ($P < 0.01$)	↓ ($P < 0.05$)	↓ ($P < 0.05$)
19	7	0.13	0.21	0.21	0.36	0.17	0.17
		↓ ($P < 0.05$)	↓ ($P < 0.05$)	↓ ($P < 0.05$)	↓ ($P < 0.01$)	↓ ($P < 0.05$)	↓ ($P < 0.05$)
20	13	0.12	0.20	0.20	0.35	0.16	0.16
		↓ ($P < 0.05$)	↓ ($P < 0.05$)	↓ ($P < 0.05$)	↓ ($P < 0.01$)	↓ ($P < 0.05$)	↓ ($P < 0.05$)
21	11	0.11	0.19	0.19	0.33	0.15	0.15
		↓ ($P < 0.05$)	↓ ($P < 0.05$)	↓ ($P < 0.05$)	↓ ($P < 0.01$)	↓ ($P < 0.05$)	↓ ($P < 0.05$)
22	5	0.11	0.18	0.18	0.32	0.15	0.15
		↓ ($P < 0.05$)	↓ ($P < 0.05$)	↓ ($P < 0.05$)	↓ ($P < 0.01$)	↓ ($P < 0.05$)	↓ ($P < 0.05$)
23	6	0.10	0.17	0.17	0.30	0.14	0.14
		↓ ($P < 0.05$)	↓ ($P < 0.05$)	↓ ($P < 0.05$)	↓ ($P < 0.05$)	↓ ($P < 0.05$)	↓ ($P < 0.05$)
24	5	0.10	0.16	0.16	0.29	0.13	0.13

Means for growth all the examined parameters between the nine neighboring age ranges in columns differ significantly ($P < 0.05$)

Thus, an increase in length of the two main bronchi gradually slowed down with age, deviating more and more from an imaginary linear function. From a logical point of view, due to anatomical and physiological limitations of growth, it is unavoidable that growth slows down over time, and so has to be modeled by some non-linear courses of decreasing growth rate with age. In fact, this strictly resembles Porwolik's findings [19] in slowing growth dynamics of the two main bronchi. In this study, the statistical analysis showed that the left main bronchus was nearly three times longer than the right one, in keeping with other authors [2, 4, 12, 15, 16, 18–20, 25]. Furthermore, the present study has confirmed that with relation to each other, the main bronchi evolve proportionately in length. This results from a stable value of 0.41 ± 0.07 throughout the analyzed period for the right-to-left bronchial length ratio, changing little in accordance with the nearly constant linear function $y = 0.444 - 0.002\,x$.

According to the anatomical and radiological literature, the right main bronchus was always found to be considerably wider than the left one [12, 15, 16, 19, 20, 25]. In the material under examination, both the proximal and distal external transverse diameters of the right bronchus (2.13 ± 0.41, 4.24 ± 0.20 mm) were greater than those of

the left one (1.84 ± 0.06, 3.67 ± 0.66 mm). Therefore, in terms of biophysics the tracheobronchial segment can be considered as a system of distributing channels, consisting of the primary channel (distal part of the trachea) divided into the two secondary channels (right and left main bronchi) of different diameters. In accordance with Poiseuille's equation, airway resistance is directly proportionate to the length of the main bronchus, and inversely proportionate to its diameter to the fourth power. Thus, being exquisitely sensitive to changes in diameter, airway resistance dramatically increases and reduces flow in response to a decrease in diameter. Because the right main bronchus is approximately 1.1- to 1.2-fold wider and 2.5- to 3-fold shorter than the left one, the resistance has to be much higher on the left.

