Age and Sex Dependence of Forced Expiratory Central Airway Collapse in Healthy Volunteers

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Background: A recent estimate for the normal range of forced expiratory tracheal collapse differs substantially from that in an earlier study performed with comparable measurement methods. Given differences in subject characteristics between the two samples, we hypothesized that these discrepant findings may reflect a heretofore unrecognized association between forced expiratory tracheal collapse and age or sex.

Methods: We enrolled 40 female and 41 male healthy volunteers between 25 and 75 years of age who were without respiratory symptoms or known risk factors for tracheomalacia. Subjects underwent low-dose CT scanning at total lung capacity (TLC) and during forced exhalation (Expdyn) with spirometric monitoring and coaching. Percentage forced expiratory collapse was regressed on age for the total sample and separately within sex.

Results: Mean tracheal cross-sectional area (CSA) was $2.54 \text{ cm}^2 \pm 0.57 \text{ cm}^2$ at TLC and $1.15 \text{ cm}^2 \pm 0.53 \text{ cm}^2$ at Expdyn. Mean percentage forced expiratory collapse (%collapse) was $54\% \pm 20\%$. Men aged 24 to 31 years ($n = 12$) had mean %collapse of $36\% \pm 19\%$, comparable to results previously reported for similarly aged men ($35\% \pm 18\%$). Men, but not women, showed a significant positive correlation ($R^2 = 0.40$, $P < .001$) between %collapse and age. Older men had both greater CSA at TLC ($P = .02$) and smaller CSA at Expdyn ($P = .001$) than younger men.

Conclusions: Men exhibit positive age dependence of forced expiratory tracheal collapse. The influence of age and sex on forced expiratory tracheal collapse should be considered in the diagnostic evaluation of expiratory dynamic airway collapse and/or tracheomalacia.

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Abbreviations: CSA = cross-sectional area; Expdyn = forced (dynamic) expiratory; %collapse = percentage forced expiratory collapse; PFT = pulmonary function test; TLC = total lung capacity

Although much is known about changes in lung dimensions during various respiratory maneuvers, there is relatively little data regarding the normal range of forced expiratory airway collapse.^{1,2} With growing interest in the use of CT scanning to evaluate forced

expiratory collapse of the trachea in patients with suspected tracheomalacia,³ there is a need to determine whether a single threshold of percentage forced expiratory collapse (%collapse) can be applied in the diagnostic evaluation of this disorder.

Stern et al,¹ in a study of 10 healthy young men aged 24 to 31 years, reported a mean 35% forced expiratory collapse of the intrathoracic trachea. In contrast, we recently reported on a sample of 51 healthy men and women aged 25 to 75 years with an approximate 55% average forced expiratory collapse of the intrathoracic trachea.² We wondered whether this

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disparity might reflect age or sex differences in the tendency for forced expiratory collapse of central airways. Therefore, we recruited additional healthy subjects in order to attain a sample of sufficient size to determine whether expiratory central airway collapse is influenced by age and sex.

MATERIALS AND METHODS

Study Population

From February 2008 through September 2008, we prospectively enrolled 51 healthy adults in a study designed to assess the normal range of forced expiratory tracheal collapse.² To increase the sample size for regression of forced expiratory tracheal collapse on age within sex, an additional 30 subjects were enrolled between January 2011 and August 2011. Volunteers ranged in age from 25 to 75 years and were lifetime nonsmokers without respiratory symptoms or known respiratory disease. Exclusion criteria were pregnancy, known risk factors for tracheomalacia, including prolonged intubation, mediastinal radiation therapy, tracheal surgery, or relapsing polychondritis. Enrolled subjects underwent spirometry in our hospital pulmonary function testing (PFT) laboratory using American Thoracic Society guidelines.⁴ Participants with abnormal spirometry results were excluded from further study.

A total of 91 participants were enrolled in the study. Six were excluded on the basis of abnormal spirometry, three were excluded because they were unable to perform acceptably reproducible forced expiratory maneuvers, and one was excluded following incidental detection of a benign tracheal condition.⁵ The final study cohort comprised 81 participants, including the initial sample of 51 volunteers reported in our recent publication on global tracheal parameters which did not include analysis by age and sex.² During 2008 recruitment, 91% of enrolled subjects completed the study as compared with 86% of subjects enrolled during 2011. All subjects provided written informed consent under a protocol approved by the institutional review board of the Beth Israel Deaconess, where all research was performed (protocol no. 2007P-000348).

