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FULL PAPER

Effect of total lung capacity, gender and height on CT airway measurements

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Objective: Testing the hypothesis that CT airway measurements could be influenced by total lung capacity (TLC), gender and height in normal individuals.

Methods: In this ethics committee-approved prospective trial, 87 healthy never-smoking volunteers who provided written informed consent were included. From a helical CT scan of the chest, the wall thickness (WT) and the lumen area were twice measured in the third- and fourth-generation airways by three readers using a dedicated software. In addition, the TLC was also measured using CT (TLC_{CT}). The percentage of airway area occupied by the wall (WA%) and the square root of wall area at an internal perimeter of 10 mm ($\sqrt{\text{WAPI}10}$) were calculated. CT airway measurements were compared between genders by using a mixed linear model. The correlations between height, TLC_{CT} and CT airway measurements

were tested by using a Pearson correlation analysis. These correlations were arbitrarily considered as significant if there was a significant correlation observed for each of the six measurement sessions.

Results: $\sqrt{\text{WAPI}10}$, WT^{3rd} and WT^{4th} were significantly different between genders. For both genders, there was no significant correlation between any airway measurements and TLC_{CT}. In females only, WT^{3rd} and WT^{4th} were significantly and negatively correlated with height.

Conclusion: $\sqrt{\text{WAPI}10}$, WT^{3rd} and WT^{4th} are different in males and females. WT^{3rd} and WT^{4th} are correlated with height in females only but not with TLC or in males.

Advances in knowledge: CT airway measurements are influenced by gender and by height in females only but not by TLC. They should be adjusted according to gender and height in females.

INTRODUCTION

Airway measurements can currently be obtained from thin-section CT scan of the lungs by using dedicated software.¹ Several studies reported that these measurements could be useful in the work-up of various diseases such as asthma, chronic obstructive pulmonary disease and cystic fibrosis.^{2–7}

CT airway measurements can be expressed through four indexes: the wall thickness (WT), the lumen area (LA), the percentage of airway area occupied by the wall (WA%) and the square root of wall area at an internal perimeter of 10 mm ($\sqrt{\text{WAPI}10}$). In healthy non-smoking adults, two studies showed that LA and WA% are influenced by age and the total lung capacity (TLC), and WA% by gender, but reported contradictory results concerning the relation between $\sqrt{\text{WAPI}10}$ and gender.^{4,8} These two studies, however, considered subjects older than 50 years among a wide range of age (standard deviations larger than 7 years).^{4,8} Moreover, these two studies did not consider the subject's height, whereas a recent study revealed that CT lung densitometry indexes are influenced by TLC, gender and height as well.⁹

The aim of this study was therefore to investigate the effects of TLC, gender and height on CT airway measurements in healthy young adult volunteers within a narrow range of age.

METHODS AND MATERIALS

Subjects

This prospective investigation was approved by the local ethics committee, and written informed consent was obtained from all subjects. In this trial, we recruited 87 healthy never-smoking volunteers without any history of cardiopulmonary disease, aged from 18 to 27 years (42 males and 45 females). For each subject, the height (cm) was measured. This cohort of young adult volunteers within a narrow range of age was specifically constituted to avoid the influence of age on CT lung densitometric indexes and CT airway measurements. By considering this cohort, our group of investigators was therefore able to conduct two separate studies addressing the influence of TLC, gender and height on, respectively, CT lung densitometric indexes⁹ and CT airway measurements.