Tahir et al. [25] examined the tracheobronchial anatomy on normal chest pediatric radiographs in 156 children in the age group 0–16. Of note, in order to exclude the effect of magnification related to radiographic projections, the right-to-left main bronchus width ratio was calculated. Its value was remarkably consistent at the level of 1.1. On standard PA chest X-rays of adults, Hampton et al. [10] measured the intraluminal diameters of the two main bronchi approximately 1 cm beyond the carina. Unfortunately, with
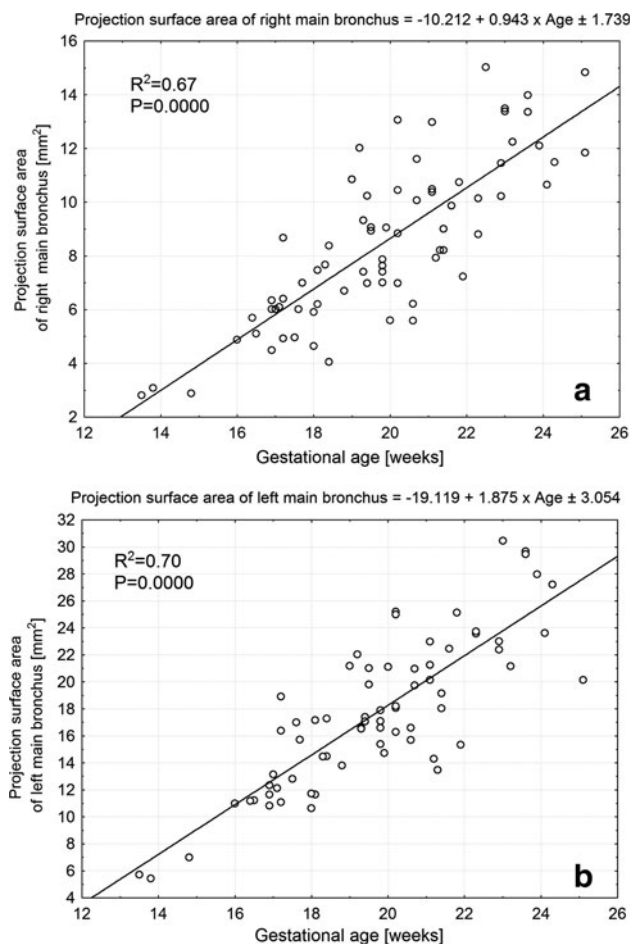
Fig. 7 Growth dynamics of the projection surface area of the right (**a**) and left (**b**) main bronchi *versus* gestational age in human fetuses
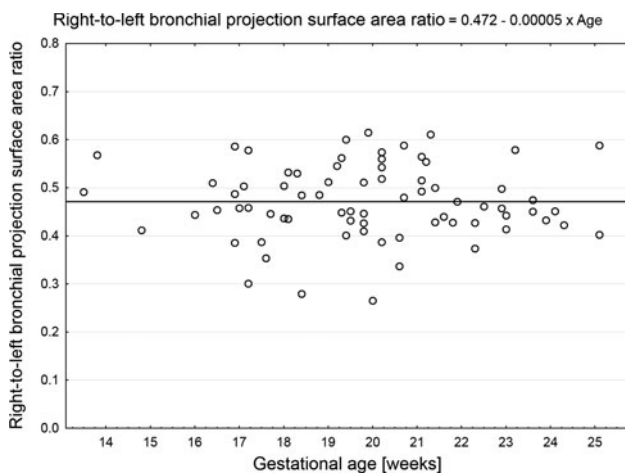
Fig. 8 Right-to-left bronchial projection surface area ratio *versus* gestational age in human fetuses

no correction for the shadow enlargement, the internal transverse diameter of the left main bronchus for the whole sample averaged 12.6 ± 1.9 mm, for men 13.0 ± 1.9 mm,

and for women 11.8 ± 1.6 mm. The internal transverse diameter of the right main bronchus amounted to 14.6 ± 2.6 mm for two sexes, 15.0 ± 2.6 mm for men, and 13.8 ± 2.4 mm for women. Furthermore, the relationship between the internal diameters of the left (LMB) and right (R) main bronchi was expressed by the following formula: LMB = 0.554 R + 4.59 ($r = 0.754$, $P < 0.0001$). With the help of a formula used to correct for the radiographic magnification, Hannallah et al. [11] studied the actual endobronchial transverse diameter of the left main bronchus on PA chest X-rays of 57 women and 43 men aged 18–89 years. As a result, in men the values obtained varied from 9.5 to 15.5 mm, on average 12.4 ± 1.5 mm, whereas in women from 9.0 to 14.0 mm, on average 10.7 ± 1.0 mm; the former being significantly greater than the latter. It is worth highlighting that the left bronchial diameter was less than 11.0 mm in 82 % of women and over 11.0 mm in 88 % of men. In females, the left bronchial diameter was not correlated with age, height, or body weight. On the contrary, in males both age and height produced a significant prediction for the left bronchial diameter, following the formula: left endobronchial diameter (mm) $= 0.032 \times$ Age (years) $+ 0.072 \times$ Height (cm) $- 2.043$ ($R^2 = 0.229$).

Porwolik [19] concluded that both the transverse and sagittal diameters of the mainstem bronchi revealed a proportionate evolution with age. The external transverse diameters were found to increase linearly, following the functions $y = 0.01x$ Age ($r = 0.70$) for the right main bronchus, and $y = 0.39 + 0.009x$ Age ($r = 0.26$) for the left main bronchus. Similarly, the growth in sagittal diameter of the right and left main bronchi was characterized by the functions $y = 0.012x$ Age ($r = 0.71$) and $y = 0.012x$ Age ($r = 0.77$), respectively. Our study did not confirm a linear growth in transverse diameter of the mainstem bronchi. Instead, we computed for them much more detailed logarithmic growth patterns. The proximal and distal transverse diameters of the right main bronchus grew in accordance with the models $y = -8.666 + 4.018x$ ln(Age) ± 0.367 and $y = -8.723 + 4.021x$ ln(Age) ± 0.392, respectively. The same parameters of the left main bronchus were modeled by the two logarithmic functions, $y = -6.938 + 3.305x$ ln(Age) ± 0.323 and $y = -6.924 + 3.280x$ ln(Age) ± 0.348, respectively.

