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Ratio of the Bronchial Lumen to Pulmonary Artery Diameter in Rhesus Macaques (*Macaca mulatta*) without Clinical Pulmonary Disease

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In human medicine, CT is widely used to detect changes in bronchial luminal diameter. The diameter of the artery that runs adjacent to the bronchus does not change dramatically along the airway path, such that this artery can be used as a reference to detect changes in the bronchial luminal diameter. The bronchoarterial ratio is increasingly used in veterinary medicine for the detection of lower airway diseases in animals. The purpose of this study was to establish the bronchoarterial ratio in rhesus macaques. We used CT to evaluate 12 rhesus macaques (*Macaca mulatta*) without clinical signs of pulmonary diseases and measured the bronchoarterial ratio in the right and left superior, middle, inferior and cardiac lung lobes. The overall bronchoarterial ratio (mean ± 1 SD) at all 7 locations in the 12 macaques was 0.59 ± 0.05. Moreover, there was no correlation between the BA ratio and age or sex in the study population. However, the BA ratio and weight of animals showed positive linear correlation. In this study, we established the reference range for the bronchoarterial ratio in clinically healthy rhesus macaques. This ratio is consistent among lung lobes and between animals.

Abbreviations: Ao, ascending aorta; MPA, main pulmonary artery

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One of the most common consequences of chronic airway diseases is the loss of bronchial wall integrity and consequent dilation of the bronchial wall lumen; this irreversible pathologic event is called bronchiectasis.[17] Other diseases that may alter the bronchial wall thickness and luminal diameter are bronchitis and bronchomalacia.[17] In bronchitis, an apparent narrowing of the bronchial lumen is evident, accompanied by bronchial wall thickening and oversecretion by the mucosa.[29] Bronchomalacia in dogs caused by weakened bronchial wall results in bronchial lumen narrowing.[27] In severe forms of bronchitis and bronchiectasis, radiography is the main diagnostic tool.[4] In conventional radiography of animals with bronchitis, 'doughnut rings' may be visible. In bronchiectasis, lack of terminal tapering of the bronchus and abnormal dilation of the luminal diameter may be seen.[10] In less severe forms of bronchitis and bronchiectasis, CT and bronchoscopy may be used for accurate diagnosis. The bronchoarterial ratio has been suggested as an appropriate index in the diagnosis of bronchiectasis in people.[9,22] The mean ratio is 0.62 in adult people.[13] In recent years, the bronchoarterial ratio has been used in veterinary medicine. A bronchoarterial ratio greater than 2 in dogs[2] and greater than 0.91 in cats[23] have been proposed as diagnostic of bronchiectasis. The aim of the current study was to establish an accurate bronchoarterial ratio criterion for rhesus macaques (*Macaca mulatta*) without clinical evidence of pulmonary involvement.

Materials and Methods

The study population comprised 12 clinically healthy rhesus macaques; due consideration was given to minimize the number of animals used. All the animals were kept at the Royan Research Institute (ACECR, Tehran, Iran) under the same standard living conditions; animals are housed one per cage and have free access to food and water.[24] We did all our experimental procedures in exact accordance with the ethical values of the NIH *Guide for the Care and Use of Laboratory Animals*.[8] We avoided any invasive and minimally invasive procedures such as fine-needle aspiration, biopsy, and bronchoalveolar lavage, to prevent any possible harm to animals.

Physical examination, CBC, full biochemistry profile, arterial blood gases, and thoracic radiographs (right and left lateral, anterior–posterior, and posterior–anterior views) were performed. Providing that all clinical, laboratory, and radiographic signs were normal, the macaques were entered into the study. To obtain CT scans, the rhesus macaques were intubated; general anesthesia was achieved through injection of medetomidine (0.05 mg/kg IM) and maintained through isoflurane inhalation (1% to 1.5%). To avoid step artifacts, a single breathhold technique was performed a maximum duration of 60 s. Thoracic CT was performed with macaques in supine position, with the head toward the gantry, by using a helical scanner (Somatom Spirit Series II CT scanner, Siemens, Berlin, Germany) at the animal veterinary hospital of the Tehran University.

