0.843.($p < 0.001$) Considering potential bias due to using 2 CT scanners, each participant is indicated using different styles of dots, depending upon which CT scanner was used.(Figure 2) Even when we separately examined only 9 individuals who had also been examined using the Siemens scanner, the close correlation between the overall bronchodilator response and %increase in FEV1 persisted.($r = 0.800$, $p = 0.010$)

Because average bronchodilation was more obvious (although not statistically significant) at the distal, than at the proximal bronchi, we examined the relationship between improved FEV_1 and the average %increase in inner luminal area at the same generation of all 8 bronchi. Figure 3 shows that the data from the 4th, 5th and 6th generations significantly correlated, but not those from the 3rd generation. Importantly and interestingly, the slope of regression lines between the 2 variables became steeper as the airways became more distal from the 3rd to the 6th generation. Separately analyzed data based on lobes are also shown in the online supplement.(Figure E1)

We then defined good responders as those who exhibited a %increase in FEV_1 of > 20%, considering that the mean %increase in FEV_1 was 19.7% in this study. Figure 4A shows a significant trend insofar as the magnitude of bronchodilation increased as the airways became smaller from the 3rd to the 6th generation ($p = 0.006$) in the good responders ($n = 7$), but not at all in the poor responders ($n = 8$), and the difference in bronchodilation between the 2 groups was statistically significant only at generations 4, 5, and 6. There were no significant differences among lobes in either good or poor responders.(Figure 4B)

Lung volumes before and after 1 week inhalation of tiotropium were 5.44 ± 0.35 and 5.19 ± 0.38 L, respectively. Although lung volumes significantly differed on 2 occasions ($p = 0.029$), changes in lung volume did not significantly correlate with those of airway caliber among the subjects.

DISCUSSION

We showed using 3-dimensional computed tomography that the caliber at the 3rd to 6th generation of the airways induced by inhaled anticholinergics increased in proportion to physiological improvements in pulmonary function. Among pulmonary function parameters, FEV_1 correlated most closely with the magnitude of bronchodilation overall. The close correlation between the magnitude of bronchodilation at deep inspiration under static conditions and that of functional improvement on forced expiration might be surprising. However, considering that FEV_1 is the volume that is expired during the first second from fully inspired lungs, widening of airway caliber at the beginning of expiration might be a determinant of initially expired volume. In this study, we unfortunately had not obtained lung volume data by body plethysmography. Those data would be interesting for comparison with bronchodilation elicited by inhaled anticholinergics.

Of particular note is that the slope factor of regression lines between the improvement of FEV_1 and the magnitude of bronchodilation was steeper from the 3rd to the 6th generation. Theoretically, if the same degree of vagal cholinergic tone operates in various sizes of airways, then widening of airway caliber by anticholinergic agents should be greater in the smaller airways,[13] particularly when the magnitude of bronchodilation is evaluated as a %increase in inner luminal area. We then considered such relationships using the absolute increase in inner luminal area instead of the % increase. The total luminal area per generation increases as the airway bifurcates,[14] so that the absolute increase in inner luminal area per generation should be larger at more distal airways. Indeed, if we could correct a total increase in inner luminal area per generation, multiplying by 2, 4 and 8, respectively, for the 4th, 5th, and 6th generation, in comparison of the 3rd generation, considering increased number of airways, we would similarly find that the slope of regression line between the two variables were steeper at more distal airways. (Online supplement, FigureE2) These findings indicate that bronchodilation at distal, rather than proximal airways, is the determinant of the functional improvement exerted by inhaled anticholinergics in COPD.

The magnitude of bronchodilation in some good responders might be surprising, considering that they are all patients with COPD. However, several recent studies have found that a significant proportion of patients with COPD indeed display more reversibility of airflow limitation than has generally been thought.[3, 4, 15] The present findings might have some important clinical implications and provide intriguing insights into therapy with bronchodilators for patients with COPD. Firstly, a poor response to inhaled anticholinergics might well be explained by limited responses at the 5th to 6th generations rather than at the 3rd generation of airways, because the magnitude of bronchodilation between good and poor responders did not significantly differ, at least at the 3rd generation of airways.(Figure 4A) If so, more attention should be directed towards delivering drugs to the 5th - 6th generations of airways in patients who do not respond well to inhaled anticholinergics. Secondly, when considering how to maximize bronchodilation for patients with COPD not only in the short term but also in the long term, the more distal airways should be focused, rather than the 3rd (segmental) generation of airways.

