Annals of Nuclear Medicine Vol. 16, No. 6, 369–376, 2002

Measurement of heterogeneous distribution on Technegas SPECT images by three-dimensional fractal analysis

Michinobu NAGAO* and Kenya MURASE**

*Department of Radiology, Matsuyama Medical Center for Cancer and Cardiovascular Disease
**Department of Medical Engineering, Division of Allied Health Sciences, Osaka University Medical School

This review article describes a method for quantifying heterogeneous distribution on Technegas (^{99m}Tc-carbon particle radioaerosol) SPECT images by three-dimensional fractal analysis (3D-FA). Technegas SPECT was performed to quantify the severity of pulmonary emphysema. We delineated the SPECT images by using five cut-offs (15, 20, 25, 30 and 35% of the maximal voxel radioactivity), and measured the total number of voxels in the areas surrounded by the contours obtained with each cut-off level. We calculated fractal dimensions from the relationship between the total number of voxels and the cut-off levels transformed into natural logarithms. The fractal dimension derived from 3D-FA is the relative and objective measurement, which can assess the heterogeneous distribution on Technegas SPECT images. The fractal dimension strongly correlate pulmonary function in patients with emphysema and well documented the overall and regional severity of emphysema.

Key words: heterogeneity, SPECT, Technegas, fractal analysis, pulmonary emphysema

INTRODUCTION

TECHNEGAS (^{99m}Tc-carbon particle radioaerosol; Daiichi Radioisotope Co. Ltd., Tokyo, Japan) has been used recently for ventilation studies of the lung. Burch et al. reported that Technegas has particles of a considerably smaller size, and these can reach the peripheral parts of the lung.[1,2] Technegas has the advantage of not being cleared from the lung once the particles stick to the alveolar wall and therefore is suitable for SPECT studies.[3,4]

Technegas SPECT images reveal peripheral irregularity in mild emphysema and further hot spot formation and regional defects in severe emphysema (Fig. 1).[3,4] The consequent heterogeneous appearance of Technegas distribution has been used as a diagnostic index for emphysematous severity, but an objective quantification of such severity is difficult to make because of the lack of a convenient and widely accepted standard for quantifying spatial heterogeneity. We thought that the three-dimensional fractal analysis (3D-FA) could be applied as a reproducible and sensitive quantification of emphysematous severity.[5,6] Fractal analysis is potentially suitable for an objective quantification of spatial heterogeneity because it is believed to be effective in helping to characterize complex systems that are hard to describe by means of conventional Euclidean geometry.[7,8]

In this review, we introduce 3D-FA for quantifying the heterogeneous distribution on Technegas SPECT images and investigate the meaning and clinical application of 3D-FA.

THREE-DIMENSIONAL FRACTAL ANALYSIS

Characteristics of Technegas

The ideal size of aerosol droplets in order to get good uniformity in the lungs during deep tidal volume breathing was considered to be between 0.1 and 0.5 μm.[9] Because particles larger than 2 μm are likely to be deposited in the proximal bronchial trunci, ^{99m}Tc-phytate aerosol images had a limitation due to intense bronchial foci in cases with severe chronic obstructive pulmonary

Received July 3, 2002, revision accepted August 1, 2002.

For reprint contact: Michinobu Nagao, M.D., Department of Radiology, Matsuyama Medical Center for Cancer and Cardiovascular Disease, Yanaimachi 2–85, Matsuyama, Ehime 790–0014, JAPAN.

