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Original Article

3-D computed tomographic airway analysis detects mild bronchiectasis in *mycobacterium avium complex* pulmonary disease

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Abstract: Purpose: *Mycobacterium avium complex pulmonary disease* (MACPD) causes respiratory tract lesions, and it is often difficult to recognize bronchiectasis macroscopically on CT when only mild bronchodilation occurs. The aim of this study was to evaluate such normally appearing bronchi, and quantify bronchial changes in patients with MACPD by 3-D airway analysis. Methods: Thirty-one women bacteriologically diagnosed with *mycobacterium avium complex* (MAC group) and 20 healthy women (control group) were enrolled. We measured the area of the inner lumen (Ai) of the bronchi from the third to sixth generations of the right apical bronchus (B1) and the right basal bronchus (B8) using computed tomography data. We also analyzed Ai values of both the MAC group and the control group. Additionally, we examined the correlation between Ai values and the CT scores (cellular bronchiolitis, nodules, bronchiectasis, air spaces, and cavities) assigned by radiologists in MAC group. Results: The Ai values indicate that bronchodilation at each of the 4th to 6th generations of the right B1 was significantly greater in the MAC group than in the control group ($P < 0.05$). The Ai values and the CT scores were significantly correlated at each of the 5th to 6th generations of right B1 ($r = 0.58$, $P < 0.001$; $r = 0.67$, $P < 0.0001$, respectively). Conclusions: The study suggests that the mild bronchiectasis of peripheral bronchus in patients with MACPD could be detected by 3-D airway analysis, even in normally appearing bronchi.

Keywords: *Mycobacterium avium complex,* bronchiectasis, bronchodilation, airway analysis, CT, 3-D

Introduction

Mycobacterium avium complex pulmonary disease (MACPD) is a common disease, and its prevalence is increasing, particularly among middle-aged women [1-4]. There are several types of MACPD, but nodular bronchiectatic disease is common among non-smoking women aged 50 years or older [5] and commonly occurs in non-immunocompromised individuals. Recently, computed tomography (CT) has become essential for the diagnosis of MACPD and for the assessment of its severity.

Bronchiectasis is present in many patients suffering from MACPD [6-8]; it is often caused by respiratory infections and is defined as chronic dilation of the bronchi with adjacent pulmonary parenchymal damage [9]. In many cases of MACPD, bronchiectasis is accompanied by peribronchial lesions such as small nodules, which is mainly found in the middle lobe and lingular segment. Such bronchiectasis is easy to identify, and its morphology is classified as cylindrical, varicose, or cystic (**Figure 1A**). However, cases of mild bronchiectasis in which peribronchial lesions are not present, particularly in the upper and lower lobes, are often difficult to identify because the bronchus is relatively perpendicular to the slice of the CT imaging. No previous studies have quantitatively assessed such “normally appearing” bronchi (**Figure 1B**). Transbronchial and lung biopsies are highly invasive and difficult to perform for assessment of peripheral airways in cases of

