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FULL PAPER

Effect of total lung capacity and gender on CT densitometry indexes

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

Methods: In this ethics committee-approved prospective study, 100 healthy non-smoking volunteers who provided written informed consent were included. From a helical scan of the chest, the relative area (RA) of the lung with attenuation coefficients lower than -960 HU and the 1st and 15th percentiles of the distribution of attenuation coefficients were calculated. Regression lines were drawn between each CT index and volunteers' height and total TLC at CT.

Results: In males, there was no statistically significant correlation between any CT index and height. In females, there was a statistically significant correlation between the RA of the lung with attenuation coefficients lower

than -960 HU and the 1st percentile and height but not with the 15th percentile. For both genders, there were significant correlations between all CT indexes and TLC. The relationships between CT indexes and TLC were different in males and females.

Conclusion: CT indexes are correlated with TLC and height but more closely with TLC than with height, and differently in males and females.

Advances in knowledge: CT indexes are influenced by TLC, gender and height in normal individuals and are more closely correlated with TLC than with height. The relationships between CT indexes and TLC or height are different in males and females. CT indexes used to quantify emphysema should thus be adjusted according to TLC and gender.

INTRODUCTION

Pulmonary emphysema is defined as a condition of the lung characterized by abnormal, permanent enlargement of airspaces distal to the terminal bronchioles accompanied by destruction of their walls, without obvious fibrosis.¹ Using CT, emphysema is associated with a shift of the frequency distribution curve of attenuation coefficients towards negative numbers.² Percentiles of this distribution and relative areas (RAs) of the lung occupied by attenuation coefficients lower than certain thresholds reflect this shift and therefore enable objective quantification of the extent of emphysema.²⁻¹⁰ Such an objective approach has been reported to be more accurate and reproducible than visual assessment but is influenced by lung volume.^{11,12} In a small group of normal subjects, Madani et al¹⁰ have shown that these CT densitometry indexes are indeed linked to total lung capacity (TLC), which in normal individuals is influenced by gender and height¹³ raising the hypothesis that CT densitometry indexes could be also influenced by them. If this hypothesis was to be true, CT densitometry indexes used in clinical practice should be interpreted taking the subject's TLC and gender into account. The

purpose of the present study, therefore, was to explore the possible relationships between height and CT densitometry indexes in a large group of normal individuals of both genders.

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 study, we recruited 100 healthy never-smoking volunteers without any history of cardiopulmonary disease, aged from 18 to 26 years [49 males; mean age, 21 years $\pm$ 2 (standard deviation) and 51 females; mean age, 20 years $\pm$ 2].

CT

CT scans were obtained by using commercially available multidetector row CT scanners (Somatom® Sensation 16 and 64; Siemens Healthcare; formerly Siemens Medical Solutions, Forchheim, Germany). The CT scanners were calibrated periodically and always after major maintenance work. Volunteers 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 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 (including the costophrenic sulci) 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,¹⁴ effective tube current–time product corresponds to the tube current–time product divided by the pitch, whereby pitch is defined by Silverman et al¹⁵ 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. The volume CT dose index averaged $1.27 \text{ mGy} \pm 0.18$ and ranged from 0.98 to 1.70 mGy . The dose–length product averaged $47 \text{ mGy cm} \pm 9$ and ranged from 32 to 69 mGy cm . The effective dose was calculated considering

a conversion factor of $0.015 \text{ mSv mGy}^{-1} \text{ cm}^{-1}$ and averaged 0.7 mSv .¹⁶

From the raw data, 1-mm-thick sections were reconstructed with a soft-tissue kernel (B20f smooth; Siemens Medical Solutions) at 10-mm intervals. This interval was considered because it has been commonly used in CT studies quantifying diffusely distributed lung diseases including pulmonary emphysema.^{5,6,9,17} Attenuation coefficients of each lung CT section were measured by using the Pulmo CT program (Siemens Medical Solutions), which automatically recognizes the lungs and traces lung contours. The RA of the lung with attenuation coefficients lower than -960 HU (RA_{960}) and the 1st and 15th percentiles of the distribution of attenuation coefficients were calculated for both lungs. We restricted our computations to these three indexes, as they have been recommended as the most appropriate to quantify pulmonary emphysema.^{9,18} In addition, the Pulmo CT program was used to calculate the TLC for each subject based on the surface covered by lung parenchyma on each slice and slice interval.¹⁹ As TLC was also measured using the plethysmography (see 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 examinations, pulmonary function tests were performed with the patient seated. Vital capacity