To our knowledge, Brown *et al.* pioneered the use of CT to demonstrate changes in the airway caliber of animal lungs.[16] They attempted to measure airways considered to be located at the

same site in the lungs before and after bronchoconstriction induced by methacholine. They later reported that airway narrowing in human lungs was heterogeneous with no predilection for any particular airway size, and that changes in the mean airway luminal area measured by CT and the mean partial spirometric outcomes closely correlated in a small number of healthy, as well as asthmatic individuals.[17, 18] On the other hand, the 2 other studies found significant differences in the airway narrowing after methacholine challenge according the baseline airway size in both healthy and asthmatic subjects.[19, 20] However, all of the studies [17-20] had inherent technical limitations because they analyzed 2-dimensional images of the airways and thus could not identify which airway generation they were actually measuring. Moreover, the relationship between improved pulmonary function and bronchodilation at various sites of the airways and the degree to which such bronchodilation occurs in the lung have never been demonstrated in patients with COPD.

We recently showed using the three-dimensional airway analysis that we applied herein, that %predicted FEV_1 significantly correlates with the dimensions of airways of various sizes in a large number of patients with COPD.[8] In addition, the correlation coefficients between the two variables improved as the airway size decreased from the 3rd to the 6th generation. These results support the concept that distal (smaller), rather than proximal (larger) airways are more important determinants of airflow limitation in COPD as previous pathology-function correlation studies have indicated.[21-24] As the average calculated inner diameter of the 6th generation of bronchi was 2.1 mm at baseline before bronchodilator inhalation in this study, these airways are not defined as "small airways".[25] However, the findings from our 2 studies jointly suggest that airways located near "small airways" are functionally important in COPD.

Several classical studies have attempted to physiologically determine the site of bronchodilation in response to bronchodilators in humans. These efforts have included measuring anatomical dead space as an indicator of central airway changes,[26] generating maximal expiratory flow-volume curves with inspired gases of different densities [27, 28] and sensing the lateral pressure of the airway using a catheter-tipped micro manometer.[29] Although these studies were theoretically sound, they could not determine bronchodilatory heterogeneity of in the lung because they are all based on the assumption that lung activity is homogeneous and so overall physiological parameters were measured. Most of these studies agreed that inhaled anticholinergic agents act mainly on the large central airways in normal individuals as well as in patients with bronchial asthma,[26, 28, 30] although some disagreed.[27, 31] Since resting vagal tone is thought to be maintained under normal circumstances throughout the bronchial tree,[30] the exact site of bronchodilation over the whole lung remains to be elucidated. Our CT imaging method can analyze only large airways from the standpoint of respiratory physiology because small airways are defined as having an inner diameter of < 2 mm. However, the advantage of our method is the potential for examining the heterogeneous behavior of bronchodilation in individual lungs.

Some limitations of the study should be mentioned. Firstly, the use of 2 different types of CT scanners for this kind of study could be debatable, particularly for lung densitometry.[32-34] However, we carefully considered possible bias associated with the use of the 2 scanners in this study and obtained data from specific individuals using the same instrument. We also conducted preliminary validation studies for both scanners using the same phantoms and used

the % increase in inner luminal area as a marker of bronchodilation after inhalation rather than actual values. Secondly, some potential drawbacks are inherent in our experimental protocol and also in our software. Although we obtained CT images on 2 occasions while the patients held their breath at deep inspiration, the CT images might not have been obtained at precisely the same lung volume each session, leading to some potential errors for comparison before and after bronchodilator inhalation. Indeed, the lung volumes that we measured on 2 occasions significantly differed for unknown reasons. However, this would not significantly affect our conclusions because lung volume was rather smaller at the second measurement and changes in volume and airway caliber were not associated among the subjects. Finally, to select exactly the same measurement sites of the airways using data obtained on different occasions would be impossible due to the technical limitations, although we attempted to select the same sites before and after treatment as much as possible. Despite such drawbacks, we demonstrated a close correlation between the overall magnitude of bronchodilation and improved airflow limitation index among the patients. This is probably because we measured 32 sites in a single lung and averaged all of the measurements, thus minimizing errors associated with the technical limitations noted above. For the same reasons, heterogeneous bronchodilation must be considered with caution when 3-dimensional airways are analyzed by computed tomography. However, by averaging data from a sufficient number of measurement sites, for instance, analysis per generation and/or per lobe, we feel that we could overcome this issue.

In conclusion, we demonstrated using 3-dimensional computed tomography that overall bronchodilation occurs in airways from the 3rd to the 6th generation in response to inhaled anticholinergics in proportion to improved FEV_1 in patients with COPD. More importantly, improvements in airflow limitation are significantly correlated with bronchodilation at the 4th to the 6th but not at the 3rd generation of bronchi. In addition, the slope of regression lines became steeper from the 3rd to the 6th generation.