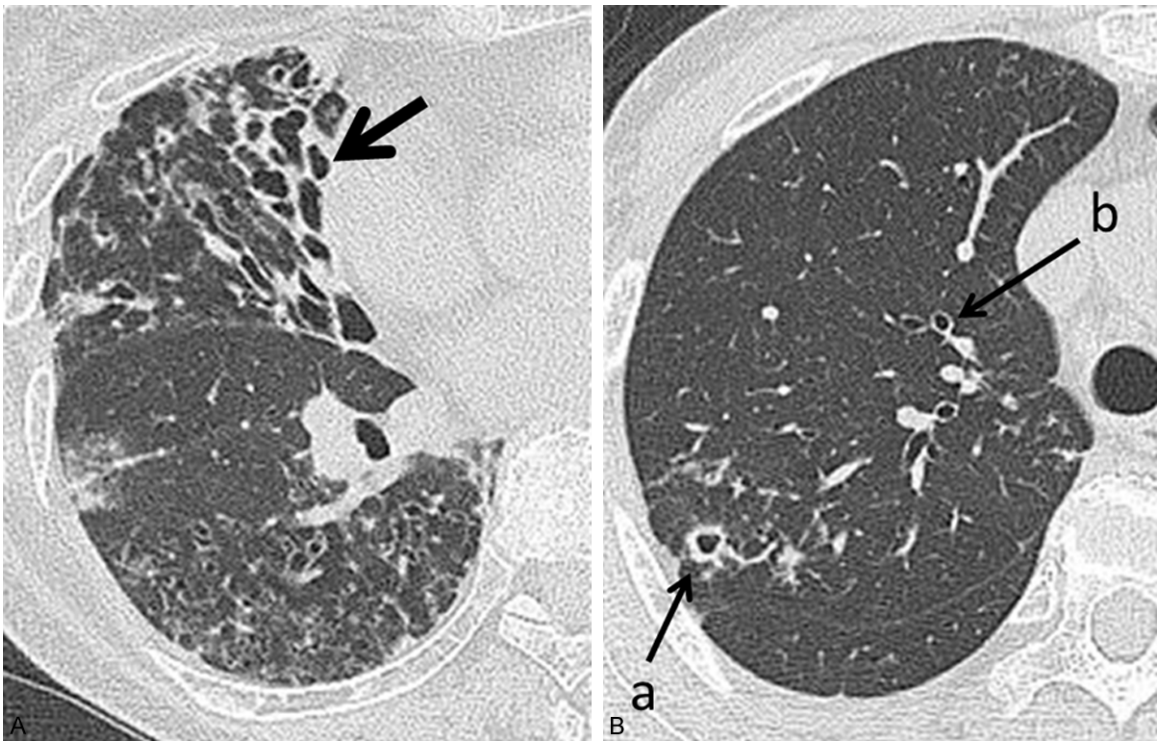

Figure 1. Example of MACPD findings in computed tomography images. A. This image shows distinct cylindrical and varicose bronchiectasis associated with MACPD in the middle lobe (arrow). B. Cavities and small nodular shadows associated with MACPD are present in the right S2 (arrow a); however, "normally appearing" bronchi without small nodular shadows in the right S1 are also present with no clear bronchiectasis (arrow b).

MACPD, whereas CT is a minimally invasive useful tool that can be repeatedly used for airway analysis. However, because bronchi run in all directions, accurate tomographic images cannot always be obtained from previous CT systems. High-resolution CT imaging utilizing three-dimensional (3-D) airway analytical software can be used to track and visualize the airways. In addition, short-axis images perpendicular to the long axis can be drawn and measured at any site, which enables the measurement of small spaces such as the bronchial lumen [10-19].

The aim of this study was to quantitatively measure the area of the inner lumen (Ai) of "normally appearing" bronchi in patients with MACPD without peribronchial lesions and evaluate the bronchi using 3-D airway analysis. In addition, we assessed whether this analysis could be used to detect mild bronchiectasis, for which assessment through bronchi macroscopic diagnosis of CT findings is difficult, and we characterized the features of bronchiectasis of MACPD.

Materials and methods

Subjects

Patients who were diagnosed with MACPD and underwent a thoracic CT scan from July 2012 to October 2015 at the Department of Respiratory Medicine of Chuno Kosei Hospital were included. MACPD was diagnosed in accordance with criteria set by The American Thoracic Society (ATS) and the Infectious Diseases Society of America (IDSA) [1]. Other diseases were excluded in patients who had CT features that suggested MACPD and who had positive mycobacterial avium-intracellular cultures in at least one bronchoalveolar lavage fluid or two sputum tests. The criteria for inclusion in the *Mycobacterium avium complex* (MAC) group were as follows: patients who received a diagnosis of MACPD and, i) were women; ii) were non-smokers; iii) were 20 years of age or older; iv) in whom thoracic CT did not reveal lesions such as cellular bronchiolitis, nodules, or air spaces in the measured peribronchial region of the right apical bronchus