Table 1. Summary of pulmonary function data

Pulmonary function tests	Male	Female	<i>p</i> -value
Vital capacity (l)	5.4 ± 0.8 (4.2–7.1)	3.7 ± 0.6 (2.2–5.1)	<0.001
Vital capacity (%)	94 ± 11 (76–121)	94 ± 11 (71–118)	0.959
Total lung capacity (l)	7.6 ± 1.2 (5.7–10.2)	5.6 ± 1.0 (2.9–7.8)	<0.001
Total lung capacity (%)	104 ± 13 (80–132)	106 ± 16 (71–146)	0.416
Functional residual capacity (l)	4.3 ± 0.9 (2.3–6.0)	3.2 ± 0.8 (1.7–5.0)	<0.001
Functional residual capacity (%)	128 ± 25 (75–176)	119 ± 27 (60–180)	0.074
Residual volume (l)	2.2 ± 0.8 (0.9–4.3)	1.8 ± 0.7 (0.7–3.6)	0.012
Residual volume (%)	139 ± 45 (58–264)	136 ± 53 (59–258)	0.745
Forced expiratory volume in 1 s (l)	4.6 ± 0.6 (3.3–6.7)	3.3 ± 0.5 (2.0–4.5)	<0.001
Forced expiratory volume in 1 s (%)	100 ± 12 (75–138)	95 ± 11 (68–115)	0.063
Forced expiratory volume in 1 s/vital capacity	86.1 ± 7.1 (68.9–98.2)	89.5 ± 5.8 (74.9–100.0)	0.011
Forced expiratory volume in 1 s/vital capacity (%)	103 ± 8 (83–117)	105 ± 7 (87–117)	0.225
Diffusing capacity of carbon monoxide ($\text{ml min}^{-1} \text{ mmHg}^{-1}$)	39.2 ± 7.2 (26.8–58.1)	26.5 ± 5.8 (13.5–44.5)	<0.001
Diffusing capacity of carbon monoxide (%)	104 ± 17 (69–155)	89 ± 17 (55–142)	0.004
Diffusing capacity of carbon monoxide/effective alveolar volume ($\text{ml min}^{-1} \text{ mmHg}^{-1} \text{ l}^{-1}$)	5.7 ± 0.7 (4.3–7.7)	5.3 ± 0.8 (3.1–6.7)	0.150
Diffusing capacity of carbon monoxide/effective alveolar volume (%)	86 ± 11 (65–116)	82 ± 12 (48–103)	0.360

Data are mean $\pm$ standard deviation.

Data in parentheses are the range.

Pulmonary function data are expressed in absolute values and as percentages of predicted values established by the European Respiratory Society.^{13,19}

Total lung capacity was measured by plethysmography.

p-value: statistical significance of men–women difference.

(VC), forced VC and forced expired volume in 1 s were measured using a spirometer while functional residual capacity was measured by using a constant-volume body plethysmograph (Zan; Oberthulba, Würzburg, Germany). TLC and residual volume were calculated by using the values of functional residual capacity and the subdivisions of VC. As TLC was also measured at CT, TLC measured using plethysmography is abbreviated TLC_{pleth}. The effective alveolar volume and the diffusing capacity of the lung for carbon monoxide were measured by using the single-breath method (Zan). The measured values were then compared with the predicted values established by the European Respiratory Society.^{13,20}

Statistical analyses

In all analyses, data from males and females were evaluated separately and compared.

Normality of height, TLC_{CT} and CT indexes (RA₉₆₀ as well as the 1st and 15th percentiles of the distribution of attenuation coefficients) were assessed using the Lilliefors adaptation of the Kolgonorov–Smirnov test.

