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Relationship between regional severity of emphysema and coronary heart disease

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We analyzed the relationship between regional severity of emphysema, which was evaluated by three-dimensional fractal analysis (3D-FA) of Technegas SPECT images, and coronary heart disease (CHD). For 22 patients with emphysema who underwent Technegas SPECT, we followed up CHD events. The follow-up period was 5.4 ± 0.5 (mean $\pm$ SD) years. We defined the upper-lung fractal dimension (U-FD) and lower-lung fractal dimension (L-FD) obtained with 3D-FA of Technegas SPECT images as the regional severity of emphysema. FD became greater with the progression of emphysematous change. During the follow-up period, CHD events occurred in 6 (27%) of the 22 patients. The ratio of U-FD to L-FD for patients with CHD events (0.87 ± 0.22) was significantly smaller than for patients without CHD events (1.52 ± 0.38) ($p = 0.0015$). These findings suggest that severer emphysema in the lower lung indicates a higher risk of CHD than that in the upper lung.

Key words: Technegas, fractal analysis, pulmonary emphysema, coronary heart disease, SPECT

INTRODUCTION

EMPHYSEMA MORTALITY is increasing with the temporal trends in cigarette smoking[1–3] but death rates for chronic obstructive pulmonary disease (COPD) acount for only about one third of all the deaths that include a COPD diagnosis on the death certificate.[1–3] The results for the multiple risk factor intervention trial participants strongly suggest that decreased pulmonary function plays an important role in cardiovascular disease mortality, and probably more persons with depressed pulmonary function die of coronary heart disease (CHD) than COPD.[1–3] CHD may influence the course and outcome of emphysema and may be an important factor for predicting the prognosis of emphysema.

As our previous studies reported, the overall and regional severity of emphysema was well demonstrated by three-dimensional fractal analysis (3D-FA) of Technegas SPECT images.[4–6] In particular, our study reported that predominant emphysema in the lower lung affected pulmonary function more than that in the upper lung.[6] Because decreased pulmonary function is a major CHD risk factor,[7,8] regional severity of emphysema might be related to CHD in patients with emphysema.

In this paper, we analyze the relationship between regional severity of emphysema, which was evaluated by 3D-FA of Technegas SPECT images, and CHD events during the follow-up period.

MATERIALS AND METHODS

Patient Selection

The subjects consisted of 22 patients with pulmonary emphysema. Their ventilation studies by Technegas were performed in 1993 and 1994 at Ehime university and Ehime Prefectural Niihama hospital. Diagnosis was made on the basis of clinical symptoms, pulmonary function tests, and CT examinations according to the American

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Thoracic Society criteria.[9] We selected patients who had a heterogeneous distribution of emphysema in the entire lung, and excluded patients who had bullous type and localized emphysema only in the upper lung. Most patients had smoking-related emphysema. Table 1 shows the clinical data including physiologic indexes.

After all subjects underwent Technegas SPECT, we followed up all 22 patients for CHD events to March, 2000. The follow-up period was 5.4 ± 0.5 (mean ± SD) years (range: 0.8–7.2 year). The information sources were the medical chart of each patient and the reports by physicians.

Data Acquisition

Technegas was prepared as described in our previous paper.[4] Technegas was administered through a mouthpiece, with a nose clip *in situ,* to the patients in the sitting position. The patients slowly inhaled Technegas and then held their breath for 5 seconds at the maximal point of inspiration. This procedure was repeated three to five times.

SPECT imaging was performed with a three-headed system (TOSHIBA GCA9300, Toshiba, Tokyo, Japan) equipped with low-energy high-resolution collimators (full width at half maximum = 12 mm) and interfaced to a dedicated computer. Projection data were acquired with 5° angle intervals on a 128 × 128 matrix over 360° by rotating each detector head 120°. The acquisition time was 40 seconds/projection, corresponding to a total acquisition time of 16 minutes. The voxel size was 3.2 mm × 3.2 mm × 3.2 mm. Reconstruction of images was done by means of the filtered back-projection method with a ramp back-projection filter and a Butterworth filter (order = 8, cut-off frequency = 0.15 cycles/pixel). Attenuation correction was not done.