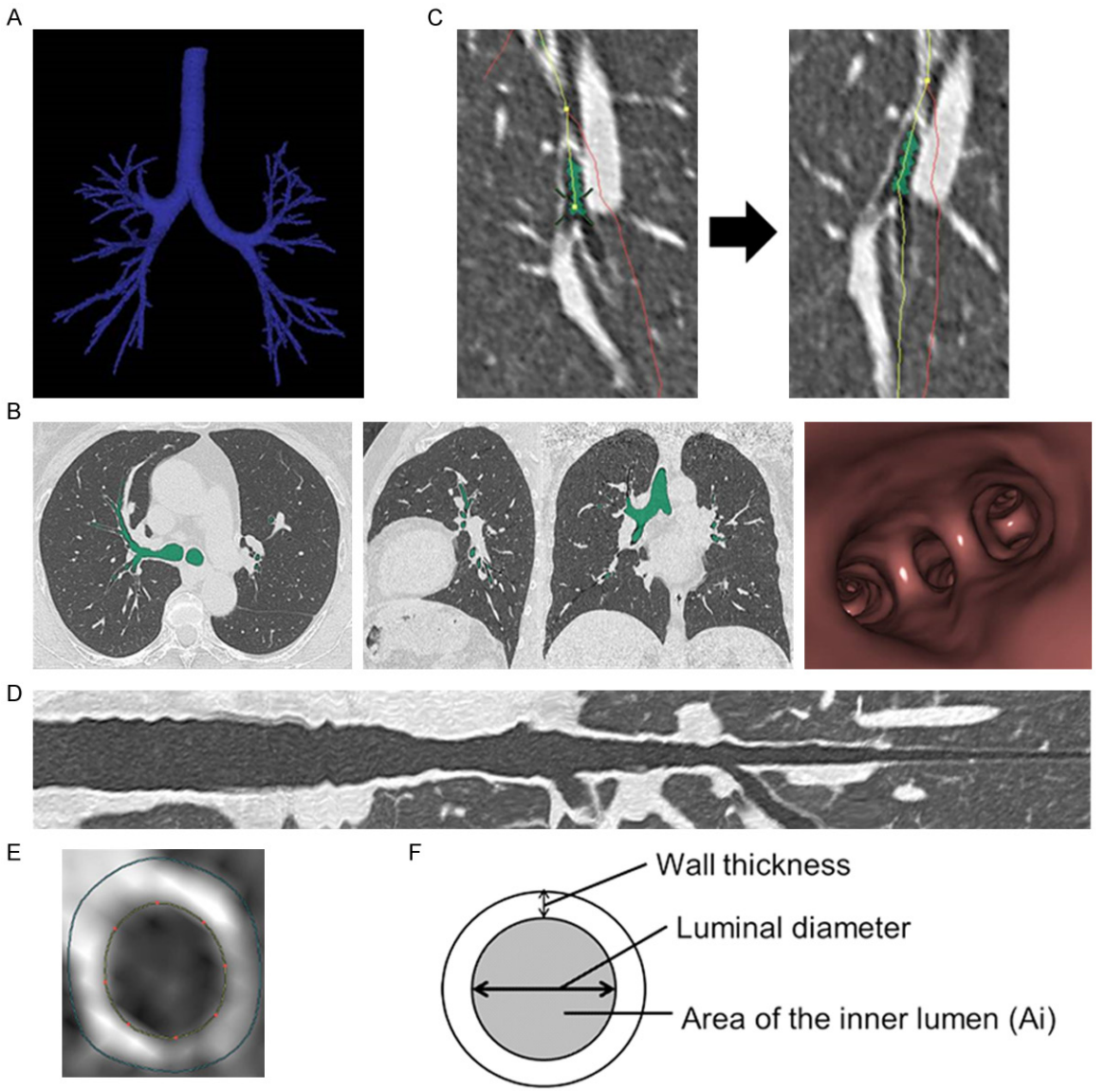

Figure 2. Three-dimensional reconstruction of the bronchial tree. A. The bronchial airways were automatically tracked and extracted to recreate the entire bronchial tree structure. B. We used multiplanar reconstruction (MPR) and virtual bronchoscopy. The bronchial lumen observed in CT images is highlighted in green. C. A CT image of the bronchus running in the lower right side is displayed using linear MPR. Even though sufficient imaging of the bronchi could not be obtained, a bronchiole model was created by manually identifying the bronchioles. The green area highlights the bronchial lumen, the yellow line indicates the selected bronchial branch, and the red line indicates a branch that splits into another branch. D. Long-axis images of the right B8 in healthy subjects are shown in a linear arrangement. E. Manual tracing of the short-axis view of the bronchi. F. We calculated the area of the inner lumen (Ai) of the bronchial branches.

(B1) and anterior basal bronchus (B8) and did not reveal clear bronchiectasis of any morphology; and v) did not have other pulmonary diseases such as chronic obstructive pulmonary disease (COPD), bronchial asthma, lung cancer or infectious pulmonary disease (e.g., pneumonia, pneumomycosis, or tuberculosis).

Subjects in the control group were non-smoking healthy women 20 years of age or older who visited the same hospital during the same period as the MAC group for abnormal thoracic radiographic findings, but for whom no abnormalities were detected in thoracic CT scans and pulmonary function tests.

Table 1. Macroscopic assessment criteria for computed tomography imaging

Scoring system for evaluation of radiological findings		
Radiological findings	Degree	Score
Cellular bronchiolitis (< 5 mm)	None	0
	0-50% in segment	1
	50-100% in segment	2
	All	3
Nodules (≥ 5 mm)	No	0
	Yes	1
Bronchiectasis	No	0
	Mild	1
	Moderate	2
	Severe	3
Air space	No	0
	Yes	3
Cavity	No	0
	Yes	3

Bronchiectasis was defined as follows: 1 point = bronchus smaller than two times the diameter of the artery running parallel to it (mild); 2 points = twice or more than twice the diameter (moderate); 3 points = cylindrical, varicose, or cystic bronchiectasis (severe).

Written consent was obtained from all participants for the use of thoracic CT and clinical data for research purposes. Our study was approved by the Chuno Kosei Hospital Institutional Review Board (approval number: 65).