CT scans

CT scans were obtained by using commercially available multi-detector row CT scanners (Somatom Sensation 16 and 64; Siemens Medical Solutions, Forchheim, Germany). Subjects were examined craniocaudally and in the supine position. A frontal scout view was obtained at 120 kVp and 50 mA with the Sensation 16 scanner or at 120 kVp and 35 mA with the Sensation 64 scanner. This acquisition was followed by a single helical scan from apex to base of the lung, during a full-inspiration breath-hold. No volunteer received intravenous contrast material. CT examinations were performed at 120 kVp on both scanners and with 16×0.75 - and 32×0.6 -mm collimations, respectively, on the Sensation 16 and 64 scanners. Other parameters included tube rotation times of 0.5 and 0.33 s and pitches of 1.15 and 1.4:1, respectively, for each scanner. An automated exposure control system was switched on during all acquisitions (Care Dose 4D®; Siemens Medical Solutions) with a quality reference effective current–time product of 20 mAs. As defined by Mahesh *et al*,¹⁰ effective tube current–time product corresponds to the tube current–time product divided by the pitch, whereby the pitch is defined by Silverman *et al*¹¹ as the ratio between the table feed per rotation and the X-ray beam width. We used a dose modulation technique to reduce the radiation dose delivered to our volunteers and to abolish the effect of soft-tissue thickness of the chest wall in order to set lung attenuation measurements free of this thickness, including the influence of breasts (and their size) in females and not in males. From raw data, 1-mm-thick section images were reconstructed at 0.7-mm intervals by using a high spatial algorithm (B60S; Siemens Medical Solutions). Information on CT examinations that could identify the patients was removed, and CT examinations were randomly numbered by using tables from Fisher and Yates.¹² From our patients, the size-specific dose estimates (SSDEs) per CT scan was 1.85 ± 0.22 mGy (mean $\pm$ standard deviation). The SSDE value for each CT scan was calculated from the CT dose index reported on the scanner for the 32-cm-diameter polymethyl methacrylate phantom and from the patient's effective diameter.¹³ For computing the subject's effective diameter, the lateral diameter and the anteroposterior diameter were manually measured on each CT scan.

Airway measurements

Airways were measured using a dedicated program (Virtual Bronchoscopy, Siemens Medical Solutions). First, the program automatically segmented the lung parenchyma and the airway tree and calculated the TLC for each subject. The trachea was identified within the first slices of the CT scan and seeded for an initial point of segmentation. A region-growing algorithm was then applied to roughly determine the airway tree. The threshold was continually increased from -1000 HU while a mathematical morphology algorithm repeatedly monitored the obtained airway tree to ensure that an ideal threshold was reached.^{14,15} This threshold was different for each CT scan. Secondly, the program provided airway measurements by using a modified full-width at half-maximum approach.¹⁶ Briefly, the standard full-width at half-maximum approach was applied on calculated cross-sections that are perpendicular to the central axis of the airway. It estimated the lumen location along a linear sampling direction as the location with gray level of the average of the

maximum and minimum. The modified approach allowed for more robust comparison by using the segmentation as an estimate for the location of the inner lumen. In addition, this modified approach also computed consecutive measurements with different angles in order to eliminate incorrect measurements that may occur on the section that was perpendicular to the central axis of the airway with adjacent arteries or reconstruction artefacts.^{17,18} The measurements obtained with this modified approach were previously validated through comparison to scanned polyvinyl chloride tubes with the inner diameter varying from 2 to 10 mm and with the WT varying from 1 to 3 mm.¹⁷

Airways were measured twice (in two separate measurement sessions) by three radiologists. Reader 1 (M.H.) was a radiologist with 8 years of experience in measuring airways using CT, Reader 2 (D.F.) was a medical student without experience in measuring airways using CT and Reader 3 (T.S.G.) was a radiologist with 16 years of experience in thoracic imaging and 1 year of experience in measuring airways using CT. The following standardized procedure for measurement was applied to each CT examination:⁵ (a) the third (segmental)- and fourth (subsegmental)-generation airways were labelled following the Boyden nomenclature¹⁹ on the segmented airway tree; (b) the third- and fourth-generation airway segments that were not located at a branching division were selected; (c) these selected segments were measured by using the dedicated program described above that automatically delineated the airway contours and (d) the fitting of airway delineation with airway contours was visually controlled (Figure 1). The program finally measured the WT and the luminal area of the third (respectively, abbreviated WT^{3rd} and LA^{3rd}) and fourth (respectively, abbreviated WT^{4th} and LA^{4th}) generations of airways. The percentage of total airway area occupied by the wall was calculated for the third and fourth (respectively, abbreviated WA%^{3rd} and WA%^{4th}) generations of airways. The square root of the wall area at an internal perimeter of 10 mm ($\sqrt{\text{WAPI}10}$) was computed by plotting each third and fourth generations of airways on a graph, with the inner perimeter along the x-axis and the square root of the wall area along the y-axis. The slope of the straight-line relationship between these two measurements was then calculated as well as the value of the square root of the wall area corresponding to an inner perimeter of 10 mm.⁴ In addition, the number of third- and fourth-generation airways actually considered by the reader was recorded. Furthermore, a dedicated program was used to calculate the TLC for each subject based on the volume covered by lung parenchyma. As the TLC was also measured using plethysmography (see in the Pulmonary function tests section), the TLC measured using CT is abbreviated as TLC_{CT}.