Posture dependence of total lung capacity

A comparison was performed between TLC measured in the sitting position (TLC_{pleth}) and TLC_{CT} measured in the supine position, using a correlation and a Bland–Altman analysis.

Prediction equations

A linear regression was performed to test the effect of either height or TLC_{CT} on each CT index ($y = bx + a$, where y is any CT index and x either height or TLC_{CT}). The accuracy of the linear model was tested by using the Lilliefors adaptation of the Kolgonorov–Smirnov test to assess the normality of the distribution of residuals. To test the homoscedasticity of the residual variance, the Breusch–Pagan test was utilized.

Figure 1. Bland–Altman plot shows TLC measured at CT (TLC_{CT})–TLC measured in the sitting position (TLC_{pleth}) as a function of the mean between the two values. (The solid line is the mean difference and the dashed lines delimit the 95% confidence interval of the differences.) The solid and dashed lines represent the mean difference and the 95% confidence intervals of the differences, respectively.

Table 2. CT densitometry indexes and their correlations with height and TLC measured at CT (TLC_{CT})

CT Indexes	Males				Females			
		Height		TLC _{CT}		Height		TLC _{CT}
		<i>r</i>	<i>p</i> -value			<i>r</i>	<i>p</i> -value	
RA ₉₆₀ (%)		0.022	0.879	0.462	0.001	0.321	0.022	0.699
1st Percentile (HU)		0.001	0.995	0.401	0.004	0.219	0.122	0.690
15th Percentile (HU)		0.053	0.718	0.396	0.005	0.277	0.049	0.746

r, Pearson correlation coefficient; RA₉₆₀, the relative area of the lung with attenuation coefficients lower than −960 HU.

Data are mean ± standard deviation.

Data in parentheses are the range.

p-value: statistical significance of *r* compared with zero.

Figure 2. Graph shows the individual values of the relative area of the lung with attenuation coefficients lower than -960 HU (RA_{960}) as a function of height in males (open circles) and females (closed circles). Dashed and solid lines represent the regression lines and 95% prediction intervals for males and females, respectively. The boxed text gives the p -values of the slope (S) difference and of the residual variance (RV) difference. The RV in males (M) is greater than the RV in females (W).

Gender comparison

For each CT index, and with either height or TLC_{CT} as the independent variable, the slopes of regressions and residual variances were compared by a test of homogeneity of slopes and an F -test, respectively.

Figure 3. Graph shows the individual values of 1st percentile as a function of height in males (open circles and dashed lines) and in females (closed circles and solid lines). Dashed and solid lines represent the regression lines and 95% prediction intervals for males and females, respectively. The boxed text gives the p -values of the slope (S) difference and of the residual variance (RV) difference. The RV in females (W) is greater than the RV in males (M).

Figure 4. Graph shows the individual values of 15th percentile as a function of height in males (open circles and dashed lines) and in females (closed circles and solid lines). Dashed and solid lines represent the regression lines and 95% prediction intervals for males and females, respectively. The boxed text gives the p -values of the slope (S) difference and of the residual variance (RV) difference. The RV in females (W) is greater than the RV in males (M).

Statistical significance was defined as a p -value of <0.05 . The statistical software used in this study was Statistica v. 6.0 (StatSoft France; Maisons-Alfort, France).

Figure 5. Graph shows the individual values of the relative area of the lung with attenuation coefficients lower than -960 HU (RA_{960}) as a function of TLC measured at CT (TLC_{CT}) in males (open circles and dashed lines) and in females (closed circles and solid lines). Dashed and solid lines represent the regression lines and 95% prediction intervals for males and females, respectively. The boxed text gives the p -values of the slope (S) difference and of the residual variances (RV) difference. The RV in males (M) is greater than the RV in females (W).

Figure 6. Graph shows the individual values of 1st percentile as a function of TLC measured at CT (TLC_{CT}) in males (open circles and dashed lines) and in females (closed circles and solid lines). Dashed and solid lines represent the regression lines and 95% prediction intervals for males and females, respectively. The boxed text gives the p -values of the slope (S) difference and of the residual variances (RV) difference. The slope in males (M) is greater than the slope in females (W).