E-mail: minagao@ehime.med.or.jp

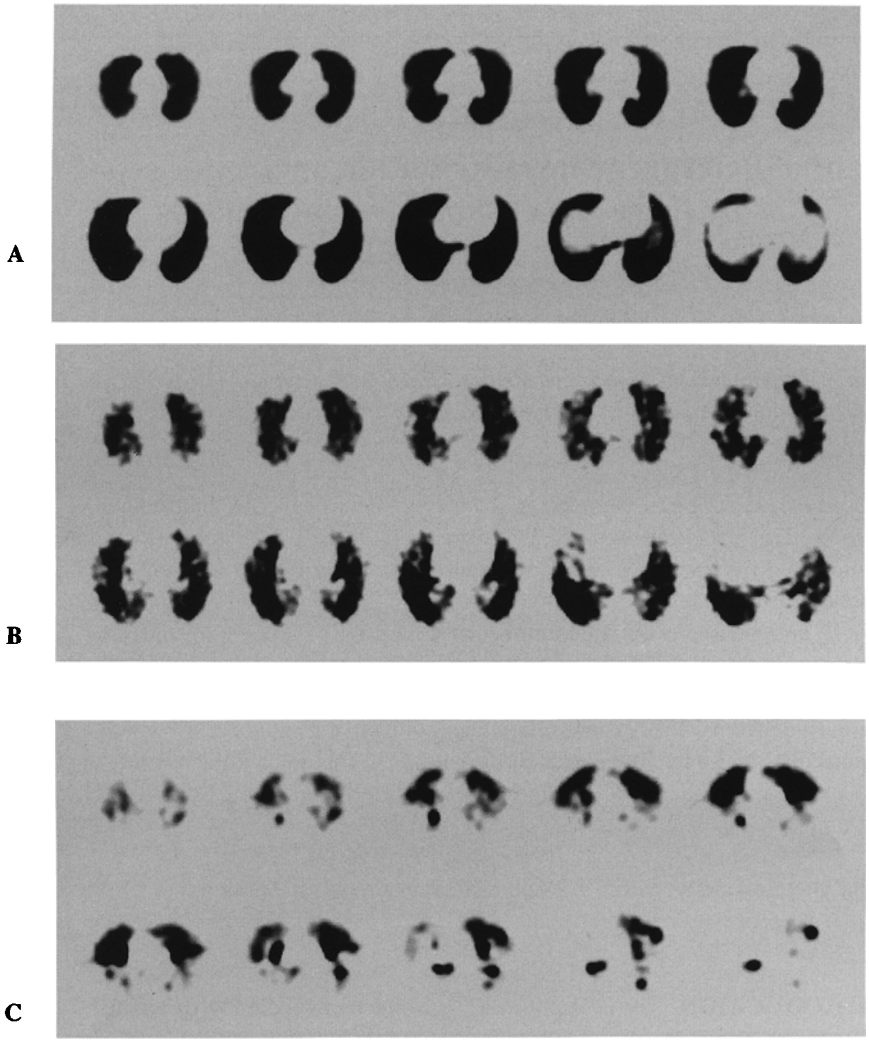

Fig. 1 A: 45-year-old healthy male. Technegas SPECT images show homogeneous distribution in whole lung. His fractal dimension for total lung is 0.46. B: 65-year-old male with mild emphysema. Technegas SPECT images show heterogeneous distribution in whole lung. His fractal dimension for total lung is 0.79. C: 63-year-old male with severe emphysema. Technegas SPECT images show heterogeneous distribution of cold and hot spots throughout peripheral lung field. His fractal dimension for total lung is 2.54.

disease.[10] Technegas is ultra fine carbon particles of the order of 0.005 μm.[1] Technegas imaging also provides similar or better diagnostic information on lung ventilation imaging than ^{133}Xe and ^{81m}Kr.[2,11] ^{81m}Kr and ^{133}Xe scintigraphy needs a ventilation system. Technegas is readily available, is easy to use, is inexpensive, and delivers a low radiation dose.[1,2]

Data acquisition for Technegas SPECT

Technegas was generated in a proprietary generator (Technegas Generator, Tetley Manufacturing Ltd., Sydney, Australia) by the resistive heating of a graphite crucible to 2500 °C in which a saline solution of 266–600 MBq of ^{99m}Tc-pertechnetate had been placed and dried. After generation of the aerosol, it was dispersed in a lead-lined chamber in an atmosphere of 100% argon. Technegas was administered through a mouthpiece, with a nose clip *in situ*, to 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 with 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 performed by 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 performed (Fig. 1).

Fractal analysis
Fractals have been introduced by Mandelbrot[7,8] to characterize structures and processes occurring in nature. The principal features of fractal objects are: 1. a large degree of heterogeneity, 2. scaling similarity over many scales of observation, and 3. the lack of a well-defined scale.[12] Strictly speaking, a structure (such as lung vasculature or vermis of the cerebellum) is fractal if its small scale appears similar to its large scale form. Fractal geometry characterizes where the relationship between a measure (M) and the scale (ε) is expressed as

$$M(\varepsilon) = k \cdot \varepsilon^{-D}, \quad (1)$$

where k is a scaling constant and D is called the fractal dimension.[7,8] As equation (1) implies, the quantity M to be measured is a function of the ruler scale and can be a nonconstant. The fractal dimension (D) is one parameter that is useful for this purpose in characterizing organizationally complex structures.[12] The fractal dimension is a scale-independent measure of spatial or temporal heterogeneity ('complexity'). As the fractal dimension increases, the structure occupies more space and is more 'complex'.