Pulmonary function tests

On the same day as the CT scans, pulmonary function tests (PFTs) were carried out with the patient in a seated position. Forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV₁) were measured with a Lilly-type pneumotachograph, whereas the functional residual capacity (FRC) was measured in a constant volume body plethysmograph (Master-Screen Body; Jaeger, Würzburg, Germany). The TLC and residual volume were calculated using the values of FRC and the

Figure 1. Standardized procedure for measuring an airway in a particular patient: (a) the third (segmental)- and fourth (subsegmental)-generation airways are labelled following the Boyden nomenclature,¹⁹ on the segmented airway tree; (b) the third- and fourth-generation airway segments that are not located at a branching division are selected—for instance, a segment of the posterior branch of the apical segmental bronchus is selected (square); (c) these selected segments are measured by using a dedicated program that automatically delineated the airway contours [the average (Avg) inner and outer diameters (Diam), the inner area and the average wall thickness are obtained]; and (d) the fitting of airway delineation with airway contours is visually controlled—for instance, an unfitted delineation.

subdivisions of vital capacity. As the TLC was also measured using CT, TLC measured using plethysmography is abbreviated as TLC_{pleth}. The diffusing capacity of carbon monoxide (DLCO) was measured by the single-breath method (MasterScreen Body). The measured values were then compared with the predicted normal values established by the European Community of Coal and Steel.^{20,21}

Statistical analyses

Before further statistical analyses, normality of TLC_{CT} and CT measurements was established using the Lilliefors adaptation of the Kolmogorov–Smirnov test. The characteristics of the subjects and the results of the PFTs were compared between genders by using a *t*-test. The CT airway measurements were compared between genders by using a mixed linear model, the fixed effects being gender and the random effects being CT number, reader and session. A comparison was performed between TLC_{CT} and TLC_{pleth} by using a Bland–Altman analysis. The correlations between height, TLC_{CT} and CT airway measurements were then tested separately in both genders by

using a Pearson correlation analysis. These correlations were arbitrarily considered as significant if there was a significant correlation observed for each of the six measurement sessions. Statistical significance was defined as a *p*-value of <0.05. The statistical software used in this study was Statistica v. 6.0 (Statsoft, Maisons-Alfort, France) and the R software.²²

RESULTS

The characteristics of the subjects and the results of the PFTs are compared between genders in Table 1. There were significant differences between genders for height, TLC_{CT}, FEV₁, FVC, FVC (% predicted), FEV₁/FVC ratio, FRC, TLC_{pleth}, residual volume, DLCO, DLCO (% predicted) and DLCO/VA ratio (*p*-values ranging from <0.001 to 0.045).

CT airway measurements from all six measurement sessions are detailed in Table 2 and compared between genders. There were significant differences for $\sqrt{\text{WAPi10}}$, WT^{3rd} and WT^{4th} (*p*-values ranging from <0.001 to 0.003).