Axial CT scan images were obtained at 130 KVp, 200 mA, pitch of 1, and slice thickness of 2 mm by using the Fast/Thorax algorithm. The technical parameters were the same for all macaques. This protocol was repeated immediately after intravenous injection of nonionic iodinated contrast (3 mL/kg; Iohexol, Omnipaque 240 I/mL, GE Healthcare, Little Chalfont, United Kingdom) through an automatic injector at the rate of 2 mL/s. All CT scan images were reconstructed to 1-mm slice thickness as sagittal and coronal planes in a pulmonary window (window width, –500; window level, +1400) by using a dedicated Dicom CT image analyzer program (Syngo 5.5, Siemens).

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The acquired images were interpreted by 2 unblinded readers, a veterinary radiologist (RM) and a small animal internist (AR), to evaluate interobserver error. The bronchoarterial ratio in the superior right, middle right, inferior right, cardiac, superior left, middle left, and inferior left lung lobes was measured on postcontrast cross-sectional CT images after enhancement of arteries. The superior right bronchoarterial ratio was measured at the level of the T5 vertebra, the middle right at the level of T6, the inferior right at the level of T8, and the cardiac lobe at the level of T7. The ratio for the superior left lobe was evaluated at the level of the T5 vertebrae, the middle left at the level of T7, and the inferior left at the level of T8. Moreover, in the case of oblique cross-sections, the immediate superior or inferior section in each plane that contained the most accurate bronchus–artery pair as deemed by the readers was used.

All the measurements were performed in cross section, except for the right middle and left middle lung lobes, for which longitudinal sections were the most accurate. The narrowest internal diameter of the bronchus and narrowest total diameter of the adjacent artery were determined to avoid errors caused by oblique orientations (Figures 1 and 2). These measurements (which were performed by RM) were done 6 times for each location at 6 different times to avoid intraindividual measurement inaccuracies and assess intraobserver errors statistics, as described previously.[23]

To assess the dimensions of normal pulmonary arteries, the diameters of the main pulmonary artery (MPA) and ascending aorta (Ao) was measured in all 12 animals, the widest diameter of the MPA was measured perpendicular to its long axis just above the bifurcation; the diameter of the Ao was measured in the same cross-sectional plane.

The statistical analysis was performed by using commercial software (SPSS for Mac 20.0, SPSS, Chicago, IL). Normality was tested through the one-sample Kolmogorov–Smirnov test. Means and the SD of the bronchoarterial ratio were calculated for each animal and every lung lobe. Correlation of body weight, age, and sex with the mean bronchoarterial ratio was determined by means of Pearson correlation and independent-samples t tests. Interobserver and intraobserver errors were determined by using the interclass correlation coefficient method.

Results

The study population consisted of 5 female and 7 male rhesus macaques. Body weight ranged from 5.0 to 8.6 kg (mean ± 1 SD, 8.00 ± 3.94 kg). Age varied from 4 to 20 y (mean ± 1 SD, 7.8 ± 5.8 y).

A total of 504 bronchoarterial ratios in 7 different locations from the 12 rhesus macaques were obtained. There were no significant subjective differences between cases and locations, according to the radiologist's opinion. Both intraobserver and interobserver errors were nonsignificant ($P = 0.41$ and $P = 0.09$, respectively). The bronchoarterial ratio ranged from 0.51 to 0.80 among all animals. The bronchoarterial ratio in each lung lobe is shown in a box-and-whisker plot (Figure 3). The bronchoarterial ratio for each animal and the overall bronchoarterial ratio for the study population are shown in Table 1. The bronchoarterial ratio did not differ between lung lobes ($P = 0.41$). The overall mean bronchoarterial ratio for all lung lobes in all 12 rhesus macaques was 0.59 ± 0.04, and the upper limit of the 95% CI was 0.61. The mean MPA diameter in all 12 monkeys was 0.95 ± 0.08 cm, and the mean Ao diameter is 1.03 ± 0.08. The MPA and Ao were positively correlated ($r = 0.665$, $P = 0.02$), whereas the mean bronchoarterial ratio was not correlated with either MPA ($r = 0.210$, $P = 0.51$) or Ao diameter ($r = 0.133$, $P = 0.68$).