Thus, bronchodilation at distal, rather than proximal airways is the determinant of functional improvement in airflow limitation in response to inhaled anticholinergics in COPD.

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Competing interests

The authors declare that they have no competing interests to disclose.

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FIGURE LEGENDS

Figure 1. Long and short axis images of right posterior basal bronchus of one individual before (A) and after 1 week of tiotropium inhalation (B). Generation 3 of bronchi are defined as segmental.

Figure 2. Relationship between % increase in inner luminal area and in FEV_1 from baseline after 1 week of tiotropium bromide inhalation in patients with COPD

(n =15). Each dot represents 1 patient; ■ and ● , patients scanned using Siemens and Toshiba instruments, respectively. Bronchodilation is expressed as mean luminal area of 4 sites of 8 bronchi (total 32 sites). Imaging and physiological data significantly correlate.

Figure 3. Relationship between % increases in luminal area and in FEV_1 from baseline according to airway generation after 1 week of tiotropium inhalation in patients with COPD (n =15). Data are expressed as (A) 3^{rd}, (B) 4^{th} (C) 5^{th} and (D) 6^{th} generations. Ai: inner luminal area of airway.

Figure 4. Percent increase in inner luminal area (Ai) before and after tiotropium inhalation according to airway generation (A) or lobe (B). Good responders are defined as those whose % increase in FEV_1 was > 20%. This trend is significant insofar as the magnitude of bronchodilation increased as the airways became smaller from the 3^{rd} to the 6^{th} generation ($p = 0.006$) in good

responders (n = 7), but not at all in poor responders (n = 8). Difference in bronchodilation between two groups was statistically significant only at generations 4, 5, and 6. Moreover, bronchodilation was significantly more extensive at 6^{th} than 3^{rd} generation only in good responders (A, p = 0.011). No differences were evident among lobes in either good or poor responders (B).

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Online data supplement

Relationship between improved airflow limitation and changes in airway caliber induced by inhaled anticholinergics in chronic obstructive pulmonary disease

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METHODS

Exclusion criteria

We excluded patients with signs of any other major pulmonary diseases such as bronchial asthma, pulmonary fibrosis, and pulmonary cancer according to chest radiographs, CT and other laboratory findings. Bronchial asthma was excluded mostly based on clinical history and laboratory findings, including levels of IgE and/or eosinophils in the blood and/or sputum, but not on the reversibility of airflow limitation in response to bronchodilators. Patients with apparent diffuse bronchiectasis were also excluded.

Computed tomography and airway analysis

We used 2 models of multidetector-row spiral CT scanners, one with 4-detector arrays (SOMATOME plus Volume Zoom, Siemens, Berlin, German), and the other with 64-detector arrays (Aquilion Multi, TSX-101A/HA; Toshiba Medical Systems, Japan). The same CT model was used for both measurements for any given individuals to avoid bias due to the use of different types of CT scanners.

Data were acquired using the following parameters: 140 kVp, 150 mA, 0.5 sec/rotation, 4 detector × 1 mm collimation, helical pitch 7 at Siemens scanner and 120 kVp, 300 mA, 0.5 sec/rotation, 64 × 0.5 mm collimation, helical pitch 41 at Toshiba scanner. Slices were 1.25 and 0.5 mm thick, respectively. Whole lungs were scanned with the patients in the supine position while holding the breath at deep inspiration. All the data sets were transferred to a workstation and then reconstructed into three-dimensional chest images (AZE Ltd., Tokyo, Japan). On this workstation, using original software with volume rendering technique, three dimensional lung objects for analyses were obtained at 3steps as follows; First, only trachea, bronchus and entire lung were extracted by using opacities under -740 HU. Second, trachea and central bronchus until second order bronchus were extracted from the object after the first step by using opacities from -740 to -975 HU. Third, only the entire lung object was obtained by subtraction of the second object from the first object. In these steps, the software automatically removed central pulmonary arteries and veins until the second order branch, which had similar opacities of lung, using original algorithm recognizing morphology. This software enables us to obtain lung volume at the occasions before and after inhalation of tiotropium. We described in detail how the inner luminal areas of airways could be measured at the 3rd to the 6th generation in our previous publication (E1). We defined the 3rd generation of any bronchi as segmental. We then selected 3 upper, 2 middle and 3 lower bronchi from the right lung and analyzed the inner luminal area at 4 sites in each bronchus from the 3rd to the 6th generation, for a total of 32 sites per patient. The site of measurement at each generation of any bronchus was selected around the center between bifurcations, and because of this and the fact that identical CT images could not be obtained on any two occasions, we anticipated that taking the average of multi-site measurements from each individual would provide a representative overall value of bronchodilation. Pre- or post-bronchodilation images were analyzed at random by one of the authors (M.H.), who was totally blinded to the background data. This was because delineation

