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Bronchoarterial ratio in non-smoking adults: Implications for bronchial dilation definition

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Summary at a glance

In 106 never-smoking adults the mean ratio of the diameters of the bronchial lumen and adjacent pulmonary artery, a defining radiologic feature of bronchiectasis, was 0.79, varied by airway generation and in 8.5% of them was >1. This metric was directly related with expiratory airflow regardless of body size.

ABSTRACT

Background and objective: Bronchiectasis manifests as recurrent respiratory infections and reduced lung function. Airway dilation, which is measured as the ratio of the diameters of the bronchial lumen (B) and adjacent pulmonary artery (A), is a defining radiologic feature of bronchiectasis. A challenge to equating the BA ratio to disease severity is that the diameters of airway and vessel in health are not established. We sought to explore the variability of BA ratio in never smokers without pulmonary disease and its associations with lung function.

Methods: Objective measurements of the BA ratio on volumetric CT scans and pulmonary function data were collected in 106 never smokers. The BA ratio was measured in the right upper lobe apical bronchus (RB1) and the right lower lobe basal posterior bronchus. The association between the BA ratio and forced expiratory volume in one second (FEV1) was assessed using regression analysis.

Results: The BA ratio was 0.79 ± 0.16 and was smaller in more peripheral RB1 bronchi ($P<0.0001$). The BA ratio was >1, a typical threshold for bronchiectasis, in 10 (8.5%) subjects. Subjects with a BA ratio >1 (vs. ≤1) had smaller artery diameters ($P<0.0001$) but not significantly larger bronchial lumens. After adjusting for age, sex, race, and height, the BA ratio was directly related to FEV1 ($P=0.0007$).

Conclusion: In never smokers, the BA ratio varies by airway generation and is associated with lung function. A BA ratio >1 is driven by small arteries. Using artery diameter as reference to define bronchial dilation seems inappropriate.

Clinical trial registration: NCT00608764 at ClinicalTrials.gov

Keywords: bronchoarterial ratio, bronchiectasis, non-smoking, volumetric CT, normal

Short title: Bronchoarterial ratio in never smokers

INTRODUCTION

Bronchiectasis is an important cause of morbidity in the US population with a hospitalization rate of 16.5 per 100,000 population and the burden of the disease is greater in older individuals.[1] The clinical manifestations of bronchiectasis include productive cough, recurrent infections, and lung function impairment.[2] The current gold standard to diagnose bronchiectasis is visual inspection on thoracic computed tomography (CT) scans.[2] A defining radiographic feature is an increased bronchial lumen diameter relative to the adjacent pulmonary artery diameter, the bronchoarterial (BA) ratio.[3, 4] A BA ratio greater than 1 is typically considered discriminatory for the presence of disease.[2] A challenge of the BA ratio is that there are scarce data on its variability in never smokers, and its potential association with lung function has not been extensively explored.

A few CT studies have provided data on the BA ratio in normal subjects with a mean ranging from 0.62 to 0.695.[5-8] Interpretability of these data are limited due to inconsistencies in the measurement techniques such as using the outer bronchial diameter instead of the inner luminal diameter to assess airway size. A second limitation was the lack of exploration of relationships between the bronchovascular structure and spirometric measures of lung function. Also sample sizes of non-

smoking subjects were small.[5-7] It is known that subjects with bronchiectasis have lung function impairment,[9-11] and thus exploring bronchovascular structure-lung function relationships in non-smoking subjects without clinical pulmonary disease might be relevant to understand whether intrinsic lung structure has implications for disease. Therefore we hypothesize that in never smokers the BA ratio is related to expiratory airflow. We also sought to explore the variability of this imaging metric in this population.

METHODS

Subject selection

We used data from a cohort of 108 never smokers enrolled into the chronic obstructive pulmonary disease (COPD) gene (COPDGene) Study (12March13 dataset).[12] Briefly, this study was designed to determine the genetic and epidemiological determinants of COPD in Non-Hispanic white and African-American smokers aged 45-80 years. The control population of COPDGene was recruited based on an eligibility questionnaire and pulmonary function data.[13] Participants were considered non-smoking controls if they responded No to the following

questions: “Have you ever smoked cigarettes?”, “Have you ever been told by a physician that you had a lung disease?”, and “Have you ever had lung surgery?” In addition, these subjects had to meet a ratio of forced expiratory volume in 1 second (FEV1) to forced vital capacity (FVC) of ≥0.7. Never–smoker controls were enrolled in different clinical sites across the US with the majority of them (N=68) in two centers (University of Iowa and Brigham and Women’s Hospital). The COPDGene study was approved by the institutional review board at each participating clinical center, and all subjects provided written informed consent. The Partners HealthCare Research Committee (2007P-000554) approved the current study.