Fractal Analysis

As mentioned in our previous paper,[4–6] with natural objects, familiar matrices from classical geometry such as length, area and volume depend on the scale at which we decide to look at the object. Fractal geometry characterizes where the relationship between a measure (M) and the scale (ε) is expressed as

$$M(\varepsilon) = k \cdot \varepsilon^{-D}, \qquad \text{Eq. 1}$$

where k is a scaling constant and D is the fractal dimension.[10]

We delineated the lung at 15, 20, 25, and 30% cut-off level of the maximal pixel radioactivity in all slices of SPECT images, and measured the total number of pixels in the areas surrounded by the contours obtained with each cut-off level. In this study, the cut-off level of the maximal pixel radioactivity was used as ε and the total number of pixels measured was used as $M(\varepsilon)$ in Equation 1. In practice, we calculated a linear regression equation from the total number of pixels and cut-off levels transformed into natural logarithms, and obtained the fractal dimension from the slope of the linear regression equation.

We calculated the fractal dimensions for total-lung, upper-lung, and lower-lung and defined the total-lung fractal dimension (T-FD), upper-lung fractal dimension (U-FD) and lower-lung fractal dimension (L-FD) as the severity of emphysema for the overall or regional lung.

Statistical Analysis

The significance of differences in pulmonary function tests and the FD between patients with CHD events and patients without a CHD event was determined by using the Mann-Whitney's U test. In all tests, $p < 0.05$ was regarded as significant.

Technegas was provided by Daiichi Radioisotope Co. Ltd. (Tokyo, Japan).

Table 1 Clinical data and physiologic idexes in 22 patients with emphysema

	mean ± s.d.	range
Number (male/female)	22 (20/2)	
Age (year)	69.1 ± 8.4	49–83
Smoker	18 (82%)	
Forces expiratory volume in 1 second (FEV_1) (% predicted)	38.8 ± 13.7	21.8–69.2
Forced vital capacity (FVC) (% predicted)	74.6 ± 22.2	36.6–106
FEV_1/FVC	35.6 ± 9.3	18.3–57.6
Residual volume (RV) (% predicted)	187.8 ± 39.9	134.6–334.5
RV/total lung capacity (TLC)	47.3 ± 7.5	40.3–75.9
Diffusing capacity of lung for carbon monoxide (mL/min per mmHg)	7.7 ± 2.1	2.5–11.2
PaO_2 (mmHg)	75.2 ± 10.3	65.6–88.2
$PaCO_2$ (mmHg)	47.8 ± 7.6	39.7–56.4

Table 2 CHD risk factors and pulmonary function tests for patients with CHD event versus those without CHD event

	with CHD event	without CHD event	p value
Number	6	16	
Male	6 (100%)	14 (88%)	NS
Age (year)	72 ± 5.9	68 ± 8.9	NS
Smoker	5 (83%)	13 (81%)	NS
Hypertension	0 (0%)	2 (13%)	NS
Hyperlipidemia	0 (0%)	2 (13%)	NS
Diabetes	0 (0%)	2 (13%)	NS
FEV_1 (mean ± s.d.)	30.5 ± 6.3	44.1 ± 15.7	NS (0.055)
FVC (mean ± s.d.)	50.9 ± 11.3	84.7 ± 15.3	0.017

FEV_1: Forced expiratory volume in 1 second
FVC: Forced vital capacity
NS: not significant