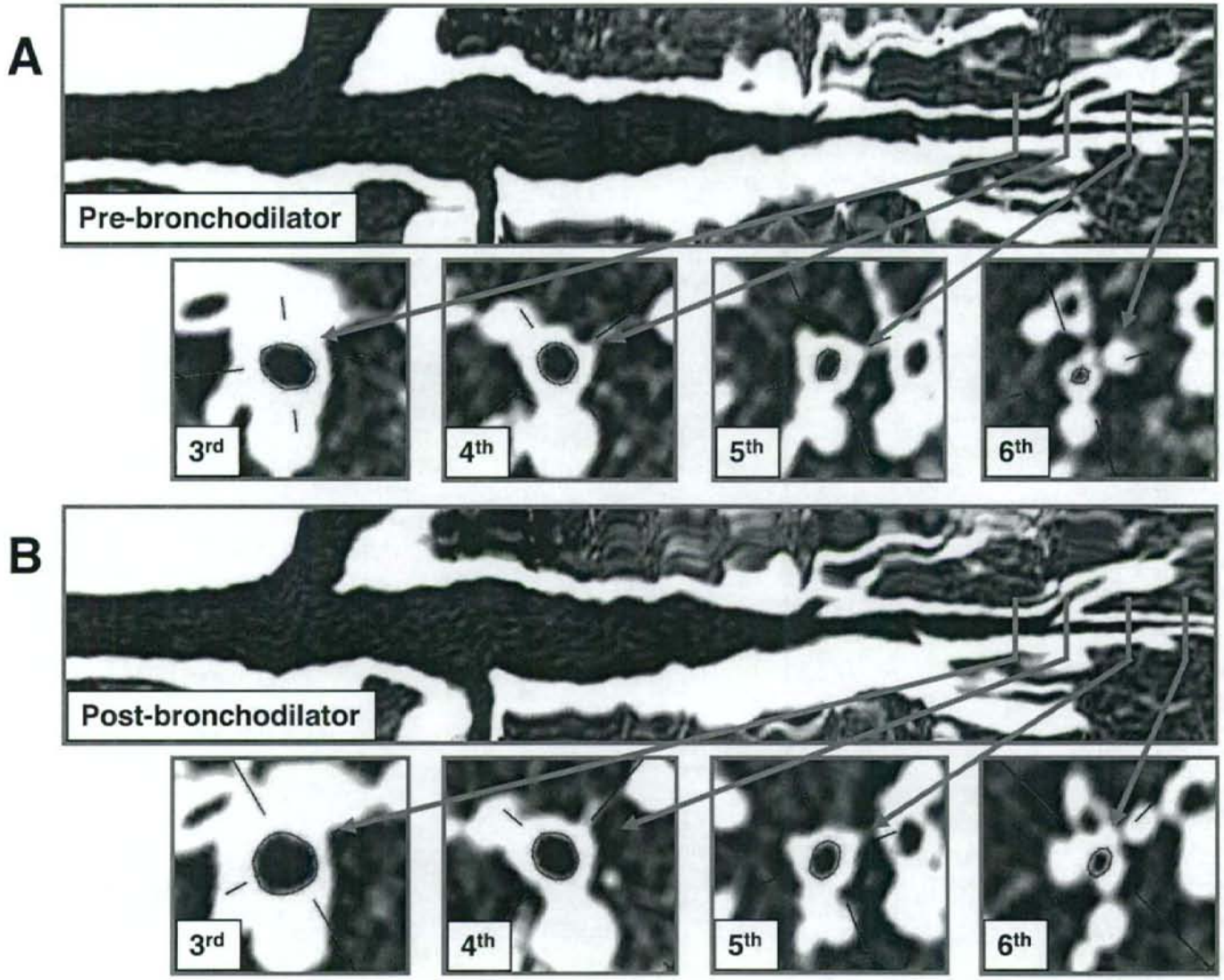
of the inner circle for the short-axis image of each bronchus was manually driven to some extent, and we tried to minimize investigator bias.