Clinical and Physiologic Assessments

Demographic and clinical data with standardized questionnaires including a modified Adult Respiratory Questionnaire were collected.[12] Spirometric measures of lung function were performed before and after the administration of albuterol according to American Thoracic Society recommendations. Post-bronchodilator FEV_1 and FVC were used for analysis. The two latter spirometric measures of lung function were expressed as percent of predicted values.[14] Total lung capacity (TLC) was measured using CT scan.[15]

CT analysis

All subjects underwent volumetric CT scanning without intravenous contrast in the supine position at coached full inspiration and relaxed exhalation; analyses in this study focused on the inspiratory CT scans. Acquisition parameters were the following: 120 kVp, 200 mAs, and 0.5 rotation time. Images were reconstructed as follows: standard, B31f, and B kernel; 0.625, 0.75, and 0.90 mm slice thickness; and 0.625, 0.5, and 0.45 mm slice interval for General Electric Medical System, Siemens, and Philips scanners, respectively.[16] After segmenting the lung to exclude vessels and airways, CT lung volume was calculated by multiplying the voxel volume by the number of voxels. CT lung volume at maximal inflation approximates total lung capacity (TLC_{CT}). TLC_{CT} is expressed as % of predicted values.[17]

Bronchoarterial ratio measurements

A single trained-analyst, a laboratory technician, with 3 years of experience in lung imaging performed the BA ratio measurements on inspiratory CT scans using Slicer software (www.slicer.org). Workstation screen was set at window width of 1500 and window level -450.[6] CT measures of BA ratio were collected based on anatomic locations in two bronchial paths: in the right upper lobe apical bronchus

(RB1) and the right lower lobe basal posterior bronchus (RB10). We chose these bronchial paths because the airway branches are usually orthogonal to the axial plane, which facilitates accurate measurement in both bronchi and pulmonary artery branches.[18] We chose to perform manual, instead of automated measures, to compare with prior research in this area. The airway and pulmonary artery branches to be measured in a given generation were selected based on their rounded appearance on the axial plane. The analyst first identified RB1 and RB10 using all the three image planes as needed and then performed two measurements in the middle portion of one bronchial branch of the 4^{th}, 5^{th} and 6^{th} generations and its closest corresponding artery branch. For the purpose of this investigation, the first segment of RB1 and RB10 is designed as 3^{rd} airway generation. A ruler within Slicer was used to measure the airway lumen (inner edge to inner edge) and artery diameters at both the longest and shortest axes. Because a vein and artery close to an airway might look similar on non-contrast CT scans, the analyst distinguished them by tracing back the vessel to the central pulmonary artery. The BA ratios were computed using the diameters of both axes and averaged for each generation and bronchial path, and for both RB1 and RB10. This latter was used for correlative investigation. The analyst made a second set of above measurements in 20 randomly selected subjects to assess the intra-analyst reproducibility. A second

trained analyst took these measurements in the same 20 subjects to assess the inter-analyst reproducibility.

Statistical analysis

Measurements are presented as mean standard deviation. Unless otherwise noted, the "BA ratio" is referred as the mean BA ratio for RB1 and RB10. Intra- and inter-analyst reproducibility assessment of the BA ratio was performed using concordance correlation coefficient (CCC) and Bland-Altman analysis.[19, 20] Differences between subjects with the BA ratio >1 vs. <=1 were performed with Wilcoxon sum rank test. Differences in the BA ratio by airway generation and between RB1 and RB10 were tested with mixed models to account for within-subject correlation in these metrics. Univariate relationships between mean BA ratio and demographic data and spirometric measures of lung function were tested using Pearson correlation coefficients. Multivariable regression analysis was used to assess the association between FEV1 and the BA ratio. Age, sex, race, and a measure of body size, height, were used as covariates. These four covariates were chosen because they are the main determinants of expiratory airflow in normal subjects.[14] Analysis was performed with SAS 9.4 (SAS Institute, Cary, NC). A P value <0.05 was considered significant.