Acquisition of computed tomography data and 3-D analysis

We used a 64-slice multiple detector CT scanner (Aquilion CX, Toshiba, Japan): 120 kVp, Real-EC (SD 10.0), 64 detector × 0.5 mm collimation, slice thickness 0.5 mm, 0.5 s/rotation, helical pitch 53 (PF 0.828). Patients were placed in the supine position and asked to breathe deeply while the entire lung was scanned. The obtained CT data were sent to a workstation (AZE Ltd., Tokyo, Japan) for reconstruction using 3-D imaging. First, bronchial airways were automatically tracked and extracted, and the entire bronchial tree structure was recreated (**Figure 2A**). The selected bronchi were displayed using curved multiplanar reconstruction, orthogonal cross-section, or virtual bronchoscopic imaging (**Figure 2B**). If sufficient imaging of the bronchi could not be obtained, a bronchiole model was created by manually identifying bronchioles (**Figure 2C**). The selected bronchus was shown linearly in a long-axis image (**Figure 2D**). The inner and outer lumen diameters of bronchi were automatically traced using the full-width at half-maximum principle, but tracing can be manually performed if the automatic tracer is inaccurate (**Figure 2E**). We searched for bifurcations and identified bronchial generations while paying close attention to short-axis, longitudinal, sagittal, and coronal plane views, as well as virtual bronchoscopic findings. Furthermore, whenever possible we selected linear bronchi for evaluation. Through this process, we calculated the Ai at each 0.5 mm mark. We analyzed the third (i.e., segmental branches) to sixth generations of the right B1 and B8, and calculated the mean Ai values (mm^2) for each generation (**Figure 2F**).

Selection and tracing of bronchi for 3-D CT were performed by a single experimenter who was blinded to the subjects' diagnosis, and another experimenter who was similarly blinded confirmed the results.

Radiological evaluation

We conducted two studies (Study 1 and 2).

In Study 1, we compared the mean Ai values for the MAC group to those of the control group at each bronchial branch of the right B1 or B8 bronchus.

In Study 2, based on the study of Moore et al. [20], we divided the right lung of each patient of the MAC group into five sites (i.e., S1+2, S3, S4+5, S6, S7+8+9+10) using CT. Based on the study of Obayashi et al. [21], we assigned severity scores of 0-3 points to five items (cellular bronchiolitis, nodules, bronchiectasis, air spaces, and cavities) in each region (i.e., right S1+2, S7+8+9+10). See **Table 1** for scoring system details. We examined the correlation between scores of the right S1+2 CT scans and Ai values of each bronchial branch of the right B1, in addition to the correlation between scores of the right S7+8+9+10 CT scans and the Ai values of each bronchial branch of the right B8.

The CT scans were reviewed with consensus reading by two blinded observers experienced in CT.

Statistical analysis

Data are presented as the mean value ± standard deviation (SD). Statistics Program for

Table 2. Characteristics of subjects

Characteristics of subjects			
Group	Control	MAC	*P* values
Sex (male/female)	0/20	0/31	
Age (years)	58.0 ± 17.7	65.9 ± 12.6	NS 1)
Height (m)	1.56 ± 0.07	1.52 ± 0.08	NS 1)
Body weight(kg)	52.3 ± 8.3	45.3 ± 6.4	< 0.01 1)
BMI (kg/m^2)	21.5 ± 2.6	19.6 ± 1.9	< 0.05 1)
Smoking (BI)	0	0	
Hematologic data			
WBC (/μL)		4665 ± 1399	
RBC (× 10000/μL)		425.2 ± 39.6	
Hb (g/dL)		12.7 ± 1.4	
CRP (mg/dL)		0.08 ± 0.09	
Alb (g/dL)		4.04 ± 0.31	
Biological diagnosis			
Sputum/bronchial lavage		11/20	
Symptoms			
Cough	0	16 (51.6%)	
Sputum	0	15 (48.4%)	
Hemosputum	0	3 (9.7%)	
Shortness of breath	0	16 (51.6%)	
Medication			
None		18 (58.1%)	
CAM, RFP, EB		5 (16.1%)	
CAM, RFP, LVFX		4 (12.9%)	
CAM, RFP		4 (12.9%)	
Duration of medication (months)		5.19 ± 11.8	

Data are presented as the mean value ± standard deviation. 1) Data were analyzed using the Mann-Whitney U test. Definitions: medication (pharmacotherapy): pharmacotherapy at time of computed tomography imaging; sputum = patients who received a diagnosis of positive sputum culture at least two times; bronchial lavage = patients who received a diagnosis of positive culture of bronchoalveolar lavage fluid by bronchoscopy; BMI = body mass index, BMI was calculated as the weight (kg) divided by the square of the height (m); BI = Brinkman index; N.S. = not significant; WBC = white blood cell; RBC = red blood cell; CRP = C-reactive protein; Alb = albumin; CAM = clarithromycin; RFP = rifampicin; EB = ethambutol; LVFX = levofloxacin; SM = streptomycin.

Social Science for Windows (IBM, SPSS Statistics ver.22) was used for data analysis. The Mann-Whitney U test was used for group comparisons of the age, height, body weight, BMI, and Ai values of subjects in Study 1. Spearman's rank-order correlation was used to compare CT scores and Ai values in Study 2. Statistical significance was defined as $P < 0.05$.