Concept of three-dimensional fractal analysis (3D-FA)
We used four or five cutoffs of the maximal voxel radioactivity in SPECT images to segment the organic tissue, so that the total apparent area occupied by the organic tissue varied as a function of the radioactivity thresholds. The four or five chosen thresholds were used as the ruler scale ε in equation (1), and the total number of voxels with radioactivity higher than the corresponding thresholds were used as $M(\varepsilon)$. Clearly, $M(\varepsilon)$ decreases as ε increases; hence a linear regression on the $M(\varepsilon)$ versus ε graph, when plotted on a natural logarithm versus natural logarithm scale, yields a negative slope with magnitude equal to the fractal dimension D. As the fractal dimension increases, the distribution of radionucleoids on SPECT becomes more heterogeneous.[5,6]

Calculating fractal dimension
The reconstructed axial Technegas SPECT images transferred to a computer for analyzing medical imaging (Dr View, Asahikasei, Tokyo, Japan). The computer in Dr View automatically delineated the lung at 15, 20, 25, 30 and 35% cut-off levels of the maximal voxel radioactivity in all slices of SPECT images, and measured the total number of voxels in the areas surrounded by the contours obtained with each cut-off level. Figure 2 is the histogram of the number of voxels with changing cut-off levels in two patients with emphysema. In practice, we calculated a linear regression equation from the total number of voxels and cut-off levels transformed into natural logarithms, and obtained the fractal dimension from the slope of the linear regression equation. In Figure 3, the graphs show the calculation of fractal dimension for the same cases in Figure 2.

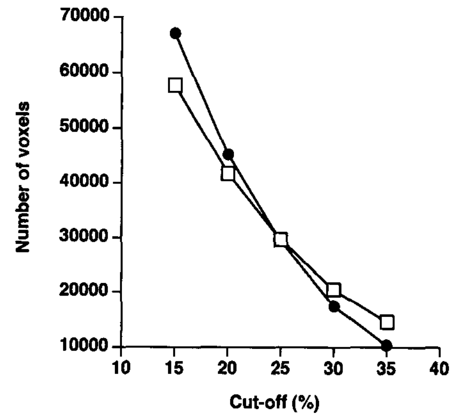

Fig. 2 Histogram of the number of voxels with changing cut-off in two patients with emphysema.

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. The upper lung was defined as the axial SPECT images above the subcarina and the lower lung was defined as those below the subcarina. To identify the subcarina level of a subject, the level was marked with a pen on the anterior chest when undergoing chest radiography, and then a small quantity of $^{99m}TcO_4^-$ was placed on this marked point when performing a SPECT study. The number of axial SPECT slices both for the upper and the lower lung zones was the same.

Selection of cut-off range
The important factor in calculating the fractal dimension is the range of cut-off levels. The decrease in the apparent tissue area with the increase in the cut-off is a natural trend in digital images as shown in Figure 2. In a Technegas SPECT study, when a cut-off of less than about 10% is used, regions outside the lung also tend to be delineated, especially in patients with severe emphysema.[3–6,13] Furthermore, hot spot formation in the central air way in emphysema had a high radioactivity with a cut-off of more than about 40%.[3–6,13] In this analysis, we targeted the ventilatory impairment of the peripheral airway in emphysema and selected the 15–35% cut-off range. The numbers of voxels from 15% to 35% cut-off were 59459 ± 33090 (mean ± SD) and 19311 ± 20498 and the

histogram decreased greatly with the increase in the cut-off level (Fig. 2). Since patients with emphysema inhale a small amount of Technegas, the maximal pixel radioactivity in patients with emphysema is much smaller than that in healthy controls. Hot spots, which were seen in patients with emphysema, had a high radioactivity with more than a 40% cut-off. Consequently, a relative low radioactivity area with a 15–35% cut-off range is enough to account for the greatest ventilatory volume in patients with emphysema.

Mathematical meaning of fractal dimension

Chung et al. suggested that the fractal dimension tends to be large when the tissue area at low cut-off (15%) is small.[14] The fractal dimension in a patient with a large tissue area at 15% cut-off was smaller than that in a patient with a smaller tissue area (Fig. 3). Although the tissue area at low cut-off in patients with emphysema sometimes becomes larger than that in healthy controls caused by air-trapping and thoracic hyperinflation, the fractal dimension for patients with emphysema was greater than that for healthy controls.[5] These results indicate that the fractal dimension is not only an indicator of the percentage area of low radioactivity.