RESULTS

Pulmonary function data are summarized and compared between genders in Table 1. All variables were seen to have a normal distribution (p ranging from 0.127 to 0.756).

Posture dependence of total lung capacity

A strong correlation was found between TLCs measured in the sitting and supine positions ($r = 0.864$, $p < 0.001$). The Bland–Altman plot (Figure 1) showed that TLC_{CT} is, in average, 14% smaller than TLC_{pleth} .

Regression analyses

Residual distributions were normal for all regression analyses (p ranging from 0.079 to 0.731). All regression analyses met the condition of residual variance homoscedasticity (p ranging from 0.104 to 0.953). The RA_{960} and 1st and 15th percentiles (and their correlations with height and TLC_{CT}) for males and females are shown in Table 2 and illustrated in Figures 2–7. Slopes and ordinates at the origin of the linear regression lines, and the corresponding residual standard deviations are listed in Table 3.

Gender comparison

With height as the independent variable, regression slopes did not significantly differ for any indices (RA_{960} : $p = 0.201$; 1st percentile: $p = 0.120$; 15th percentile: $p = 0.081$), whereas the residual variances did (RA_{960} : males > females, $p = 0.004$; 1st percentile: females > males, $p = 0.011$; 15th percentile: females > males, $p = 0.008$). With TLC_{CT} as the independent variable, regression slopes differed for the 1st percentile (males > females, $p = 0.002$) and the 15th percentile (males > females, $p < 0.001$), but not for the RA_{960} ($p = 0.658$), whereas residual variances differed for the RA_{960} (males > females,

$p < 0.001$) but not for the 1st percentile ($p = 0.168$) or the 15th percentile ($p = 0.326$).

Given that slope differences or heteroscedasticity preclude the use of an analysis of covariance, we performed a gender comparison by an unpaired t -test (taking heteroscedasticity into account) in the subgroups overlapping in terms of height or TLC_{CT} , i.e. between 170 and 180 cm of height ($n = 23$ for males, $n = 21$ for females) and between 5 and 7 l of TLC_{CT} ($n = 31$ for males, $n = 21$ for females). In the 170–180 cm of height interval, all CT indexes differed [$p = 0.004$ (males > females) for the RA_{960} ; $p = 0.006$ (females > males) for the 1st percentile; and $p = 0.006$ (females > males) for the 15th percentile]. In the 5–7 l TLC_{CT} interval, no gender differences were observed ($p = 0.180$, $p = 0.506$ and $p = 0.428$, for the RA_{960} , the 1st and the 15th percentiles, respectively).

DISCUSSION

Our results show that in normal individuals, (a) CT indexes are correlated with TLC_{CT} ; (b) CT indexes are more closely correlated with TLC_{CT} than with height; and (c) the relationships between CT indexes and TLC_{CT} are different in males than in females. This study is important as it shows that CT densitometry indexes should be interpreted taking the subject's TLC_{CT} and gender into account. It also suggests that normal values, if they were to be established, should take height and gender into account as for the pulmonary function test.¹³

An effect of TLC (expressed in absolute value; litres) measured with CT was evidenced for all CT indexes—as TLC increases,

Figure 7. Graph shows the individual values of 15th percentile as a function of TLC measured at CT (TLC_{CT}) in males (open circles and dashed lines) and in females (closed circles and solid lines). Dashed and solid lines represent the regression lines and 95% prediction intervals for males and females, respectively. The boxed text gives the p -values of the slope (S) difference and of the residual variances (RV) difference. The slope in males (M) is greater than the slope in females (W).