Results

Patient characteristics

Patient characteristics are shown in **Table 2**. The control group contained 20 patients, whereas the MAC group contained 31 patients. In Study 1, there were no significant differences between the two groups with regard to age and height. Thirteen patients of the MAC group received combination therapy (e.g., clarithromycin or rifampicin) at the time of the CT scans. There were no immunocompromised subjects in the MAC group.

Airway measurement in patients with MACPD

Comparisons of the mean Ai values between the two groups in Study 1 are shown in **Figure 3** (right B1). The Ai value and bronchodilation were significantly greater in the MAC group than in the control group at each of the 4th to 6th generations of the right B1 (4th generation $P < 0.05$; 5th and 6th generations $P < 0.0001$). However, no significant differences between the 3rd generations of the right B1 or the 3rd-6th generations of the right B8 were observed between the groups.

The correlations between the right S1+2 CT scores and Ai values of each bronchial branch of the right B1 observed in Study 2 are shown in **Figure 4**. There was a correlation between Ai value and severity of the CT score at each of the 5th to 6th generations of the right B1 (5th generation, $P < 0.001$; 6th generation, $P < 0.0001$). In addition, when the imaging score increased, bronchiectasis also occurred in "normally appearing" bronchi. No clear correlation between Ai value and severity of CT scores was observed at each of the 3rd to 4th generations of the right B1 (3rd generation, $P = 0.7097$; 4th generation, $P = 0.0795$) or at each of the 3rd-6th generations of the right B8 (3rd generation, $P = 0.4089$; 4th generation, $P = 0.1469$; 5th generation, $P = 0.2970$; 6th generation, $P = 0.0502$).

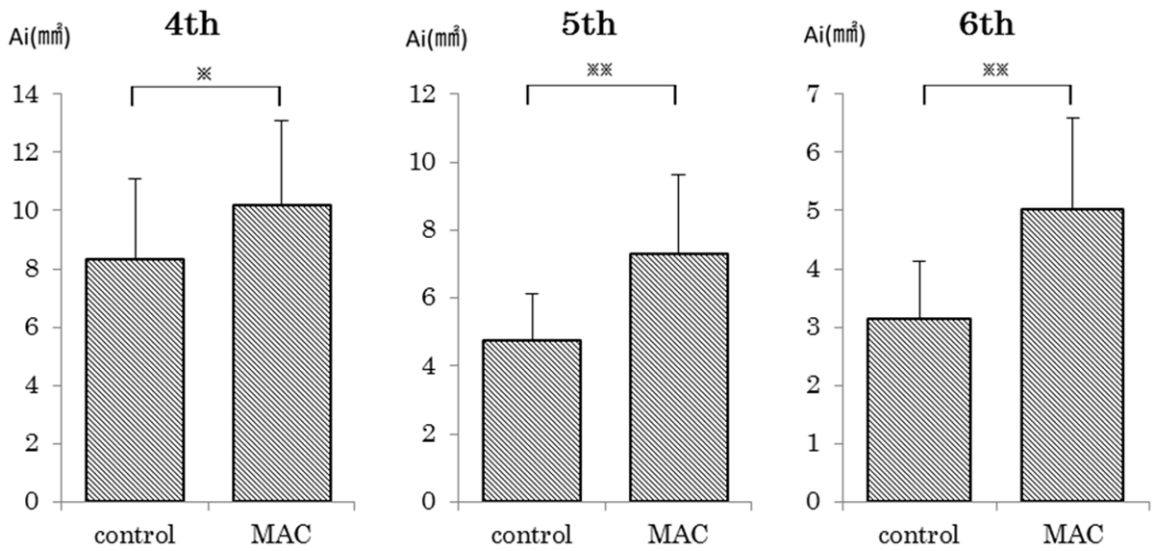

Figure 3. Comparison of mean area of the inner lumen at each of the 4th to 6th generations of the right B1 bronchus in Study 1. Analysis of the right B1 bronchus revealed that the Ai value and bronchodilation were significantly greater in the MAC group than in the control group at each of the 4th to 6th generations of the right B1. ※P < 0.05, ※※P < 0.0001.