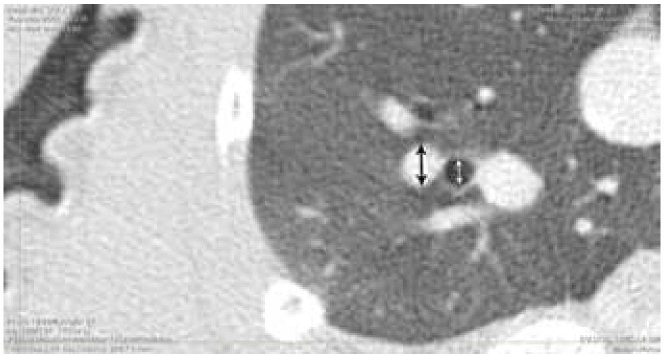

Figure 1. Cross-sectional immediate post-contrast CT image (pulmonary window) of a rhesus macaque lung at the level of the T8 vertebra, demonstrating the method for measuriing the bronchoarterial ratio in the right inferior lung lobe in cross-sectional orientation. The internal diameter of the bronchus is indicated by the white arrows, and the total diameter of the artery is indicated by the black arrows. This ratio is 0.59.

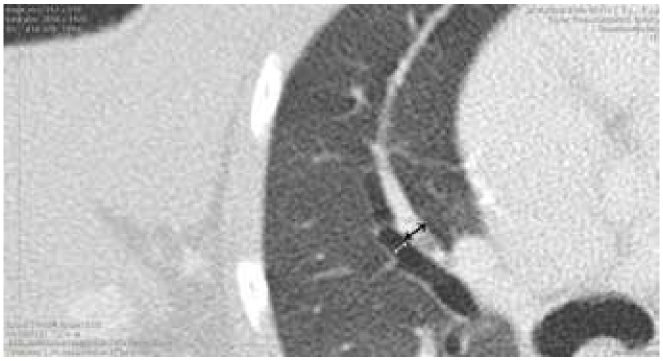

Figure 2. Cross-sectional immediate post-contrast CT image (pulmonary window) of a rhesus macaque lung at the level of the T6 vertebra, demonstrating the method for measuring the bronchoarterial ratio in the right middle lung lobe in longitudinal orientation. The internal diameter of the bronchus is indicated by the white arrows, and the total diameter of the artery is indicated by the black arrows. This ratio is 0.61.

Moreover, there was no correlation between bronchoarterial ratio and age ($r = 0.096$, $P = 0.42$) or sex ($P = 0.10$). However, the bronchoarterial ratio showed positive linear correlation with weight ($r = 0.381$, $P = 0.001$). In addition, there was positive linear correlation between age and weight ($r = 0.694$, $P < 0.001$).

Discussion

Bronchiectasis is one of the main causes of respiratory-related morbidity in humans. In Iran, the most important etiology of bronchiectasis in adult patients is postinfectious after severe pneumonia.[25] In China, the main cause of bronchiectasis is pulmonary tuberculosis.[15] Tuberculosis is a key zoonotic disease in captive rhesus macaque colonies and is transferred due to direct contact with humans.[18] Pathologic pulmonary features of rhesus macaques with tuberculosis closely resemble those of the human disease, including bronchiectasis.[14] In addition, pulmonary acariasis (*Pneumonyssus simicola*; lung mites) has been proposed as another main cause of bronchiectasis and bronchiolitis in rhesus macaques. In one report, airways in some regions were dilated by as much as 5 mm in some gross sections.[21] Furthermore, *Pseudomonas aeruginosa* is a causative agent of chronic endobronchial infection, eosinophilic granulomatous pneumonia, and bronchiectasis in rhesus macaques.[6]

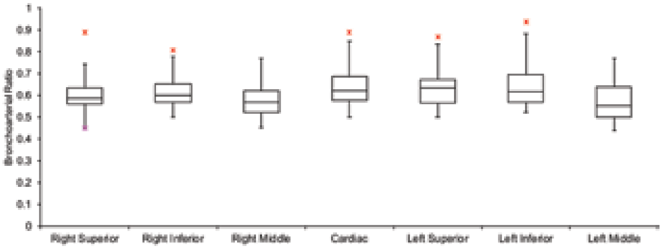

Figure 3. Box-and-whisker plot of the bronchoarterial ratio for each lung lobe (7 locations) in 12 rhesus macaques without clinical respiratory disease. red *, maximum outlier; purple *, minimum outlier.