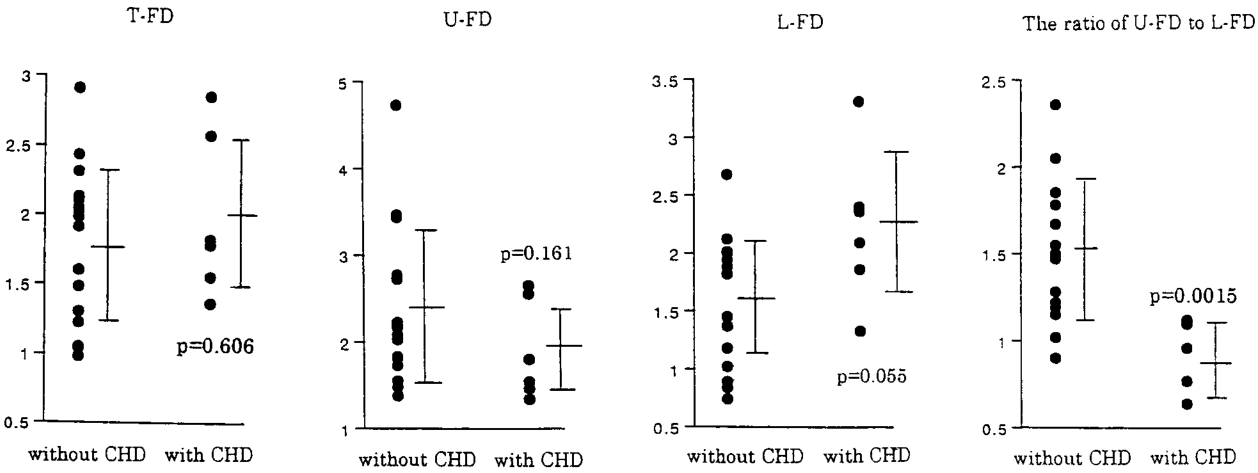

Fig. 1 Comparison of T-FD, U-FD, L-FD, and the ratio of U-FD to L-FD between patients with CHD events and those without CHD events. There was no significant difference in T-FD, U-FD, and L-FD between these two groups. The ratios of U-FD to L-FD for patients with CHD events was significantly smaller than for patients without CHD events ($p = 0.0015$). CHD = Coronary Heart Disease

RESULTS

During the follow-up period, CHD events occurred in 6 (27%) of the 22 patients. Two of the 6 patients died of cardiac failure due to myocardial infarction. One of the 22 patients without CHD died of malignant ureter tumor. CHD risk factors in patients with CHD events and those without CHD event matched. There was a high frequency of males and smokers, which were risk factors for both CHD and emphysema. There was no difference between these two groups in the other risk factors such as hypertension, diabetes and hyperlipidemia (Table 2). Forced vital capacity (FVC) for patients with CHD events was significantly smaller than for patients without CHD events ($p = 0.017$). There was no significant difference between patients with CHD events and without CHD events in forced expiratory volume in 1 second (FEV_1/FVC) (Table 2).

T-FD for patients with CHD events and those without CHD events were 1.99 ± 0.54 and 1.78 ± 0.55, respectively. U-FD for patients with CHD events and those without CHD events were 1.89 ± 0.52 and 2.35 ± 0.86, respectively. L-FD for patients with CHD events and those without CHD events were 2.23 ± 0.60 and 1.60 ± 0.53, respectively. The ratios of U-FD to L-FD for patients with CHD events and those without CHD events were 0.87 ± 0.22, and 1.52 ± 0.39, respectively (Fig. 1). The ratios of U-FD to L-FD for patients with CHD events was significantly smaller than for patients without CHD events ($p = 0.0015$).

