Online data supplement

Regional bronchodilator response assessed by computed tomography in chronic obstructive pulmonary disease

Kaoruko Shimizu[1], Hironi Makita[1], Masaru Hasegawa[1], Hirokazu Kimura[1], Satoshi Fuke[1], Katsura Nagai[1],Takayuki Yoshida[1], Masaru Suzuki[1], Satoshi Konno[1], Yoichi M. Ito[2] and Masaharu Nishimura[1]*

[1]First Department of Medicine, Hokkaido University School of Medicine

N-15 W-7, Kita-Ku, Sapporo 060-8638, Japan

[2]Department of Biostatistics, Hokkaido University Graduate School of Medicine

N-15 W-7, Kita-Ku, Sapporo 060-8638, Japan

*Correspondence to: Masaharu Nishimura, M.D.

First Department of Medicine, Hokkaido University School of Medicine

N-15 W-7 Kita-ku, Sapporo 060-8638, Japan

Fax: +81-11-706-7899; Tel: +81-11-706-5911

E-mail: ma-nishi@med.hokudai.ac.jp

Methods

Computed tomography and airway analysis

Our software provides the value of lung volume (LV) from CT measurements. In short, an image of the whole lung, including airways (A), is extracted from the 3D image of the thorax, resulting in deletion of the heart and major vessels in the lungs. Then, the bronchial skeleton (B) is extracted from the whole lung, leaving the lung parenchyma without either major vessels or proximal bronchial trees. LV is defined as (A) – (B). We confirmed that the difference in lung volume assessed by CT should be <10% in two measurements, considering the effect of lung volume on Ai.

Pulmonary Function Tests

We measured spirometry, diffusing capacity for carbon monoxide, and lung volumes assessed by the helium closed-circuit method (CHESTAC-33; Chest M.I., Tokyo, Japan).Pulmonary function tests were conducted according to the Japanese Respiratory Society guidelines,[E1] which are similar to those of the American Thoracic Society. Peak

expiratory flow within 10% of the maximum, a rapid start, absence of major flow fluctuations and adequate expiration time were required. The best results were taken as the FEV1 and FVC values obtained from acceptable maneuvers. FEV1 and FVC were expressed as percentages of predicted values following the prediction equations of the Japanese Respiratory Society. The diffusing capacity of the lung for carbon monoxide (DLco), based on the single-breath method, was also measured in all subjects according to the pulmonary function test guidelines of the Japanese Respiratory Society. DLco divided by alveolar volume (V_A) was expressed as percentage of predicted values according to the prediction equations of Burrows.[E2] Lung volumes (total lung capacity (TLC), functional residual capacity (FRC), and residual volume (RV)) were measured by the helium closed circuit method. Lung volumes were expressed as percentages of predicted values following the prediction equations of Nishida.[3]

RESULTS

Magnitude of bronchodilation caused by SFC in comparison with that of a non-intervention group

As a non-intervention group, we randomly chose patients with moderate to severe

COPD from the Hokkaido COPD cohort study, in whom CT data were obtained at an Interval of 1 year and the difference in FEV_1 was < 50 ml on two occasions. Some other pulmonary function parameters such as FEV_1/FVC (p=0.047) only slightly but significantly increased and DLco (p=0.038) decreased after one year interval (Table S1). On the other hand, in the good responders from the SFC study, vital capacity (VC) (p=0.001), FVC (p<0.001), FEV_1 (p<0.001), FEV_1/FVC (p<0.001), RV (p=0.012) and RV/TLC (p=0.008) were significantly improved, whereas in the poor responders, significant improvement was seen only FEV_1 (p=0.020) (Table S1).

There were significant differences in percentage increase in airway inner luminal area (ΔAi%) of 3rd and 4th generation bronchi even between a non-intervention group and the poor responders (3rd generation: p=0.0075; 4th generation: p=0.0475) (Figure S1). However, we could not find statistically significant difference in ΔAi% of 5th or 6th generation between a non-intervention group and the poor responders (5th generation: p=0.0824; 6th generation: (p=0.8895).