CT Imaging Breathing Maneuvers

Participants underwent CT imaging of the central airways during breath hold at total lung capacity (TLC) and during a forced expiratory maneuver (dynamic expiratory or Expdyn). A respiratory physiologist (C. R. O.) was present to monitor CT imaging studies and coach participants during TLC and Expdyn phases of the examination. While on the CT scanning table, participants were instructed in breathing maneuvers following a script.⁶ For TLC imaging, they took a deep breath all the way in and held the breath for approximately 6 s during image acquisition. For Expdyn imaging, participants took a deep breath and then blew out with maximal effort during image acquisition. Participants practiced these maneuvers prior to actual CT scan examination while on the CT scanning table, breathing through a mouthpiece, and wearing nose clips. Subsequently, for the actual CT imaging during the separate TLC and Expdyn maneuvers, the physiologist placed the mouthpiece and nose clips on each participant, directly observed a spirometric tracing while instructing the participant, and signaled the CT scan operator when to acquire images during breath hold or forced exhalation. Following acquisition at TLC, and while still connected to the spirometer, subjects exhaled completely in order to generate a volume time trace used to verify adequate breath hold volume ($\geq 90\%$ of the largest FVC measured

in the PFT laboratory). During the Expdyn maneuvers, the spirometry trace was directly observed to assure acquisition during forceful exhalation. Any maneuver judged inadequate with respect to lung volume or forceful exhalation was immediately repeated. FEV₁ was determined from the spirometric tracing and compared with the FEV₁ measured during PFT as an index of adequate effort.

Imaging Technique

Participants were imaged according to a standard protocol with a 64-detector-row scanner (LightSpeed VCT; General Electric) using a validated low-dose technique⁷: 80 mA, 120 kVp, 0.625 mm detector collimation, 0.5 s gantry rotation time, and pitch of 1.375, resulting in a 5.5 cm length of coverage per gantry rotation. Initial scout topographic images were obtained to determine the area of coverage from 2 cm above the aortic arch to 2 cm below the carina. The total time for volumetric acquisition was approximately 1 s for the entire scan. Images were reconstructed at 2.5 mm thickness with 1.25-mm reconstruction intervals according to a bronchoscopically validated protocol.⁷⁻⁹

CT Imaging Analysis and Interpretation

Each scan was prospectively interpreted by an experienced thoracic radiologist (P. M. B.) using a Picture Archiving Communication System (Centricity 3.1; General Electric Medical Systems). TLC and Expdyn images of the trachea were assessed 1 cm above the aortic arch.^{10,11} This level was chosen to aid comparison with the prior study by Stern et al¹ and to avoid analyzing the tracheal lumen at the level of the aortic arch, where it could potentially be compressed or displaced by this structure.

Using a validated technique,^{7,8,11} the cross-sectional area (CSA) of the airway was obtained by hand-tracing the inner wall of the airway with an electronic tracing tool. The percentage expiratory luminal collapse was calculated by using the equation: % luminal collapse = $100 \times [1 - (\text{luminal area at dynamic expiration} / \text{luminal area at end-inspiration})]$.

Measurements of the trachea obtained 1 cm above the aortic arch were considered representative of the intrathoracic trachea based upon similarity of measurements in the upper and lower trachea in the subset of 51 healthy volunteers in our prior study.² In addition to performing measurements at this level, the entire imaged trachea was visually assessed on images obtained at TLC and Expdyn in order to ensure that there was not a localized segment in the trachea that demonstrated substantially greater collapse compared with the site of standardized measurement.

For each case, the radiologist carefully reviewed all thoracic structures within the field of view. There were no cases in which an occult mediastinal, hilar, or lung abnormality was identified that could potentially influence airway dynamics. However, there was one participant in whom tracheobronchopathia osteochondroplastica was incidentally detected at CT scan. Based upon this finding, this participant was excluded from the study.