DISCUSSION

Fractal dimension obtained by 3D-FA of Technegas SPECT images becomes greater according to the progress of emphysematous change.[4–6] The small ratio of U-FD to L-FD means severer emphysema in the lower lung than in the upper lung. The ratio of U-FD to L-FD for patients with CHD event was significantly smaller than for patients without CHD event (Fig. 1). CHD risk factors for patients with CHD events and without CHD events were matching (Table 2). These results suggested that patients with severer lower lung emphysema will be at higher risk of CHD than those with upper lung emphysema. FVC for patients with CHD events was significantly smaller than for patients without CHD events (Table 2). This result may mean that FVC for patients who had predominant emphysema in the lower lung was decreased in many cases. In this study, patients with a ratio of U-FD to L-FD of > 1.16 had a significantly greater FVC than did patients with < 1.16 (the Mann-Whitney's U test, $p = 0.011$). The average (1.16) ratio of U-FD to L-FD for 11 healthy volunteers was considered a standard value for the difference in heterogeneity between upper and lower lungs.[6] On the other hand, no significant difference was evident between the patient groups stratified by U-FD and L-FD in FVC. These results suggested that patients with a small ratio of U-FD to L-FD had decreased FVC and confirmed that predominant emphysema in the lower lung affected pulmonary function more than that in the upper lung.[11,12] Predominant lower lung emphysema and resultant reduced lung volume might be related to CHD events. One reason is that reduced lung volume reflects impaired cardiac function due to pre-existing CHD that has not yet resulted in angina pectoris or myocardial infarction.[7,8] The second reason is that, by decreasing the oxygenation of the blood, pulmonary disease promotes myocardial ischemia and its consequences, especially when the coronary circulation is impaired.[7,8] These explanations were considered to be reasonable for a closer relationship between predominant lower lung emphysema and CHD events.

In conclusion, it is possible that patients with severer lower lung emphysema will be at higher risk of CHD than those with upper lung emphysema. 3D-FA of Technegas SPECT images which can demonstrate regional severity of emphysema might be a useful method for making a prognosis of emphysema.

REFERENCES

1. Marcus EB, Buist AS, Maclean CJ, et al. Twenty-year trends in mortality from chronic obstructive pulmonary disease: the Honolulu heart program. *Am Rev Respir Dis* 140: 64–68, 1989.
2. Kuller LH, Ockene JK, Townsend M, et al. The epidemiology of pulmonary function and COPD mortality in the multiple risk factor intervention trial. *Am Rev Respir Dis* 140: 76–81, 1989.
3. Postma DS, Sluiter HJ. Prognosis of chronic pulmonary disease: the Dutch experience. *Am Rev Respir Dis* 140: 100–105, 1989.
4. Nagao M, Murase K, Yasuhara Y, et al. Quantitative analysis of pulmonary emphysema: three-dimensional fractal analysis of single-photon emission computed tomography images obtained with a carbon particle radioaerosol. *AJR* 171: 1657–1663, 1998.
5. Murase K, Nagao M, Kikuchi T, et al. Three-dimensional fractal analysis for quantification of heterogeneity of radioisotope distribution in the organ using SPECT. *J Nucl Med* 40: 292P, 1999. (Abstract)
6. Nagao M, Murase K, Yasuhara Y, et al. Quantitative analysis of Technegas SPECT: evaluation of regional severity of emphysema. *J Nucl Med* 41: 590–595, 2000.
7. Kannel WB, Hubert H, Lew EA. Vital capacity as a predictor of cardiovascular disease. The Framingham study. *Am Heart J* 105: 311–315, 1983.
8. Friedman GD, Klatsky AL, Siegelaub AB. Lung function and risk of myocardial infarction and sudden cardiac death. *N Engl J Med* 294: 1071–1075, 1976.
9. American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease (COPD) and asthma. *Am Rev Respir Dis* 136: 225–244, 1987.
10. Mandelbrot BB. *Fractal Geometry of Nature*. San Francisco: Freeman, 1982.
11. Thurlbeck WM, Muller NL. Emphysema: definition, imaging, and quantitation. *AJR* 163: 1017–1025, 1994.
12. Gurney JW, Jones KK, Robbins RA, et al. Regional distribution of emphysema: correlation of high-resolution CT with pulmonary function tests in unselected smokers. *Radiology* 183: 457–463, 1992.