Inter-observer variability

Mean differences in the average values of ΔAi% were -0.51%, -0.65%, -11.0%, and -1.0% for the 3rd, 4th, 5th, and 6th generation bronchi, respectively. Intra-class correlation (ICC) was 66.74% for the average value of ΔAi% of 3rd generation bronchi, 83.38% for

4th generation, 34.38% for 5th generation, and 68.21% for 6th generation bronchi (Figure S2).

Table S1. The results of pulmonary function in a non intervention group, good responders and poor responders.

	non-intervention group					good responders					poor responders				
	Baseline		**after one year**			**Baseline**		**After**			**Baseline**		**After**		
VC,l (%predicted)	3.01±0.20	(98.8±4.8)	2.97±0.24	(97.7±6.3)	p=0.537	3.41±0.16	(108.6±3.1)	3.78±0.17 ‡	(120.6±3.5)	**p=0.001**	3.61±0.20	(109.8±4.0)	3.71±0.23	(112.8±5.1)	p=0.219
IC,l	1.85±0.07		1.88±0.15		p=0.834	2.32±0.15		2.45±0.12		p=0.076	2.39±0.18		2.47±0.19		p=0.290
FVC,l (%predicted)	3.10± 0.21	(101.8±5.3)	3.02±0.22	(99.5±5.6)	p=0.139	3.27± 0.16	(104.0±3.0)	3.72±0.18 ‡	(118.5±3.8)	**p<0.001**	3.51± 0.20	(106.7±4.1)	3.64±0.23	(110.6±5.0)	p=0.053
FEV1,l (%predicted)	1.14±0.09	(59.1±3.9)	1.17±0.10	(60.6±4.4)	p=0.363	1.26±0.07	(56.9±3.7)	1.58±0.09 ‡	(63.9±8.2)	**p<0.001**	1.50±0.15	(63.3±4.8)	1.59±0.17 †	(66.8±5.5)	**p=0.020**
FEV1/FVC,%	36.9±1.6		38.2±1.5†		**p=0.047**	39.1±2.4		42.9±2.5 ‡		**p<0.001**	42.5±3.3		43.2±3.4		p=0.387
DLco,ml/min/mmHg (%predicted)	11.31±1.43	(87.9±10.7)	9.99±1.62†	(80.1±13.5)	**p=0.038**	13.95±0.58	(88.8±5.7)	13.54±0.81	(86.6±6.9)	p=0.466	13.37±2.39	(76.8±10.0)	13.64±2.26	(79.1±8.6)	p=0.648
Dlco/VA,ml/min/mmHg/l (%predicted)	3.14±0.35	(76.0±8.6)	2.81±0.45	(68.4±11.2)	p=0.136	3.25±0.22	(74.7±5.5)	3.17±0.25	(73.0±6.2)	p=0.498	3.05±0.45	(67.5±9.3)	3.13±0.42	(69.9±8.5)	p=0.473
TLC,l (%predicted)	5.98±0.37	(108.9±6.0)	5.93±0.34	(107.9±5.6)	p=0.535	6.33±0.37	(116.5±4.8)	6.39±0.35	(117.7±4.6)	p=0.342	6.32±0.23	(113.2±3.5)	6.37±0.24	(114.0±3.6)	p=0.490
FRC,l (%predicted)	3.87±0.34	(116.4±9.9)	3.86±0.33	(115.4±9.6)	p=0.833	3.95±0.30	(120.8±8.2)	3.98±0.29	(119.0±7.7)	p=0.525	3.85±0.17	(116.7±5.3)	3.88±0.17	(117.4±5.1)	p=0.534
RV,l (%predicted)	2.92±0.27	(136.2±12.7)	2.93±0.28	(135.5±12.8)	p=0.920	2.89±0.25	(141.9±11.6)	2.62±0.20 †	(129.1±9.4)	**p=0.012**	2.68±0.17	(132.1±8.4)	2.64±0.13	(129.9±6.4)	p=0.573
RV/TLC,%	48.5±2.4		49.2±3.0		p=0.601	45.1±1.7		40.9±1.6 ‡		**p=0.008**	42.5±2.3		41.8±2.2		p=0.544

VC, vital capacity; IC, inspiratory capacity; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 sec;

DL_{CO}, carbon monoxide diffusing capacity; VA, alveolar volume;

TLC, total lung capacity; FRC, functional residual capacity; RV, residual volume.