Table 1. Characteristics of the population and pulmonary function tests

Characteristics	Males	Females	<i>p</i> -value
Age (years)	21 ± 2	21 ± 2	0.571
Height (cm)	180 ± 6	167 ± 6	<0.001
TLC _{CT} (l)	6.2 ± 0.9	4.3 ± 0.7	<0.001
FEV ₁ (l)	4.6 ± 0.6	3.3 ± 0.5	<0.001
FEV ₁ (% predicted)	99.5 ± 11.7	95.6 ± 11	0.107
FVC (l)	5.4 ± 0.8	3.7 ± 0.5	<0.001
FVC (% predicted)	97.7 ± 12	92.7 ± 11	0.045
FEV ₁ /FVC (%)	86.8 ± 7.3	90.6 ± 5.8	0.009
FEV ₁ /FVC (% predicted)	103.3 ± 8.5	104.9 ± 7.5	0.352
FRC (l)	4.3 ± 0.8	3.3 ± 0.8	<0.001
FRC (% predicted)	129.7 ± 22	119.6 ± 26.9	0.062
TLC _{pleth} (l)	7.6 ± 1.2	5.5 ± 0.9	<0.001
TLC _{pleth} (% predicted)	104.7 ± 12.6	106.5 ± 16.1	0.548
RV (l)	2.3 ± 0.8	1.9 ± 0.7	0.014
RV (% predicted)	143.2 ± 46.8	137.7 ± 52.9	0.604
RV/TLC (%)	29.7 ± 8.8	33.1 ± 9.3	0.081
DLCO (ml/min/mmHg)	38.4 ± 9	26.4 ± 5.5	<0.001
DLCO (% predicted)	103.7 ± 17.8	88.2 ± 16.2	<0.001
DLCO/VA (ml/min/mmHg/l)	5.6 ± 1.2	5.3 ± 0.7	0.091
DLCO/VA (% predicted)	86.7 ± 11.9	80.9 ± 11.5	0.023

DLCO, diffusing capacity of carbon monoxide; FEV₁, forced expiratory volume in 1 s; FRC, functional residual capacity; FVC, forced vital capacity; RV, residual volume; TLC_{CT}, total lung capacity measured using CT; TLC_{pleth}, total lung capacity measured by plethysmography.

Pulmonary function data are expressed as percentages of predicted values established by the European Respiratory Society.^{20,21}

Data are mean ± standard deviation of the mean.

A statistically significant correlation was found between TLC_{CT} and TLC_{pleth} ($r = 0.839$, $p < 0.001$). The Bland–Altman plot (Figure 2) showed that TLC_{CT} was, in average, 1.29 l smaller than TLC_{pleth}. Nevertheless, as CT airway measurements were performed on images acquired in the supine position, whereas plethysmography was performed in the seated position, TLC_{CT} was arbitrarily selected for the correlation analyses between TLC and other CT measurements.

For both genders, there was no significant correlation between TLC_{CT} and airway measurements (p -values ranging from <0.001 to 0.948, but inconsistent in all six measurements sessions). In males, there was no significant correlation between height and airway measurements (p -values ranging from 0.002 to 0.418, but inconsistent in all six measurements sessions). In females, there were significant negative correlations between height and WT in the third (r ranging from -0.313 to -0.482 ; p -values ranging from 0.001 to 0.018) and fourth generation airways (r ranging from -0.356 to -0.628 ; p -values ranging from <0.001 to 0.010). There was no significant correlation between height and $\sqrt{\text{WAPi10}}$, LA or WA% (p -values ranging from <0.001 to 0.462, but inconsistent in all six measurements sessions). Figure 3 shows the individual values of WT^{3rd} (all six measurements sessions) as a function of height in

both genders. Figure 4 shows the individual values of WT^{4th} (all six measurements sessions) as a function of height in both genders.

DISCUSSION

Our study shows that in normal subjects, (a) $\sqrt{\text{WAPi10}}$, WT^{3rd} and WT^{4th} are different between genders; (b) WT is negatively correlated with height in females but not in males, and (c) there is no correlation between TLC_{CT} and any CT airway measurements.