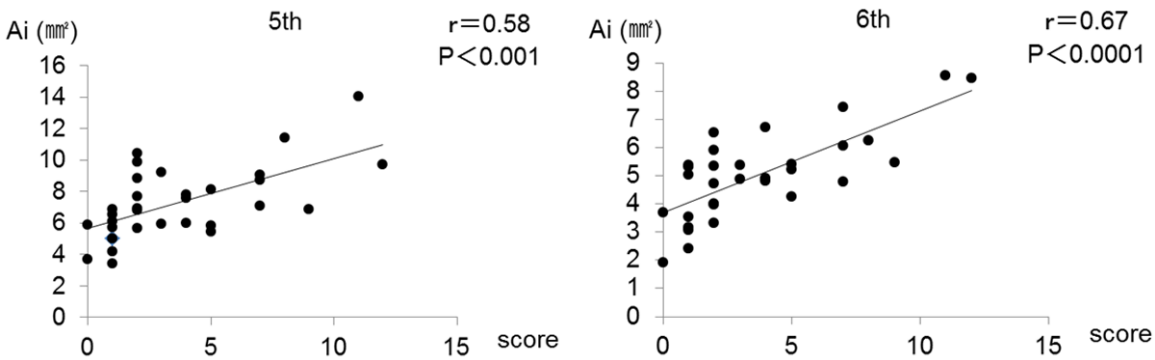

Figure 4. Correlation between computed tomography scores of the right S1+2 and area of inner lumen values from the 5th to 6th generation of the right B1 in patients with MACPD in Study 2. We observed a significant correlation between the area of the inner lumen (Ai) and computed tomography severity scores at each of the 5th to 6th generations of the right B1 bronchus (5th generation, P < 0.001; 6th generation, P < 0.0001).

There was a correlation between bronchiectasis in the periphery of the right B1, in which no peribronchial lesions were present, and the severity of MACPD observed using CT. However, no correlation between bronchiectasis and the severity of CT was observed in the central bronchi and right B8.

Discussion

In recent years, airway analysis using CT has progressed, and there have been reports of CT use for airway assessment in smokers, and in cases of COPD, asthma, and cystic fibrosis [14-19]. Hasegawa et al. demonstrated that measurement of the bronchus to the sixth generation was possible using the same software used for 4-slice CT scans (4 detector × 1 mm collimation) [14], and Nishimura et al. demonstrated the accuracy of this technique by using a cylindrical acrylic material to perform phantom tests using the same software, particularly for 64-slice CT scans (64 detector × 0.5 mm collimation) [22]. In addition, Shimizu et al. used the same software and 64-slice CT scans (64 detector × 0.5 mm collimation) for airway analysis to the sixth generation in cases of COPD and asthma [16, 18]. Therefore, we mea-

sured the bronchus to the sixth generation using 64-slice CT scans (64 detector × 0.5 mm collimation) in the present study. To our knowledge, there are no reports regarding the use of 3-D airway analysis for MACPD. In the present study, we analyzed the right B1 and B8. Patients held their breath during CT scanning, but because the beating of the left ventricle of the heart produced blurred left lung images, particularly in the lower lobe, we only analyzed bronchi of the right lung. We selected B1 and B8 because these bronchi represent the upper and lower lobes of the lung, and comparatively linear images can be obtained from them. Hasegawa et al. also selected right B1 and B8 [14]. In addition, only women with MACPD were selected for examination because this disease commonly occurs in women. Lastly, we only examined non-smokers because of the possibility of Ai values being affected by smoking [14, 15]. In Study 1, the body weight and BMI of the MAC group were significantly lower than that of the control group (**Table 2**). Body weight loss and low BMI are characteristic of MACPD [23, 24]. However the Ai value and bronchodilation were significantly greater in the MAC group than in the control group at each of the 4th to 6th generations of the right B1. Therefore these outcomes for the Ai values are not the result of build differences. In Study 2, a correlation was observed between the Ai of the 5th and 6th generations of the right B1 and the severity of MACPD scores at the segmental level. However, in both studies, this trend was not observed in the right B8. In Study 2, the mean CT scores for the right S1+2 were higher than those for the right S7+8+9 +10 (3.71 ± 3.20 and 2.71 ± 2.43, respectively), although these differences did not reach statistical significance ($P = 0.19$, Mann Whitney U test).Similarly, it was also previously reported that segments with lesions in the lower lobes occurred with lower frequency [25]. Compared to MACPD lesions in the lower lobe, a stronger trend was observed for lesions in the upper lobe, and the results suggested that even in "normally appearing" bronchi without peribronchial lesions, MAC bacteria were more strongly implicated in the right B1 than in the right B8. Our study shows that in patients with MACPD, mild bronchiectasis occurred even when peribronchial lesions were not present. Furthermore, a stronger correlation with disease severity was observed for upper than for lower lobar bronchi. The reason is unknown, although the ventilation-perfusion ratio or pH inequality of the upper and lower lobe may have played a role [26]. Moreover, compared to the proximal bronchi, a stronger relationship between the distal bronchi and disease severity was observed. Fujita et al. reported that pathologically, destruction of the smooth muscle layer is often observed in membranous bronchioles [27]. It may be characteristic of MACPD that changes of these elements, which play an important role in maintaining the airway lumen, occur in the distal bronchi, as supported by the new quantitative information from the 3-D airway analysis. In addition, although many patients were under medication, despite their medication usage, bronchiectasis was still detected in most patients, which may indicate that bronchiectasis is difficult to treat and irreversible [28].