Table 3. Regression coefficients and residual standard deviations of relative areas of the lung occupied by attenuation values lower than -960 HU, 1st percentile and 15th percentile vs height and TLC measured at CT (TLC_{CT})

CT Indexes	Males						Females					
	Height			TLC _{CT}			Height			TLC _{CT}		
	<i>b</i>	<i>a</i>	RSD	<i>b</i>	<i>a</i>	RSD	<i>b</i>	<i>a</i>	RSD	<i>b</i>	<i>a</i>	RSD
RA ₉₆₀	−0.004	7.455	3.537	1.823	−5.415	3.136	0.115	−15.791	2.408	2.087	−6.324	1.817
1st percentile	0.002	−989.342	11.067	−4.955	−955.962	10.135	−0.648	−866.586	15.405	−13.024	−913.543	11.630
15th Percentile	0.103	−957.170	12.270	−5.421	−902.448	11.283	−0.709	−804.615	17.343	−15.802	−848.722	12.032

a, ordinate at the origin; *b*, regression slope; RA₉₆₀, the relative area of the lung with attenuation coefficients lower than -960 HU; RSD, residual standard deviation.

so does the RA₉₆₀, whereas percentiles decrease—confirming the findings previously reported by Gevenois et al¹² and Madani et al.¹⁰ This confirmation of the interaction between TLC and CT indexes reinforces the need of adjusting CT indexes to TLC measured concomitantly at CT according to a predictive equation appropriate for each index. Moreover, the increase in the RA₉₆₀ and decrease in percentiles in relation to TLC implies that lung attenuation decreases with lung size.

CT indexes are more closely correlated with TLC_{CT} than with height. Although TLC measured with CT is correlated with that measured by plethysmography (which itself is correlated with height), stepwise increases in variance from one correlation to another results in weaker correlations between CT indexes and height than between CT indexes and TLC measured with CT.^{13,21} The difference of 14% found between TLC in the sitting and supine positions is compatible with previously described change in functional residual capacity and in VC.^{22,23} Measuring TLC with CT has the major advantage of using the same supine position as is used when calculating CT indexes vs the seated position used at plethysmography. CT indexes should, therefore, be adjusted for TLC measured with CT rather than for height.

The relationship between CT indexes and TLC_{CT} are different in males and females.

Regardless of their height, the RA₉₆₀ is always higher in males than in females.

Conversely, percentiles are always lower in males than in females. This suggests that for any given height, males and females have different lung structures, reflected by the difference in TLC.¹³ Therefore, considering height, normal CT index values should take gender into account. Considering TLC, where TLC_{CT} values were overlapping, no gender differences were observed. However, residual variances or slopes differed between genders so that, practically, CT indexes measured in a particular patient should be adjusted to his/her TLC measured at CT, and this adjustment should be different in males and females according to different predictive equations.

Our study does have certain limitations. First, we only used CT scanners from a single manufacturer, a constant effective current–time product and slice thickness, and one reconstruction algorithm. Since all of these parameters influence CT indexes, our study protocol should be extended to evaluate various radiation doses, slice thicknesses, reconstruction algorithms and machines from other manufacturers.^{24,25} Second, we only considered a narrow range of age of young adults. This was decided because age influences lung compliance—and therefore possibly TLC—as well as CT indexes.^{12,26} It would be prudent, therefore, to extend our study protocol to other ages. Third, we based our CT measurements on 1-mm-thick sections reconstructed at 10-mm intervals, whereas volumetric approaches are now available preventing sampling errors. Nevertheless, as we

considered only normal volunteers, there is no reason to believe that their lung attenuation would have not been homogeneously distributed. In addition, the aim of our study was not to obtain precise measurements of TLC but to investigate the effect of TLC on CT densitometry indexes. Multidetector CT scanners are now widely available and are able to scan the entire thorax in one breath-hold lasting few seconds. Fourth, we did not consider spirometrically gated acquisition. Nevertheless, it has been showed by Gierada et al²⁷ that spirometrically controlling lung volumes does not improve the repeatability of quantitative CT

scanning in assessing the amount of emphysema. Consequently, spirometrically gated acquisition has not been recommended by a panel of experts convened by the Alpha-1 Foundation¹⁸ and was thus not used in this study.

CONCLUSION

As CT indexes and TLC_{CT} are closely related in normal individuals, CT indexes used for quantifying pulmonary emphysema should be adjusted for TLC_{CT} according to gender.

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