By considering a group of healthy young adults within a narrow range of age, our study reveals that $\sqrt{\text{WAPi10}}$, WT^{3rd} and WT^{4th} are different between genders. Some of these findings confirm those previously reported by Zach et al⁸ and Grydeland et al⁴ who considered wider ranges of age groups of elderly subjects. Nevertheless, Zach et al⁸ arbitrarily selected six third-generation airways and two fourth-generation airways while Grydeland et al⁴ selected some airways with an internal perimeter >6 mm without considering their generations. In our study, however, we considered separately all third and fourth generations that we could measure. Moreover, advances in algorithms for measuring airways using CT occurred since these two previous studies providing us with a validated and robust tool for measuring airways.^{5,17}

Table 2. CT airway measurements and effect of gender

Measurements	Males						Females						Effect of gender <i>p</i> -value						
	Reader 1			Reader 2			Reader 3			Reader 1				Reader 2			Reader 3		
	Session 1		Session 2	Session 1		Session 2	Session 1		Session 2	Session 1		Session 2		Session 1		Session 2	Session 1		Session 2
	Session 1	Session 2	Session 1	Session 2	Session 1	Session 2	Session 1	Session 2	Session 1	Session 2	Session 1	Session 2		Session 1	Session 2	Session 1	Session 2	Session 1	Session 2
All measured airways																			
Number	12 ± 5	8 ± 4	17 ± 7	24 ± 8	11 ± 7	11 ± 7	11 ± 7	11 ± 7	12 ± 4	11 ± 3	20 ± 7	28 ± 6	14 ± 5	14 ± 5	4.46 ± 0.06	0.006			
√WAP10 (mm)	4.41 ± 0.1	4.42 ± 0.1	4.33 ± 0.23	4.21 ± 0.7	4.42 ± 0.08	4.41 ± 0.09	4.46 ± 0.15	4.47 ± 0.1	4.43 ± 0.14	4.42 ± 0.15	4.46 ± 0.07	4.46 ± 0.06	0.002						
Third-generation airways																			
Number	2 ± 2	1 ± 1	3 ± 2	4 ± 3	2 ± 2	2 ± 2	2 ± 2	2 ± 2	2 ± 2	2 ± 1	3 ± 2	5 ± 3	2 ± 2	2 ± 2	0.340				
LA ^{3rd} (mm ²)	12.4 ± 4.2	14.9 ± 6.5	14.1 ± 4.7	16.6 ± 5.1	15.3 ± 5.5	15.2 ± 5.2	11.4 ± 2.8	13.6 ± 4.5	14.6 ± 5.7	16.7 ± 5.2	15 ± 5	15.3 ± 4.8	0.833						
WT ^{3rd} (mm)	1.38 ± 0.08	1.41 ± 0.11	1.33 ± 0.08	1.32 ± 0.08	1.38 ± 0.04	1.37 ± 0.04	1.41 ± 0.08	1.41 ± 0.04	1.39 ± 0.08	1.36 ± 0.08	1.4 ± 0.04	1.4 ± 0.04	0.003						
WA% ^{3rd} (%)	65.8 ± 4.1	64.3 ± 4.9	63.3 ± 5	60.7 ± 4.4	63.1 ± 4.7	63.2 ± 4.8	67.4 ± 3.6	65.2 ± 4.1	64.3 ± 5.4	61.4 ± 3.9	63.8 ± 4.5	63.4 ± 4	0.444						
Fourth-generation airways																			
Number	10 ± 5	7 ± 3	14 ± 6	20 ± 6	9 ± 5	9 ± 5	10 ± 3	9 ± 3	17 ± 6	23 ± 5	12 ± 5	12 ± 5	0.003						
LA ^{4th} (mm ²)	8.4 ± 1.3	8.7 ± 1.4	9.9 ± 2.2	10.5 ± 1.9	9.8 ± 1.9	9.7 ± 1.9	8.7 ± 1.3	9 ± 1.4	10.3 ± 1.7	10.8 ± 2.1	10.4 ± 1.9	10.5 ± 2	0.193						
WT ^{4th} (mm)	1.36 ± 0.04	1.36 ± 0.04	1.34 ± 0.07	1.32 ± 0.05	1.36 ± 0.03	1.36 ± 0.03	1.39 ± 0.04	1.38 ± 0.04	1.38 ± 0.06	1.36 ± 0.06	1.39 ± 0.03	1.39 ± 0.03	<0.001						
WA% ^{4th} (%)	70.5 ± 1.9	70.1 ± 2.2	68.4 ± 2.3	67 ± 2	68.8 ± 2.5	68.9 ± 2.5	70.8 ± 1.9	70.1 ± 2.2	68.4 ± 2	67.4 ± 2.3	68.6 ± 2.1	68.4 ± 2.2	0.982						

√WAP10, square root of wall area at an internal perimeter of 10 mm; LA, luminal area; WA%, percentage of total airway area occupied by the wall; WT, wall thickness. Data are mean ± standard deviation of the mean.