No consensus has been reached regarding whether bronchiectasis in cases of MACPD results from MAC bacterial infections, or whether onset occurs during an early stage when the patient is susceptible to MAC bacterial infection. According to the primary infection theory, granulomatous lesions associated with MAC bacteria form in the bronchioles and continuously spread to the central bronchi, causing rupture of the bronchi because of inflammatory dilation [21, 27]. In contrast, and according to the secondary infection theory, MAC bacteria become attached to sites in which bronchiectasis is already present, producing secondary pulmonary lesions [29]. If it is considered that large Ai values result from MAC bacterial infection, then these values can be regarded as indicators of the severity of bronchiectasis. In contrast, if it is considered that Ai values are already higher in patients at a stage earlier than when MAC bacterial infection occurs, then Ai values might serve as screening indicators for patients who are susceptible to MAC bacterial infection, or in whom infection is easily aggravated. Ai values can be easily obtained using 3-D airway analysis, and it is also easy to compare chronological changes in CT images. It has been reported that when the number of sites of bronchiectasis increases, the efficacy of treatment decreases [30]; thus, it is possible that these findings can be used as indicators for when treatment should start. The use of 3-D airway analysis enables detailed assessments of minor bronchiolar lesions associated with

MACPD that are difficult to evaluate macroscopically using CT.

Finally, we should mention some limitations of this study. First, we examined only two bronchi and the number of patients was limited; however, to our knowledge, this is the first report regarding the use of 3-D airway analysis for MACPD, and our study showed that bronchiectasis frequently occurs in the distal and superior lobar bronchi. Second, we did not compare the airway dimensions obtained by CT measurements with those of excised lung specimens. However, because there have already been some reports using the same software for airway assessment [14, 16, 18, 22] and some studies of 3-D airway analysis [15, 17, 19], we proceeded directly to the MACPD study. We consider this study to be a pilot study. More studies are needed to fully elucidate the observed changes.

Conclusion

It is the authors' opinion that 3-D airway analysis in cases of MACPD can be a useful tool to identify mild bronchiectasis in patients for whom macroscopic diagnosis using CT imaging is difficult. The results of the present study suggest that bronchiectasis occurs in the periphery of apical bronchus, even in "normally appearing" bronchi. The measurement of Ai values can provide a quantitative indicator of bronchiectasis associated with MACPD.

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Disclosure of conflict of interest

None.

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References

[1] Grififth DE, Aksamit T, Brown-Elliott BA, Catanzaro A, Daley C, Gordin F, Holland SM, Horsburgh R, Huitt G, Iademarco MF, Iseman M, Olivier K, Ruoss S, von Reyn CF, Wallace RJ Jr, Winthrop K; ATS Mycobacterial Diseases Subcommittee; American Thoracic Society; Infectious Disease Society of America. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. Am J RespirCrit Care Med 2007; 175: 367-416.

[2] Reich JM, Johnson RE. Mycobacterium avium complex pulmonary disease presenting as an isolated lingular or middle lobe pattern. The lady windermere syndrome. Chest 1992; 101: 1605-9.

[3] Prince DS, Peterson DD, Steiner RM, Gottlieb JE, Scott R, Israel HL, Figueroa WG, Fish JE. Infection with mycobacterium avium complex in patients without predisposing conditions. N Engl J Med 1989; 321: 863-8.

[4] Hartman TE, Sweason SJ, Williams DE. Mycobacterium avium-intracellulare complex: evaluation with CT. Radiology 1993; 187: 23-6.

[5] Wallace RJ Jr, Zhang Y, Brown BA, Dawson D, Murphy DT, Wilson R, Griffith DE. Polyclonal mycobacterium avium complex infections in patients with nodular bronchiectasis. Am J Respir Crit Care Med 1998; 158: 1235-44.

[6] Tanaka E, Amitani R, Niimi A, Suzuki K, Murayama T, Kuze F. Yield of computed tomography and bronchoscopy for the diagnosis of mycobacterium avium complex pulmonary disease. Am J Respir Crit Care Med 1997; 155: 2041-6.

[7] Kubo K, Yamazaki Y, Hachiya T, Hayasaka M, Honda T, Hasegawa M, Sone S. Mycobacterium avium-intracellulare pulmonary infection in patients without known predisposing lung disease. Lung 1998; 176: 381-91.

[8] Lynch DA, Simone PM, Fox MA, Bucher BL, Heinig MJ. CT features of pulmonary mycobacterium avium complex infection. J Comput Assist Tomogr 1995; 19: 353-60.

[9] Trucksis M, Swartz MN. Bronchiectasis: a current view. Curr Clin Top Infect Dis 1991; 11: 170-205.

[10] Nakano Y, Muro S, Sakai H, Hirai T, Chin K, Tsukino M, Nishimura K, Itoh H, Paré PD, Hogg JC, Mishima M. Computed tomographic measurements of airway dimensions and emphysema in smokers. Correlation with lung function. Am J Respir Crit Care Med 2000; 162: 1102-8.