Of note, the left main bronchus could be visible on chest radiograms in 50–75 % of cases, while the trachea was actually seen in every patient [2, 10, 11]. This encouraged radiologists to indirectly estimate the left endobronchial diameter, basing on the known endotracheal diameter. On chest radiograms of 192 adults, Brodsky and Lemmens [2] examined the relationship between the internal transverse diameters of the left main bronchus and the trachea. Although the left endobronchial width (LBW) was

positively correlated with age and height in men, and with height in women, the endotracheal width (TW) turned out to be the best factor, most accurately predicted the size of the left main bronchus. The formula to predict the left bronchial width, which normalizes for the radiographic enlargement was $LBW_{mm} = 0.45\ TW_{mm} + 3.3$ mm. According to some authors [6, 18], the left bronchial width cannot be accurately estimated using patient's demographic data (weight, height, age) and ratios calculated from the endotracheal width. Estimating the left bronchial length on chest radiograms or even conventional CT scans [7] seems to be inappropriate, because the bronchus usually lies beyond an axial orientation. Olivier et al. [18] emphasized that the only reliable method (golden standard) for determining the bronchial length is a method of multiplane CT reconstructions (MPR).

To date, neither anatomical nor radiological literature has dealt with projection surface areas of the right and left main bronchi. Therefore, our study is the first to highlight their evolution in fetuses aged 14–25 weeks. An increase in projection surface area with age turned out to follow linearly as $y = -10.212 + 0.943x$ Age ± 1.739 ($R^2 = 0.67$) for the right main bronchus, and $y = -19.119 + 1.875x$ Age ± 3.054 ($R^2 = 0.70$) for the left main bronchus. It is noteworthy that the projection surface area of the left main bronchus was significantly larger ($P = 0.0000$), when compared to that of the right main bronchus. The right and left main bronchi showed a proportionate evolution, because the right-to-left bronchial projection surface area ratio was nearly constant, on average 0.47 ± 0.08, throughout the analyzed period, in accordance with the linear function $y = 0.472 - 0.00005x$.

Having performed the morphometric analysis of the main bronchi in human fetuses, we would like to highlight clinical aspects in this subject. At the level of the main bronchi, the following broncho-pulmonary malformations may occur such as agenesis, duplication, constrictions or dilatations, and invaginations (fistulae, bronchogenic cysts, diverticuli, bronchoceles) [9, 20]. Major bronchial abnormalities encompass accessory cardiac and tracheal bronchi. An accessory cardiac bronchus is a supernumerary bronchus, originating mostly from the inner wall of the right main bronchus that progresses toward the pericardium, and terminates either in a blind way or in vestigial or rudimentary bronchiolar parenchymal tissue, cystic degeneration, or ventilated lobules. A tracheal bronchus includes a variety of bronchial anomalies arising from the trachea or main bronchus and directed to the upper lobe territory on the right (0.1–2 %) or on the left (0.3–1 %). Knowledge of a patient's left main bronchus diameter is a prerequisite for choosing the optimal left double-lumen tube size. Such an optimal tube fits the bronchus with a small air leak when its bronchial cuff is deflated. If direct measurement of the left endobronchial width is impossible, it may be calculated using the formula of Brodsky and Lemmens [2], so as to select the appropriate size of the left double-lumen tube. The choice of a double-lumen tube of appropriate size is extremely important for the safe achievement of one-lung ventilation [18]. A smaller tube is likely to be introduced deeper into the left bronchus, obstructing the upper lobe [2]. A larger tube can fail to enter the bronchus and be the cause of bronchial laceration, and besides its bronchial cuff inflation requires minimal volume to achieve an effective seal, preventing from the risk of pressure damage to the bronchial mucosa [8, 18].

In summary, the present study quantitatively describes an increase in external dimensions of the right and left main bronchi, providing completely novel mathematical formulae of their growth dynamics for length, proximal and distal external transverse diameters, and projection surface area. The nomograms improve our knowledge of bronchial quantitative morphology in formalin fixed human fetuses that can be adapted in vivo to fetal airways.

Conclusions

1. The main bronchi show no sex differences.
2. The right and left main bronchi grow logarithmically in length and external transverse diameter, and linearly in projection surface area.
3. The right and left main bronchi evolve proportionately, with the right-to-left bronchial ratios of 0.41 ± 0.07 for length, and 0.47 ± 0.08 for projection surface area.

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