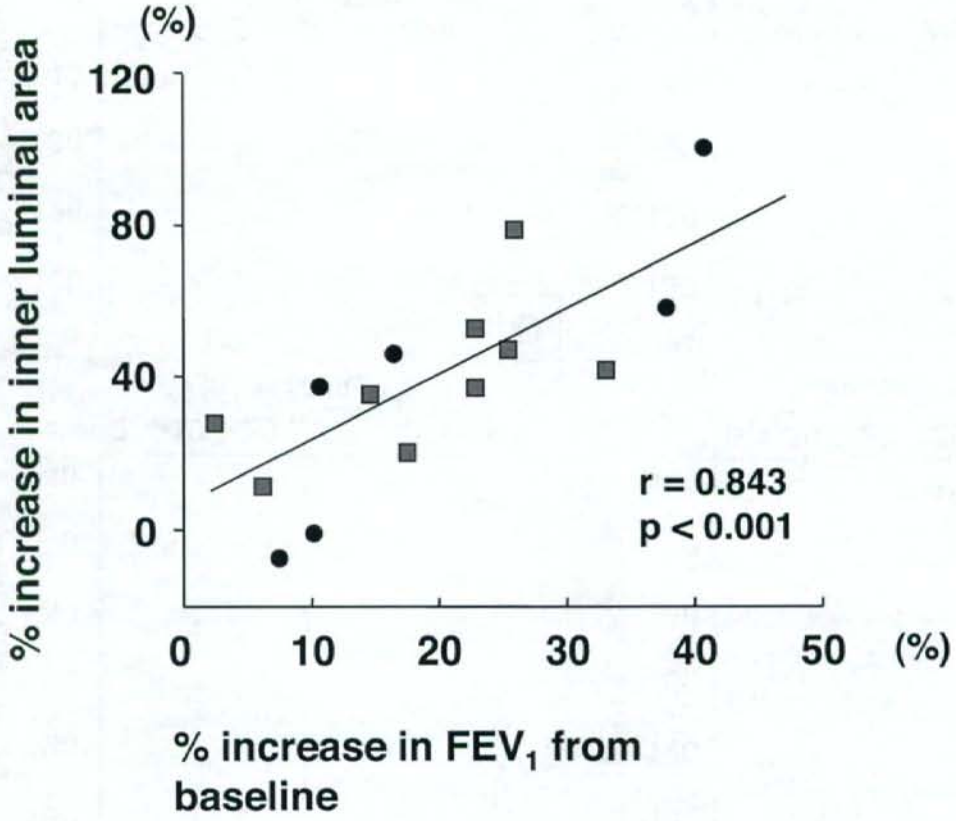
Phantom study for use of 2 different CT scanners