RESULTS

Subject characteristics

Among the 108 non-smoking subjects, two were excluded because they had interstitial lung abnormalities leaving a sample size of 106 subjects. Subjects' characteristics are shown in **Table 1**. Their mean age was 62 years and the majority were female (N=72) and non-Hispanic white (N=98). FEV1, FVC and TLC was 97% of predicted values or higher.

Intra- and inter-analyst reproducibility

The intra- and inter-analyst CCC for BA ratio was 0.80 (95% CI 0.63-0.98) and 0.77 (0.61-0.92), respectively. The Bland-Altman analysis showed no intra-analyst systematic bias across the range of BA ratio values (**Figure 1, Panel A**). The plot for the inter-analyst agreement shows a trend of increasing differences in BA ratio as the mean measure between readers increases (r=0.56, P=0.03) (**Figure 1, Panel B**).

BA measurements

The mean BA ratio was 0.79 ± 0.16 and varied by generation decreasing significantly in more peripheral airway generations (0.86 at 4th to 0.76 at 6th generation, P=0.0001) of RB1 (**Table 2**). This trend in BA ratio was not observed in RB10. In 10 (8.5%) subjects the BA ratio was >1, a usual cutoff point to define bronchiectasis. Subjects with a ratio >1 vs. ≤1 had higher FEV1 (3.2 ± 0.6 vs. 2.8 ± 0.7, P=0.049) with no differences in age (P=0.36) or height (P=0.59).

To explore the relative contribution of bronchial and vessel size to the BA ratio, we explored the differences in mean airway lumen and mean artery diameters between never smokers with the BA ratio >1 vs. ≤1. The difference between these two groups was greater and significant for the artery diameter (difference, 1 mm; P<0.0001) than for the bronchial lumen diameter (difference 0.35mm; P=0.09) (**Figure 2**).

Relationships between BA ratio, demographics, lung volume, and lung function

We found no significant associations between the BA ratio and either age (r=0.16, P=0.11) or height (r=0.07, P=0.43). The former result is in contrast with Matsuoka's[8] who observed a direct relationship between age and the BA ratio.

There was no difference in the BA ratio between men and women (0.82 vs. 0.78, P=0.26) and between Non-Hispanic whites and African-Americans (n=8) (0.80 vs. 0.79, P=0.91). We did not find statistical differences in BA ratio by scanner brands (P=0.48). In univariate analysis, the BA ratio was significantly associated with FVC (r=0.20, P=0.04) and TLC_{CT} (r=0.23, P=0.02), and marginally significantly related to FEV1 (0.19, P=0.053). In multivariable models adjusted for age, sex, race, and height, the BA ratio became significantly associated with FEV1 (**Table 3**). Results were comparable for the relationships between FEV1 and the BA ratio at RB1 and RB10 levels (**Table 3**). To understand the relative contributions of the BA ratio (lumen or vascular diameter) to the relationship with the FEV1, additional correlative analysis was performed. The FEV1 was more strongly associated with mean bronchial lumen diameter (r=0.43, P<0.0001) than with mean pulmonary artery diameter (r=0.26, P=0.006)

DISCUSSION

We examined BA ratios on volumetric CT scans obtained from 106 never-smoking healthy subjects. We found that the mean BA ratio was 0.79, varied by bronchial generations, and was >1 in 10 subjects (8.5%). Subjects with the ratio >1 had smaller artery diameters but not significantly larger bronchial lumens than those with a BA ratio ≤1. Never-smoking subjects with a larger BA ratio had higher FEV1's in multivariable analysis.

In this study we found that in never-smoking subjects the BA ratio was directly related to expiratory airflow after adjustment for age, sex, race, and height. Assuming that this population represents adults with native lung structure, this novel finding suggests that bronchovascular anatomy contributes to expiratory airflow regardless of a subject's size. Our data indicates that airway lumen and caliber of the adjacent artery are associated with spirometric measures of lung function. Furthermore, bronchial lumen size was more strongly correlated with FEV1 than pulmonary arterial diameter. These findings support the concept of dysanaptic lung development where the bronchial tree and lung parenchyma develops somewhat independently.[21] This concept has been used to explain the observed variability in peak expiratory flow independent of lung size. The FEV1-BA

ratio relationship we observed is also keeping with prior data[13] demonstrating that normal subjects with the larger extra-parenchymal and intra-parenchymal bronchial lumen volumes have the higher expiratory flows independently of body size.