Figure 2. Bland-Altman plot shows the total lung capacity (TLC) measured using CT (TLC_{CT}); TLC measured in seated position (TLC_{pleth}) as a function of the mean between the two values. The solid and dashed lines represent the mean difference and the 95% confidence intervals of the differences, respectively.

Our study also provides CT airway measurements obtained in healthy young adults from both genders. These measurements could complete those reported by Washko et al²³ who considered third- and fourth-generation airways in the apical segment of the right upper lobe and in the posterior-basal segment of the right lower lobe, in a relatively wide range of age group of never-smoking subjects aged over 60 years. Nevertheless, further studies are still required to determine normal values of CT airway measurements at various ages and in both genders, as

objective assessment of airway wall thickening requires such values.²⁴

To our knowledge, there is no previous well established study reporting the relations between CT airway measurements, TLC_{CT} and height in healthy young adults, the relations between TLC_{pleth} and height and between TLC_{pleth} and TLC_{CT} being well known.^{20,25} Including only young adults within a narrow range of age, it is likely that our trial minimizes the influence of other factors, such as age or previous respiratory diseases, that could impact airway measurements. With this design, our study reveals the negative correlation between WT and height in females. Interestingly, Walsdorff et al⁹ reported a correlation between CT densitometry indexes (*i.e.* the relative area of lung with attenuation coefficients lower than -960 HU and the first percentile of the distribution of attenuation coefficients) with height in females but not in males. In addition, these authors reported that CT densitometry indexes are correlated with TLC_{CT} in both genders, whereas our study shows no significant correlation between TLC_{CT} and any CT airway measurements.⁹ Practically, our study suggests thus that WT measured at CT should be adjusted for gender and height in females but not in males. This adjustment could be clinically significant as CT airway measurements play a major role in several chronic obstructive pulmonary disease phenotypes and asthma phenotypes that were recently proposed and that are related with clinically meaningful findings.²⁶⁻³⁰ We suggest that this adjustment could be achieved by applying a correcting formula to CT airway measurements obtained in a particular patient or by comparing these measurements with predicted values. As expected, the vast majority of the results of the PFT expressed in absolute values were different between genders, whereas they were not significantly different when expressed as percentage of predicted values.

Figure 3. Graphs show the individual values of the wall thickness in the third-generation airways (WT^{3rd}) as a function of height (all six measurements sessions), respectively, in males and females. Solid lines represent the regression lines and 95% prediction intervals.

Figure 4. Graphs show the individual values of the wall thickness in fourth generation airways (WT^{4th}) as a function of height (all six measurements sessions), respectively in males and females. Solid lines represent the regression lines and 95% prediction intervals.

Our study has limitations. First, we only used images acquired on scanners from a single manufacturer, and we performed CT airway measurements by using one dedicated software. Second, we considered only the third- and fourth-generation airways as this software has been previously validated using minimal dimensions similar to those found in the fourth-generation airways.¹⁷ In addition, this software does not provide measurements of every third- and fourth-generation airway in each subject, as some measurements were simply impossible to obtain or some contouring of the airways visually unacceptable. Therefore, this trial should be extended by using scanners from various manufacturers and various software. Third, we only considered the correlations significant for each of the six measurement sessions in order to

warrant no reader effect. We adopted this conservative approach in order to strengthen our observations and report actual relations. Fourth, as our sample size is relatively small, our study should be considered as an initial exploration. Studies with larger sample sizes should be conducted in order to complete our results.

In conclusion, $\sqrt{WAPi10}$, WT^{3rd} and WT^{4th} are different between males and females. WT^{3rd} and WT^{4th} are correlated with height in females only but not with TLC or in males. The CT airway measurements that may be used in the work-up of various diseases such as asthma, chronic obstructive pulmonary disease and cystic fibrosis should thus be adjusted according to gender and to height in females.

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