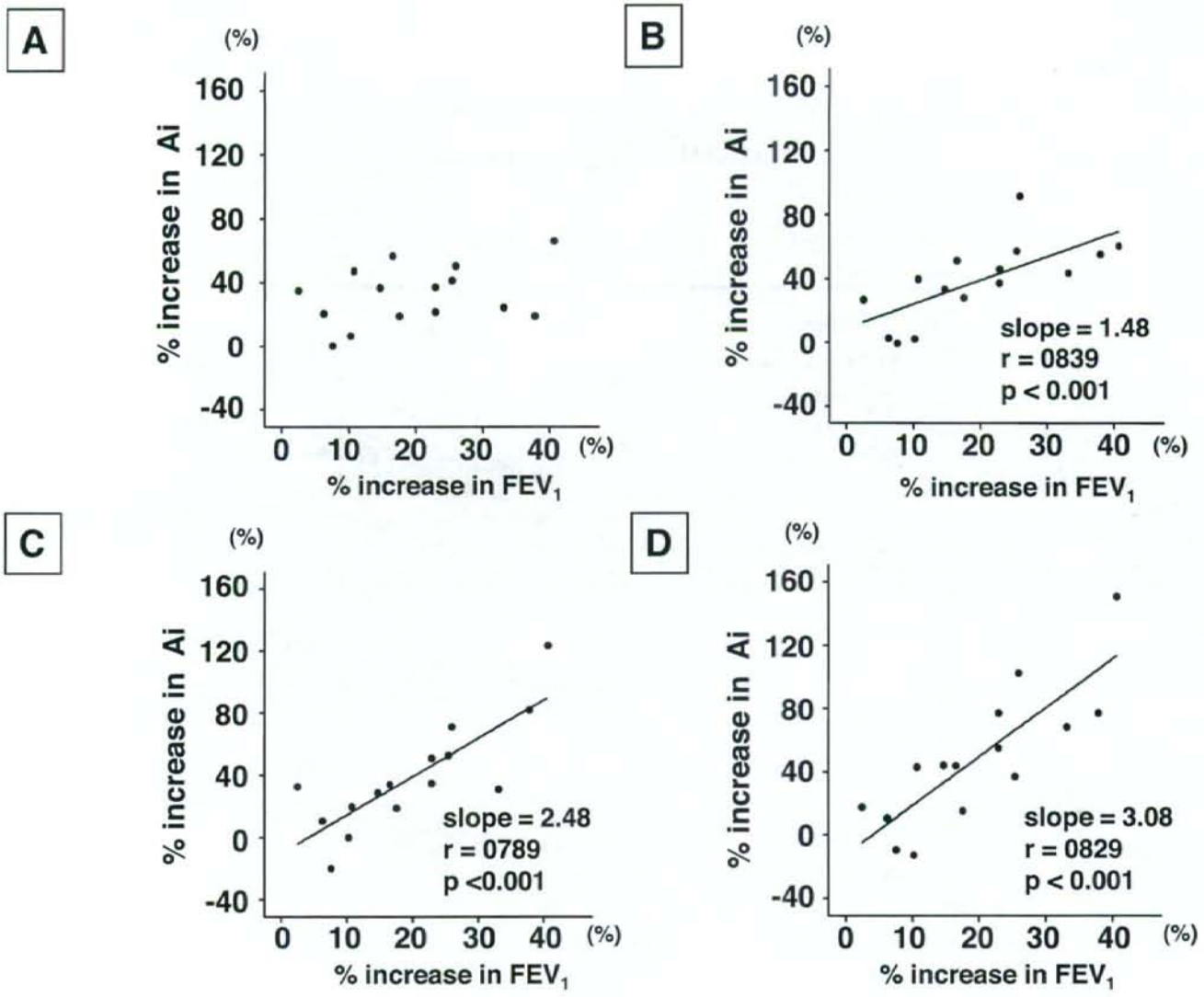
We performed a validation study using phantoms to confirm the acceptability of data using two different types of CT scanners in this study. As we reported for the 4-detector CT scanner (E1), we performed the same experiment for the 64-detector CT scanner, using 3 acrylic resin phantoms with optically accurate inner and outer diameters and wall thicknesses. Phantoms 1 and 2 were cylindrical with an inner diameter of 2.0 and 1.5 mm, respectively, and a wall thickness of 1.0 mm for both. Another was sigmoid with an inner diameter of 3.0 mm and a wall thickness of 1.0 mm. Data were acquired for the phantoms under the same conditions as we used for the clinical study. The coefficients of variation for measurements of inner luminal area were 3.3% and 6.1% for phantoms 1 and 2, respectively, which were very similar to the data obtained for the 4-detector CT scanner. Thus, we decided to measure the airways up to the 6^{th} generation as we previously reported, because the inner diameter of the 6^{th} generation of the airways averaged > 2 mm. For phantom 3, data were obtained from 40 points of the sigmoid-shaped tube, which was accurate with an inner luminal area of 7.1 mm^2. The measured area was 6.7 ± 0.1 mm^2, and the coefficient of variation was 2.2%, which was considered acceptable for further human studies, despite the small difference in absolute values. These results indicated that both CT scanners could be applied to this particular study with confidence because individual patients were assessed using the same instrument. We measured the inner luminal area, but not the airway outer wall, and considered the ratio of inner luminal areas before and after tiotropium inhalation as a marker of bronchodilation.