Table 1. Bronchoarterial ratio (mean ± 1 SD) in each of 12 rhesus macaques and overall

Macaque	Sex	Weight (kg)	Age (y)	Bronchoarterial ratio
1	M	6.0	4	0.57 ± 0.02
2	M	6.0	5	0.58 ± 0.02
3	F	8.6	20	0.58 ± 0.02
4	F	6.3	8	0.58 ± 0.02
5	F	6.0	6	0.58 ± 0.02
6	F	6.5	6	0.55 ± 0.03
7	M	6.0	6	0.56 ± 0.04
8	M	8.0	9	0.61 ± 0.04
9	F	6.5	7	0.61 ± 0.04
10	M	8.0	9	0.68 ± 0.08
11	M	5.0	8	0.56 ± 0.09
12	M	5.7	8	0.60 ± 0.04
Overall				0.59 ± 0.06

F, female; M, male

Radiographic abnormalities are useful but insufficient for diagnosing bronchiectasis.[3] CT scans provide more sensitive and accurate images than plain-film radiography and offer real-time quantitative measurements in 3 planes.[14] Many studies describe the CT appearance of bronchiectasis in humans.[7,19,20] Dilation of the bronchus, bronchial wall thickening, lack of tapering, indistinct bronchus within 1 cm of pleura, and mucus plugging (tree-in-bud sign) have all been reported as major CT signs of bronchiectasis in human patients.[7,17] Until currently, the 'gold standard' for diagnosis of bronchiectasis has been high-resolution CT imaging and the bronchoarterial ratio.[7]

Given the close physical association between the bronchus and adjacent artery in the lung field and the fact that the internal diameter of the artery does not alter significantly along the bronchial airway, it is reasonable to use this artery as a reference for bronchial diameter.[1] According to results from the current study, the bronchoarterial ratio in clinical healthy rhesus monkeys ranges from 0.54 to 0.64, with a mean of 0.59 ± 0.05 and 95% CI upper limit of 0.61. This ratio was consistent among different lung lobes and animals. In clinically healthy men and women, the bronchoarterial ratio was 0.62 ± 0.02.[1] The gross morphology of the lungs differs between rhesus macaques and humans—the cardiac lobe is well developed in rhesus macaques but generally absent in humans—but the bronchial tree is almost identical between these species. The high similarity in the bronchoarterial ratio between humans and rhesus macaques may reflect the anatomic similarity of their bronchial trees. The threshold for the bronchoarterial ratio is 1.45 ± 0.21 in normal dogs[2] and 0.71 ± 0.05 in cats.[23] The differences in the bronchoarterial ratio between rhesus macaques and these other species may simply reflect different inherent anatomic features.[26]

Little has been published regarding the CT features of normal or abnormal airways om rhesus macaques,[12,14,16] and no study has reported the prevalence of bronchiectasis in rhesus macaques. In comparison, there are 2 studies that report on bronchiectasis in rhesus macaques—one based on pathologic findings in animals infected with malaria[28] and the other focused on the features of thoracic CT scans of pulmonary tuberculosis infections.[14] Considering the anatomic similarity in the bronchial trees of humans and rhesus macaques and zoonotic pulmonary infections such as tuberculosis, we suggest that the prevalence of bronchiectasis in rhesus macaques may be considerably higher than what has been published. Regardless, rhesus macaques are widely used as animal models for human medicine, especially in the pediatric field.[5] This practice prompts the need to describe the normal appearance of the airways and reference values for evaluating healthy bronchi through CT scanning of rhesus monkeys.

In the present study, weight had a significant positive effect on the bronchoarterial ratio, whereas age and sex did not influence the bronchoarterial ratio in rhesus macaques. None of the macaques in our study was considered obese according to mean body weight only;[11] other obesity factors were not available in the current study. The positive correlation between the bronchoarterial ratio and weight may reflect the linear relationship between weight and age.

The method for measuring the bronchoalveolar ratio was used longitudinally in the right middle and left middle lung lobes because of their different anatomic orientation. The rest of the lobes were measured in cross section. Regardless of orientation, results did not differ statistically among these lobes.

This study had several limitations. Our study population was relatively small; results may differ for larger populations. The effect of age should be evaluated more thoroughly in different and larger age groups. We did not use bronchoalveolar lavage or biopsy, to prevent possible side effects and complications. The effects of different methods of ventilation were not considered in our study.

In conclusion, we established the reference range for the bronchoarterial ratio in clinically healthy rhesus macaques. This ratio is consistent among lung lobes and animals. Further evaluation on rhesus macaques with chronic airway diseases is required for comparison with healthy animals.

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