In this cohort, the mean BA ratio was 0.79 with 10 never-smoking subjects having a ratio >1. A novel finding was that when the ratio was >1 it was due to a smaller pulmonary artery rather than a larger airway. We believed that this might have implications in health and disease. First, normative data on objective measurements of both airway and vessel sizes are needed to understand their variability and how they relate each other. In the setting of disease, an increased BA ratio could imply an abnormality of the airway, vessel, or both. That is, we believe an increased BA ratio in disease might reflect a bronchovascular process rather than a bronchial abnormality alone. Another implication is that using vessel size as a reference for airway dilation might not be appropriate. Additionally, using a fixed ratio to define disease may also be inappropriate. This finding expands upon the work of Lynch et al[22] who documented that a visual BA ratio >1 was present in 36% of 142 bronchi from 27 control subjects and. Our results provide objective support that a BA ratio >1 may not suffice to diagnose bronchiectasis. In locations where the airways do not typically run orthogonal to the axial plane (e.g., middle lobe, lingula) other

radiographic features (e.g. lack of airway tapering) are useful to detect bronchiectasis.

Our mean BA ratio was larger than those ranging from 0.62 to 0.695 reported in prior CT studies on subjects without pulmonary disease.[5-8] A potential explanation for this difference is that our subjects were on average older. Matsuoka et al[8] documented in ≥65 years old subjects a BA ratio of 0.785, which is closer to ours. Additionally, differences in airway sampling methods (anatomic- vs. non-anatomic-based approaches) and populations (age and racial composition) across studies[5-8] may also contribute to these discrepancies. Variability of the BA ratio by RB1 airway generation was also observed by Kim SJ et al[7] but not in other studies.[5, 6] Further research including subjects with a wide age range and from varied racial groups is needed to investigate BA ratio variability as well as the potential clinical implications of this variation.

We did not find differences in BA ratio between sexes, a finding that is in agreement with a prior CT study.[8] There was no difference in this metric between non-Hispanic whites and African-Americans. However, the small sample of African-Americans in our cohort likely limits the ability to detect significant racial differences.

This study has several limitations. First, our study subjects are mainly Non-Hispanic white women limiting the generalizability of the current findings. Control subjects were chosen based on self-reported data and no medical records were used to verify this condition. Although we used only one analyst to perform the BA ratio measurements, our results were consistent with those reported previously.[8] We have used only cross-sectional data and thus causality of the observed relationship cannot be elucidated. We only surveyed RB1 and RB10 bronchial paths; however, we were able to capture variability of this metric between- and within-subjects, while ensuring accurate measurements on both bronchi and vessels. Some of the strengths of this study are its relative large sample size, use of volumetric CT scans allowing a detailed examination of the bronchovascular tree, and an anatomic-based selection of bronchi rather than a random airway selection, which could introduce bias.[23]

In summary, we have demonstrated that the mean BA ratio in non-smoking subjects without pulmonary disease is 0.79 with 8.5% of them having a ratio >1, a typical threshold for bronchiectasis. Interestingly, subjects with a BA ratio>1 had smaller vessel diameters but not larger bronchial lumens than those with BA ratio ≤1. The BA ratio was directly related to expiratory airflow regardless of body size. Further

investigation with larger samples of healthy individuals is required to obtain normative data in this defining imaging metric.

Acknowledgements

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Disclosure statement

AD has received speaker fees from Novartis Inc outside this work.

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Figure Legends

Figure 1 Bland-Altman plot of BA ratio. The plot shows the intra-analyst (Panel A) and inter-analyst (Panel B) agreements of BA ratio from 20 subjects.

Figure 2 Box plots of bronchial and pulmonary artery diameters in never-smoker subjects by BA ratio group. The plot shows the difference in airway lumen and artery diameters between those with BA ratio ≤1 and more than 1. Note that the artery diameter is smaller in never smokers with BA ratio >1 than those with the ratio ≤1.

Table 1 Characteristics of the 106 non-smoking subjects

Characteristic	Mean ± SD or %
Male sex (%)	32
Age (years)	62 ± 9
Non-Hispanic White race (%)	92
Height (cm)	167 ± 9
FEV_1 (L)	2.8 ± 0.7
FEV_1 (% predicted)	104 ± 14
FVC (L)	3.6 ± 0.9
FVC (% predicted)	99 ± 12
FEV_1/FVC ratio	0.80 ± 0.05
TLC_{CT} (L)	5.4 ± 1.2
TLC_{CT} (% predicted)	97 ± 12