Statistical Analysis

Descriptive data are reported as frequencies for nominal measures and as means and SDs for continuous variables. The relationship between age and airway luminal collapse, controlling for sex, was explored by linear regression and univariate analysis of variance. Given a significant cross-product term (interaction) for age by sex, regression of luminal collapse by age was performed separately within sex. Sex differences in airway diameters and CSA were compared within age groups (median split) by using the unpaired *t* test with ($\alpha = 0.05$). Analyses were performed using SPSS, version 12.0 (SPSS Inc).

RESULTS

Study Population

Descriptive characteristics of the study population, including age, height, weight, and spirometry results, are provided in Table 1. The final study population included 41 men and 40 women, with mean age of 47 ± 17 years. All subjects were able to perform satisfactory TLC and Expdyn maneuvers. Average FEV₁ during Expdyn was $94\% \pm 8\%$ of that reported by PFT. There was no significant difference in mean age, height, weight, or spirometry between the 51 subjects initially enrolled and the 30 subjects enrolled in 2011.

Tracheal Measurements

Across all participants, mean tracheal CSA decreased from $2.54 \text{ cm}^2 \pm 0.57 \text{ cm}^2$ at TLC to $1.15 \text{ cm}^2 \pm 0.53 \text{ cm}^2$ at Expdyn. The mean %collapse for all participants was $53\% \pm 20\%$. The mean %collapse was similar for men ($55\% \pm 23\%$) and women ($52\% \pm 17\%$) ($P = .48$).

Although the mean percentage luminal collapse for the entire study population is much higher than that reported by Stern et al,¹ results are similar when controlled for age and sex. Thus, among the 12 comparable subjects in our study (males aged 24-31), mean %collapse was $36\% \pm 19\%$; this approximates closely the $35\% \pm 18\%$ reported by Stern et al.¹

The relationship between %collapse and age is shown in Figure 1. Overall, there was a modest correlation between %collapse and age ($R^2 = 0.20$, $P < .001$). However, analysis of variance for %collapse by age and sex revealed a significant interaction ($F = 5.37$, $P = .023$) and analyses were, therefore, conducted separately within sex.

The relationship between %collapse and age is depicted separately by sex in Figure 2. Men (Fig 2A) showed a statistically significant positive correlation between %collapse and age ($R^2 = 0.40$, $P < .001$), whereas women (Fig 2B) showed no such tendency ($R^2 = 0.05$, $P = .17$). Figure 3 displays typical CT scan images at TLC and during Expdyn among younger and older men and women in the study population.

Results for tracheal cross section and %collapse are given by sex and age range in Table 2. Age is divided at the sample median age of 49 years, with mean $\pm$ SD

FIGURE 1. %Collapse as a function of age: all subjects. %collapse = percentage forced expiratory collapse.

of 32.2 ± 7.4 years for younger and 61.8 ± 7.2 years for older subjects. As reported in previous studies, men tended to have larger tracheal area at TLC compared with women.^{12,13} Older men had significantly greater tracheal collapse ($68\% \pm 16\%$) than older women ($55\% \pm 17\%$) ($P = .015$). Younger men also had a tendency for less tracheal collapse ($43\% \pm 21\%$) compared with younger women ($49\% \pm 17\%$, $P = .38$). While %collapse was significantly greater in older vs younger men ($P < .001$), there was no significant difference between older vs younger women ($P = .28$).

Comparing tracheal CSA by age range, older women had mean area measurements that were 14% ($P = .03$) greater at TLC than younger women, but no difference in CSA at Expdyn (0%, $P = .99$). In contrast, older men had 11% ($P = .02$) greater CSA at TLC and 40% ($P = .001$) less CSA during Expdyn than younger men.

There was no significant correlation between %collapse and either height or weight for the sample as a whole. Among men, there was a slight negative correlation of %collapse with height. However, this correlation was not significant when controlling for age. Presumably, this represents confounding related to a negative correlation of height with age.