[11] Nakano Y, Wong JC, de Jong PA, Buzatu L, Nagao T, Coxson HO, Elliott WM, Hogg JC, Paré PD. The prediction of small airway dimensions

using computed tomography. Am J Respir Crit Care Med 2005; 171: 142-6.
[12] Orlandi I, Moroni C, Camiciottoli G, Bartolucci M, Pistolesi M, Villari N, Mascalchi M. Chronic obstructive pulmonary disease: thin-section CT measurement of airway wall thickness and lung attenuation. Radiology 2005; 234: 604-10.
[13] Berger P, Perot V, Desbarats P, Tunon-de-Lara JM, Marthan R, Laurent F. Airway wall thickness in cigarette smokers: quantitative thin-section CT assessment. Radiology 2005; 235: 1055-64.
[14] Hasegawa M, Nasuhara Y, Onodera Y, Makita H, Nagai K, Fuke S, Ito Y, Betsuyaku T, Nishimura M. Airflow limitation and airway dimensions in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2006; 173: 1309-15.
[15] Montaudon M, Berger P, Lederlin M, Marthan R, Tunon-de-Lara JM, Laurent F. Bronchial morphometry in smokers: comparison with healthy subjects by using 3D CT. Eur Radiol 2009; 19: 1328-34.
[16] Shimizu K, Hasegawa M, Makita H, Nasuhara Y, Konno S, Nishimura M. Airway limitation and airway dimensions assessed per bronchial generation in older asthmatics. Respir Med 2010; 104: 1809-16.
[17] Hoshino M, Matsuoka S, Handa H, Miyazawa T, Yagihashi K. Correlation between airflow limitation and airway dimensions assessed by multidetector CT in asthma. Respir Med 2010; 104: 794-800.
[18] Shimizu K, Hasegawa M, Makita H, Nasuhara Y, Konno S, Nishimura M. Comparison of airway remodelling assessed by computed tomography in asthma and COPD. Respir Medicine 2011; 105: 1275-83.
[19] Wielputz MO, Eichinger M, Weinheimer O, Ley S, Mall MA, Wiebel M, Bischoff A, Kauczor HU, Heußel CP, Puderbach M. Automatic airway analysis on multidetector computed tomography in cystic fibrosis. Correlation with pulmonary function testing. J Thorac Imaging 2013; 28: 104-13.
[20] Moore EH. Atypical mycobacterial infection in the lung: CT appearance. Radiology 1993; 187: 777-82.
[21] Obayashi Y, Fujita J, Suemitsu I, Kamei T, Nii M, Takahara J. Successive follow-up of chest computed tomography in patients with mycobacterium avium-intracellulare complex. Respir Med 1999; 93: 11-5.
[22] Nishimura M. Application of three-dimensional airway algorithms in a clinical study. Proc Am Thorac Soc 2008; 5: 910-14.
[23] Okumura M, Iwai K, Ogata H, Ueyama M, Kubota M, Aoki M, Kokuto H, Tadokoro E, Uchiyama T, Saotome M, Yoshiyama T, Yoshimori K, Yoshida N, Azuma A, Kudoh S. Clinical factors on cavitary and nodular bronchiectatic types in pulmonary mycobacterium avium complex disease. Intern Med 2008; 47: 1465-72.
[24] Hayashi M, Takayanagi N, Kanauchi T, Miyahara Y, Yanagisawa T, Sugita Y. Prognostic factors of 634 HIV-negative patients with mycobacterium avium complex lung disease. Am J Respir Crit Care Med 2012; 185: 575-83.
[25] Kitahara Y, Harada Y, Harada S. The distribution and the characteristics in computed tomography of the lungs in primary Mycobacterium avium complex infection. Kekkaku 1997; 72: 173-80.
[26] West JB, Dollery CT. Distribution of blood flow and ventilation-perfusion ratio in the lung, measured with radioactive carbon dioxide. J Appl Physiol 1960; 15: 405-10.
[27] Fujita J, Ohtsuki Y, Shigeto E, Suemitsu I, Yamadori I, Bandoh S, Shiode M, Nishimura K, Hirayama T, Matsushima T, Fukunaga H, Ishida T. Pathological findings of bronchiectasis caused by Mycobacterium aviumintracellulare complex. Respir Med 2003; 97: 933-8.
[28] Kurashima A, Ogawa K. Forefront of the clinic and research of pulmonary MAC disease. Kekkaku 2012; 87: 433-48.
[29] Hebisawa A, Tsuchiya K, Tamura A. Mycobacterium avium complex pulmonary disease. Byori To Rinsho 2005; 23: 501-8.
[30] Kuroishi S, Nakamura Y, Hayakawa H, Shirai M, Nakano Y, Yasuda K, Suda T, Nakamura H, Chida K. Mycobacterium avium complex disease: prognostic implication of high-resolution computed tomography findings. Eur Respir J 2008; 32: 147-52.