Table 2 Bronchoarterial ratio in RB1 ad RB10

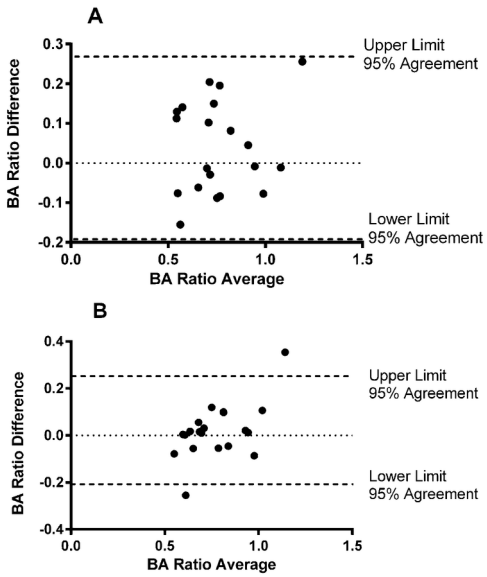
Characteristic	Mean ± SD
RB1 generation*	
4th	0.86 ± 0.27
5th	0.80 ± 0.20
6th	0.76 ± 0.23
Mean RB1	0.81 ± 0.20
RB10 generation&	
4th	0.79 ± 0.15
5th	0.79 ± 0.21
6th	0.76 ± 0.20
Mean RB10¶	0.78 ± 0.17
Mean RB1 and RB10	0.79 ± 0.16

*P trend =0.0001 by RB1 generation
&P trend= 0.14 by RB10 generation
¶ P = 0.17 between RB1 and RB10

Table 3 Multivariable model for FEV1 (in liters) using the BA ratio

Variable	Bronchial path					
	RB1 and RB10		RB1		RB10	
BA ratio	Estimate (SE)	P value	Estimate (SE)	P value	Estimate (SE)	P value
BA ratio	0.79 (0.23)	0.0007	0.54 (0.18)	0.003	0.58 (0.22)	0.0108
Age (per 10 years)	-0.28 (0.04)	<0.0001	-0.25 (0.04)	<.0001	-0.28 (0.04)	<.0001
Male Sex	0.67 (0.10)	<0.0001	0.69 (0.10)	<.0001	0.65 (0.10)	<.0001
Non-Hispanic White Race	0.35 (0.14)	0.01	0.30 (0.14)	0.03	0.38 (0.14)	0.0071
Height (per 10 cm)	0.32 (0.05)	<0.0001	0.31 (0.05)	<.0001	0.32 (0.05)	<.0001

SE, standard error.



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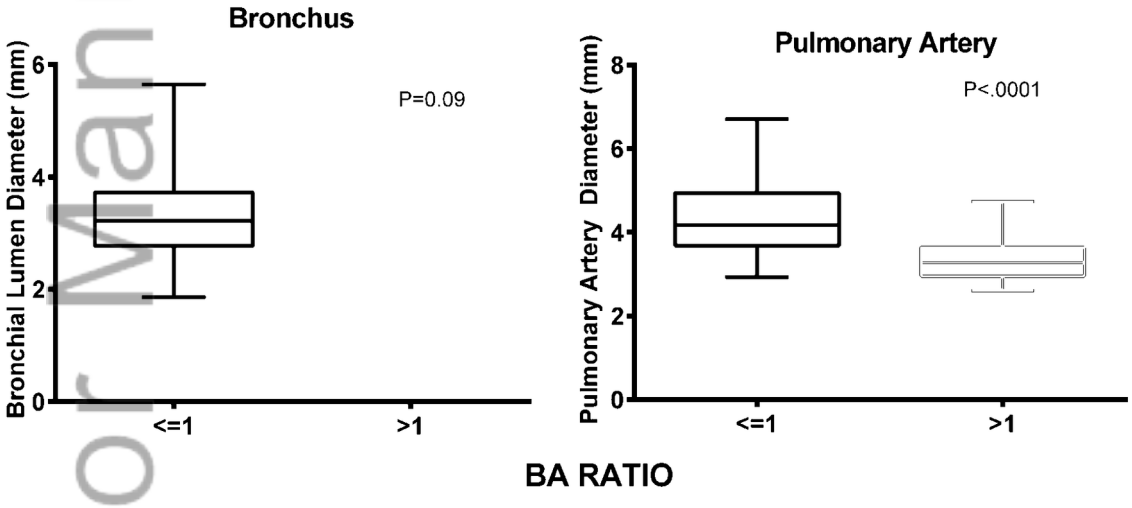

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