DISCUSSION

In this analysis of data from an age-diverse cohort of 81 healthy volunteers, we have demonstrated age dependence of forced expiratory central airway collapse in men, but not in women. On average, compared with age-matched women, younger men demonstrated less collapse and older men showed more collapse. These results suggest that sex and age differences should be considered when assessing patients for suspected tracheomalacia. Differences between recently

Table 1—Descriptive Characteristics, Mean $\pm$ SD, of the Study Population

Characteristics	Women (n = 40)	Men (n = 41)
Age, y	48 ± 17 (median = 50)	47 ± 17 (median = 48)
Height, cm	163 ± 8	175 ± 8
Weight, kg	70 ± 16	82 ± 16
FEV ₁ , % predicted	105 ± 12	106 ± 12
FEV ₁ /FVC	80 ± 6	78 ± 6

FIGURE 2. A, Scatter plot of %collapse as a function of age: men. B, Scatter plot of %collapse as a function of age: women. See Figure 1 legend for expansion of abbreviations.

published results² and those of an earlier study¹ can thus be attributed to sample demographics.

With aging, men demonstrated significant changes in tracheal cross section at both TLC and during Expdyn. Compared with younger men, older men had an average 12% greater CSA at TLC and 40% smaller CSA during forced exhalation. Although there was no significant difference between sexes in the degree of collapse aggregated across the entire age range, this apparent sex similarity occurred because younger men have less tracheal collapse than younger women, while older men had more collapse than older women. Therefore, over the entire five-decade age range represented in the sample, sex disparity in %collapse averaged out to an insignificantly small difference.

These results for tracheal CSA at TLC are comparable to those obtained in vivo by other investigators.^{1,12-14} Across studies performed using conventional chest radiographs, tracheal CSA among men averaged 3.20 cm² compared with 2.92 cm² in the sample.^{13,14} Furthermore, Gibellino et al¹⁴ found that tracheal CSA was significantly greater among older (3.22 cm²) vs younger (2.81 cm²) men. Our results (CSA = 3.09 cm² in older and 2.77 cm² in younger men) validate their radiographic findings using the more accurate method of CT imaging. Across two previous studies with female subjects, average tracheal CSA at TLC was 2.36 cm² compared with 2.15 cm² in the sample.^{12,13}

In light of our findings, it is important to consider how normal age-related changes in lung or chest wall

FIGURE 3. Representative examples of tracheal CT scan images at TLC and Expdyn. A, 27-year-old man. B, 72-year-old man. C, 27-year-old woman. D, 70-year-old woman. Expdyn = forced (dynamic) expiratory; TLC = total lung capacity. See Figure 1 legend for expansion of abbreviations.

Table 2—Tracheal Dimensions and Percent Collapse by Sex and Age Range

Sex	Age ^a	Trach Area TLC, cm ²	Trach Area Expdyn, cm ²	% Tracheal Collapse
Male	Younger (n = 21)	2.77 (0.38)	1.58 (0.65)	43.1 (21.2)
	Older (n = 20)	3.09 (0.46)	0.95 (0.41)	67.9 (16.4)
	All men	2.92 (0.45)	1.27 (0.63)	55.2 (22.6)
Female	Younger (n = 18)	2.00 (0.25)	1.02 (0.38)	48.7 (17.4)
	Older (n = 22)	2.28 (0.47)	1.02 (0.40)	54.8 (17.1)
	All women	2.16 (0.41)	1.02 (0.39)	52.0 (17.3)

Data are presented as No. (SD), unless otherwise indicated. Expdyn = forced (dynamic) expiratory; TLC = total lung capacity; Trach = tracheal.

^aAge is split at median value for entire population. Younger mean (SD) is 32.2 (7.4) years compared with older 61.8 (7.3) years.

characteristics may influence either airway expansion at TLC or dynamic compression of central airways during forced exhalation. Lung elastic recoil at a given volume is reduced with aging in both men and women.¹⁵⁻¹⁸ While this alone might result in smaller airway cross section at a given lung volume due to loss of tethering support from the lung parenchyma, Mead et al¹⁹ suggested that increases in the resting dimensions of airways with age might offset any tendency for reduced airway cross section related to decreased parenchymal tethering, thus preserving maximal expiratory flow. Indeed, Gibellino et al,¹⁴ using chest radiographs to study tracheal characteristics in a large sample of healthy men and women, found that age-associated increase in tracheal dimension at high lung volume is relatively greater than the corresponding loss of lung elastic recoil.