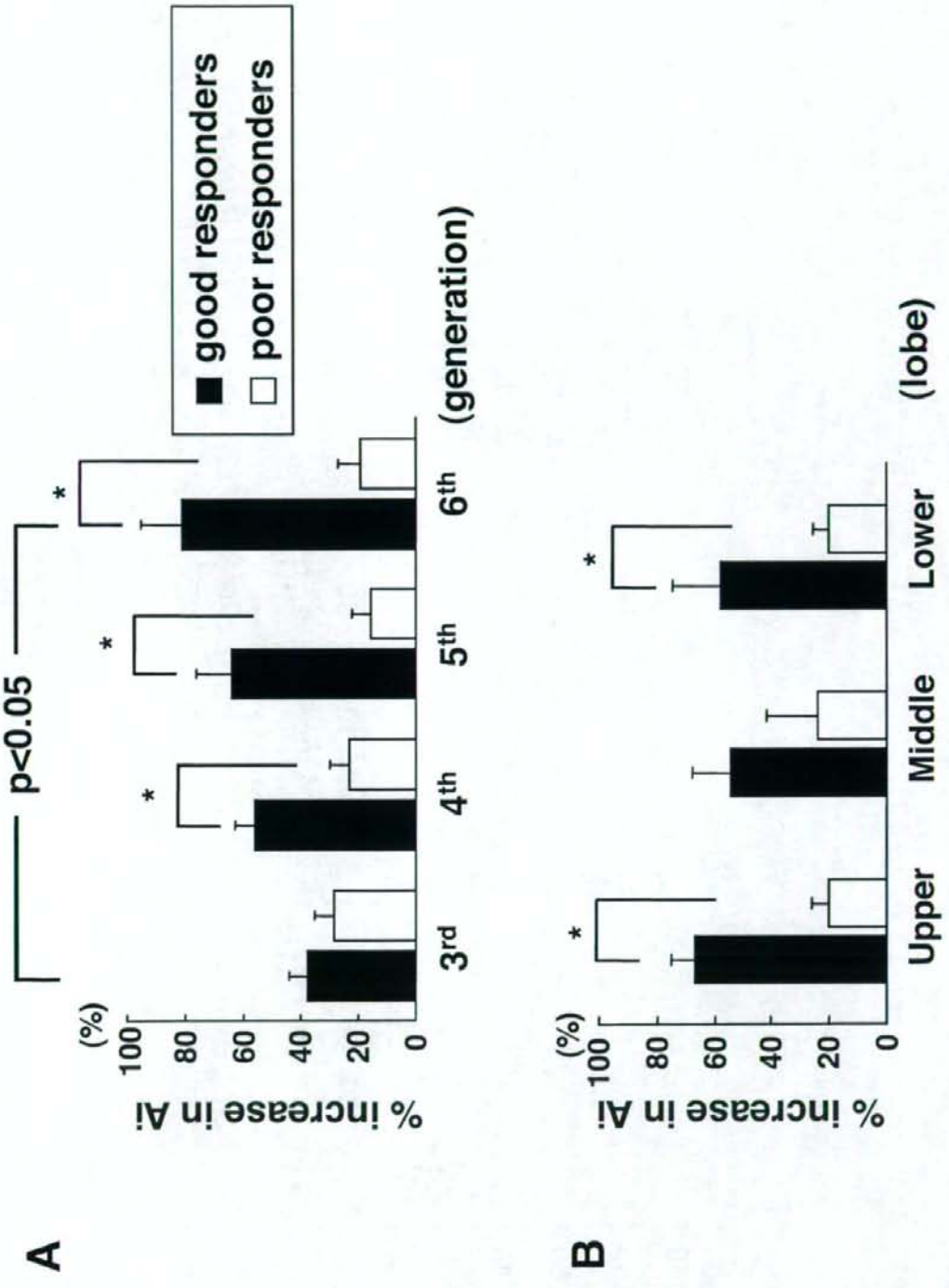
REFRENCE

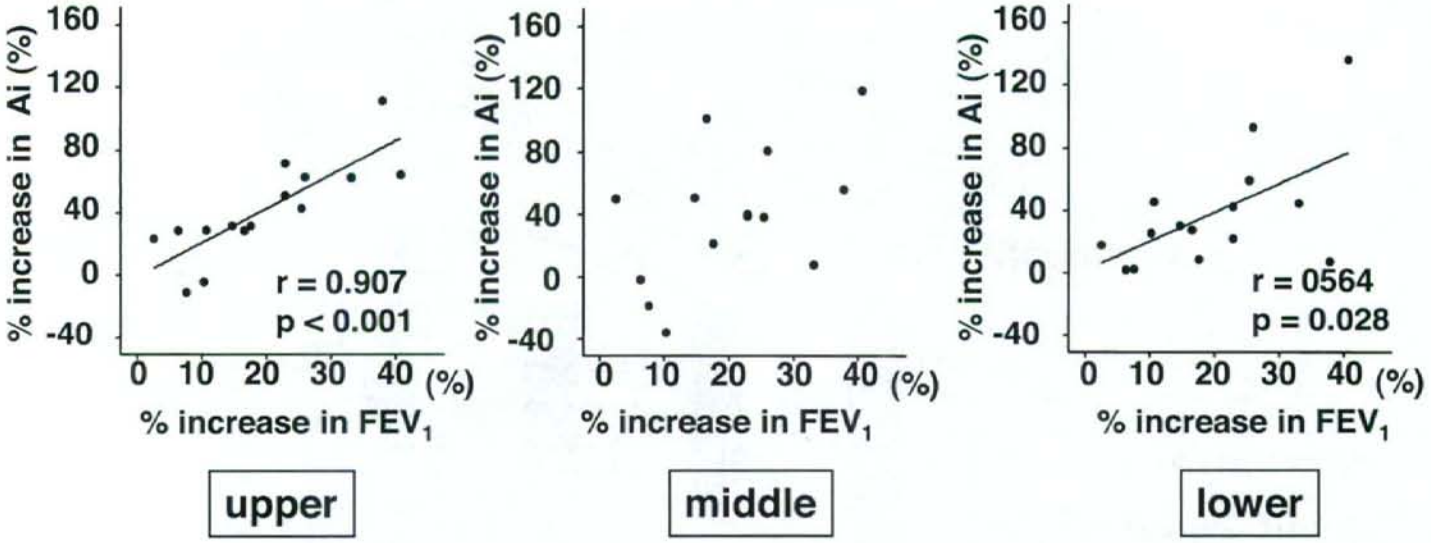
E1. Hasegawa M, Nasuhara Y, Onodera Y, Makita H, Nagai K, Fuke S, Ito Y, Betsuyaku T, Nishimura M. Airflow limitation and airway dimensions in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2006; 173: 1309-1315.