Data are shown as means ± standard error of mean.

† $p<0.05$, ‡ $p < 0.01$

References

E1 Committee of Pulmonary Physiology, Japanese Respiratory Society. Guidelines for pulmonary function tests: spirometry, flow-volume curve, diffusion capacity of the lung. The Japanese Respiratory Society; Tokyo, 2004 (in Japanese)

E2. Burrows B, Kasik JE, Niden AH, et al. Clinical usefulness of the single-breath pulmonary diffusing capacity test. Am Rev Respir Dis 1961;84:789-806.

E3. Nishida O, Sewake N, Kambe M, Okamoto T, Takano M: Pulmonary function in healthy subjects and its prediction. 4. Subdivisions of lung volume in adults. *Rinsho Byori* 1976; **24**: 837-41 (in Japanese)

FIGURE LEGENDS

Figure S1. Comparison of bronchodilation in 3rd to 6th generation bronchi between a non-intervention group and those treated with SFC.

There was a significant difference in percentage increase in airway inner luminal area (ΔAi%) of 3rd and 4th generation bronchi between a non-intervention group and the poor responders or the good responders. A significant difference was also found between ΔAi% of 5th generation bronchi between a non-intervention group and the good responders.

Figure S2. Inter-observer variability in average percentage increases in airway inner luminal area by generation from the 3rd to 6th generation bronchi.

Solid lines and dotted lines represent the values of mean and 2SD, respectively.