At any given age, men tend to have greater inspiratory and expiratory force generating capacity. Although maximal active chest wall pressures decrease with age in both sexes, normative aging studies show that maximum expiratory pressure is 30% to 50% greater among men compared with women throughout the normal adult age range.^{20,21} To the extent that older men can maintain greater pleural pressure throughout forced exhalation, one might expect greater compression of the downstream airway segment, including the trachea.

Men can also generate greater inspiratory pressures than women and, therefore, may be able to sustain greater tethering force on airways at TLC. In a study of healthy older subjects, Knudson¹⁶ found that static elastic lung recoil at TLC decreased considerably less in men than women. The static lung recoil achieved at TLC is limited by the chest wall, with static elastic lung recoil at TLC being equal to the maximum negative pleural pressure at that volume. Because the lung pressure-volume characteristic is relatively noncompliant near TLC, Knudson reasoned that the influence of this sex difference in maximum inspiratory pressure on the volume at TLC is likely to be modest. If, however, the central airways remain compliant at high lung volume, this difference in pleural pressure should tend to increase their cross section and might

explain, in part, the positive age dependence of tracheal CSA at TLC among men in the sample.

Our finding that older men have significantly greater tracheal CSA at TLC is consistent with the concurrent influences of age-associated change in central airway compliance and better preserved maximum inspiratory muscle strength among men compared with women. Correspondingly, increased central airway compliance, coupled with greater maximum expiratory muscle strength, may favor the tendency for greater forced expiratory collapse of the downstream segment among older men compared with older women.

We acknowledge primary limitations of this study. First, despite representing the largest CT imaging study of expiratory tracheal collapsibility among healthy volunteers to our knowledge, our results are still limited by a relatively small sample size of each sex and age range. The inclusion of only approximately 40 subjects within each sex limits the ability to generalize our results, even though the findings are robust within the sample. While we did not evaluate patients > 75 years of age, 20% of participants were 65 or older and likely representative of the age range of patients that might be referred for evaluation of tracheal collapsibility in clinical practice. Second, because the radiologist monitored the studies as they were being performed and interpreted the CT scans on the same date, it was not feasible to blind the radiologist to the sex of the patient. However, we have reported a high reliability of measurements among a subset of these same individuals with repeated testing over a 1-year interval, and there was no *a priori* hypothesis regarding sex differences in %collapse at the time the initial cohort was studied.²² Taken together, these two factors argue against inadvertent bias that may have resulted from a lack of blinding. Because we used a standardized method to measure airway cross section that has been previously validated with the gold standard of bronchoscopy, we do not believe that a second reviewer was necessary. Third, the study is limited by a lack of either direct respiratory pressure measurements or precise measurement of the forced expiratory volume at which images were obtained. While we sought to avoid even

minimally invasive testing among the healthy participants, esophageal manometry could provide more direct information regarding the uniformity of expiratory efforts, as well as information about the overall relationship between expiratory pressure and %collapse. Fourth, we imaged the trachea during the initial second of forced exhalation, a time interval that incorporates a large fraction of the total exhaled volume. Therefore, we cannot assess the precise volume at which expiratory measurements were made, or whether our measurements of airway cross section reflect the maximal degree of forced expiratory collapse. However, we emphasize that several non-invasive techniques were used to ensure maximal expiratory efforts, including: standardized respiratory instructions; practice maneuvers; direct observation; and spirometric monitoring. Furthermore, the entire imaged trachea was visually assessed on images obtained at TLC and Expdyn in order to ensure that there was not a localized segment in the trachea that demonstrated substantially greater collapse. As discussed here, we have reported a high reliability of measurements among a subset of these same individuals with repeated testing over a 1-year interval.²² Thus, it seems unlikely that our results were substantially biased due to effort or volume dependence of forced expiratory tracheal collapse.

In summary, we have shown that there is positive age dependence of forced expiratory central airway collapse in men, but not in women. These findings have potential relevance to the increasingly common application of multidetector CT scan to assess forced expiratory tracheal collapse in patients at risk for tracheomalacia.^{23,24} Just as sex and age influence the interpretation of pulmonary function tests, our results suggest that these same characteristics should be considered when assessing forced expiratory airway collapse for suspected tracheomalacia.

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Dr Loring: contributed to the planning of research, data analysis, and manuscript preparation.

Dr Boisselle: contributed to the planning and conduct of all research, data analysis, and manuscript preparation.

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