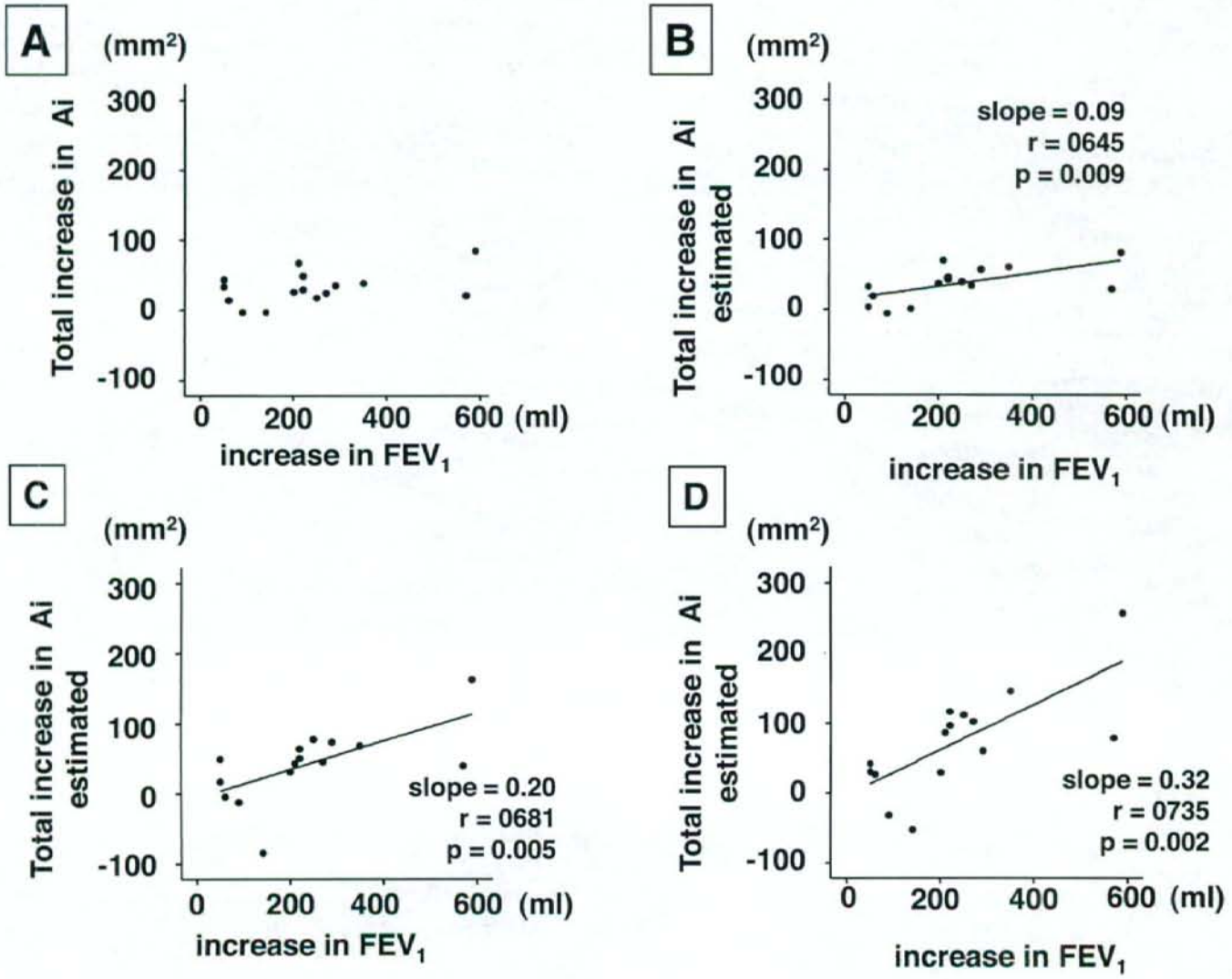












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Diversity of protein carbonylation in allergic airway inflammation

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