Figure S1

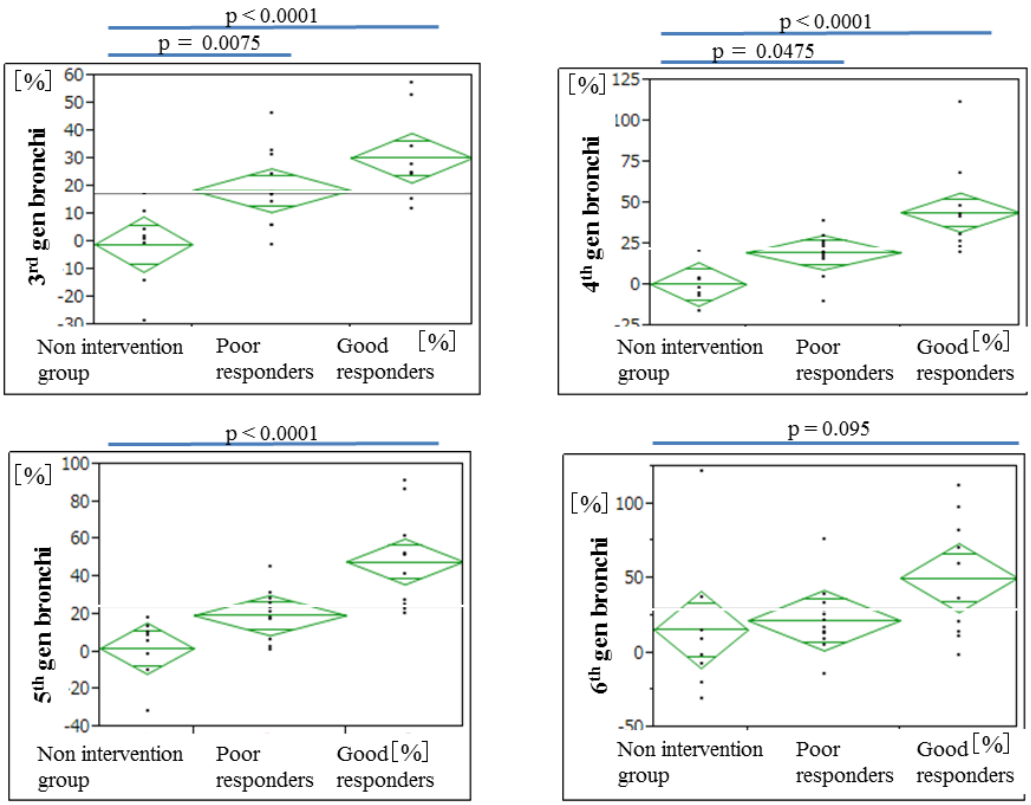
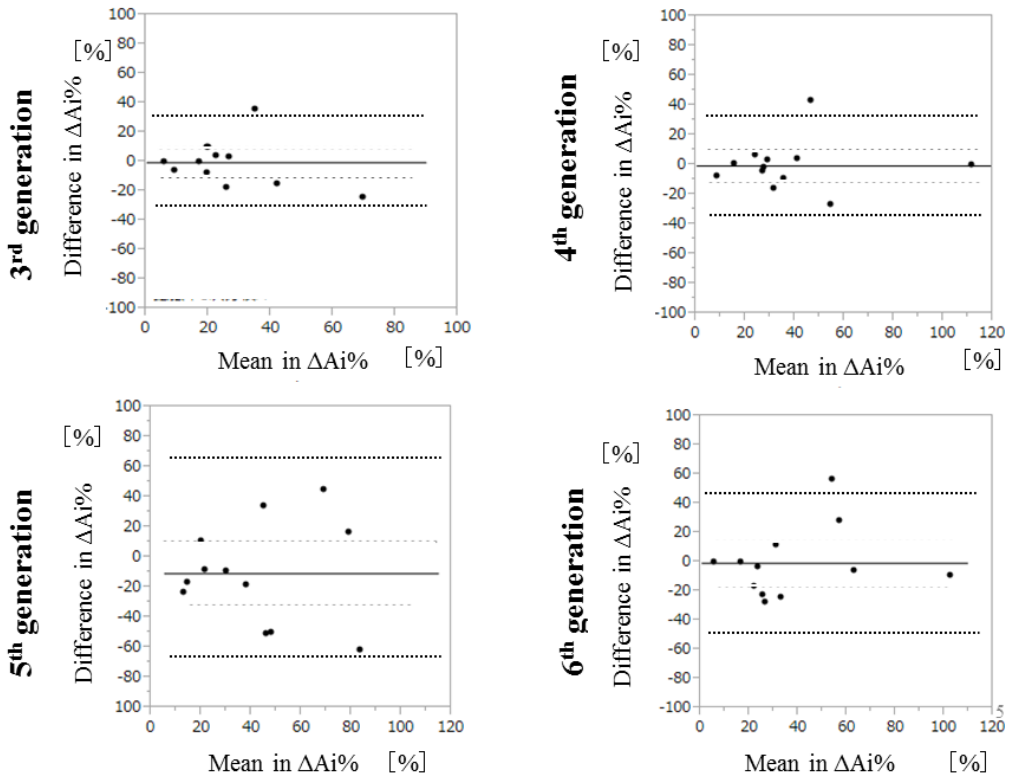

p < 0.0001
p = 0.0075
[%]
3rd gen bronchi
Non intervention group
Poor responders
Good responders
[%]
p < 0.0001
p = 0.0475
[%]
4th gen bronchi
Non intervention group
Poor responders
Good responders
[%]
p < 0.0001
[%]
5th gen bronchi
Non intervention group
Poor responders
Good responders
[%]
p = 0.095
[%]
6th gen bronchi
Non intervention group
Poor responders
Good responders
[%]

Figure S2


3rd generation
4th generation
5th generation
6th generation
Difference in ΔAi%
Mean in ΔAi%
[%]