If the five data points fall exactly on the regression line (Fig. 3), the fractal dimension is directly proportional to the ratio of lung tissue area when segmenting at two different cut-offs (i.e., 15% and 35% of the maximal radioactivity). Consequently, the fractal dimension strongly correlate with the natural logarithms of the ratio of lung tissue areas segmented at 15% and 35% cut-off ($r = 0.999$) (Fig. 4). In five cases with a U-FD greater than 3.0, the relationship between the cut-off level and the total number of voxels transformed into natural logarithms tends to become non-linear. In such cases, the fractal dimension did not closely correlate with the ratio of lung tissue areas segmented at 15% and 35% cut-off.

The fractal dimension mathematically associates with the ratio of the alterative ventilatory volume from the low radioactivity area to the high radioactivity area on Technegas SPECT images. We consider that the fractal dimension may demonstrate the spatial heterogeneity of Technegas distribution.

Accuracy of three-dimensional fractal analysis (3D-FA)

The accuracy of fractal analysis is evaluated by a linear regression on the $M(\varepsilon)$ versus ε graph, when plotted on a natural logarithm versus natural logarithm scale.[7,8] In 25 patients with emphysema, the relationship between the cut-off and the number of voxels transformed into natural logarithms became linear (Fig. 3), and the correlation coefficient (mean ± SD) between them was 0.99 ± 0.01. Three-dimensional distribution of Technegas obtained from the selected cut-off range appeared to have a fractal form. The selected cut-off range is reasonable for fractal analysis.

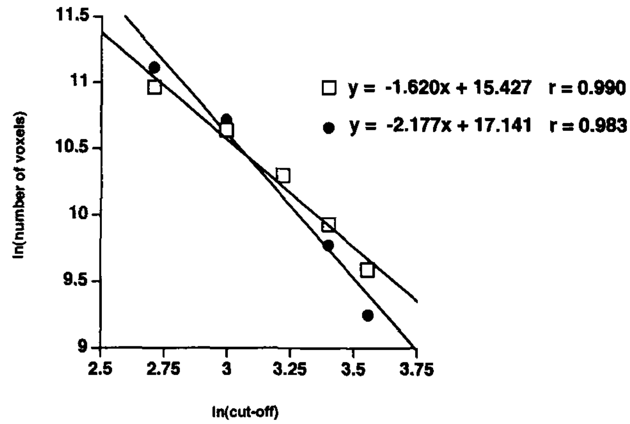

Fig. 3 Graph shows method of calculating fractal dimensions. The X-axis represents cut-off levels transformed into a logarithm, while the Y-axis represents logarithm of total number of pixels in areas surrounded by contours obtained with each cut-off level. Slope of linear regression equation corresponds to fractal dimension. □; $y = -1.62x + 15.43$, $r = 0.99$, ●; $y = -2.18x + 17.14$, $r = 0.98$

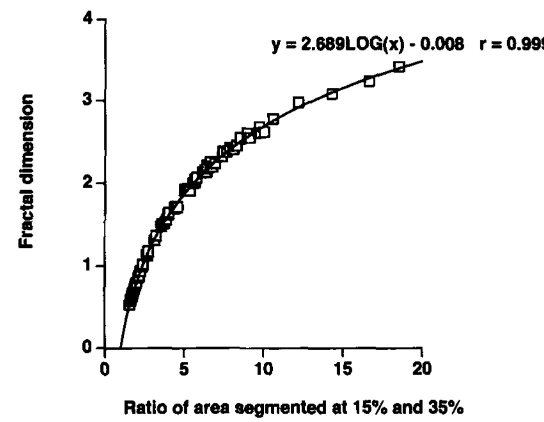

Fig. 4 Scatter plot of fractal dimension and ratio of apparent tissue areas segmented at 15% and 35% of maximal radioactivity in 72 cases. The three cases had a greater than 3.5 of U-FD were excluded.

We recently reported that quantification of the heterogeneous distribution in Alzheimer's disease on cerebral blood flow (CBF) SPECT images was possible by 3D-FA.[15] The fractal dimension was closely correlated with the cognitive impairment, as assessed in neuropsychological tests and may be useful for evaluating the progression of Alzheimer's disease. In 6 patients with probable Alzheimer's disease, CBF SPECT was performed twice in more than one year (mean; 12.5 months). In all the patients, the fractal dimension slight increased (mean; 0.14) with the cognitive impairment progressing during the interval accordingly. This result confirms that the reproducibility of 3D-FA is probably satisfactory. If we could investigate the change in the fractal dimensions over a long period of time, we could elucidate more clearly the clinical usefulness of 3D-FA in evaluating the progression of Alzheimer's disease.

Other quantitative analysis of heterogeneity

Spatial variation in ventilation, regional blood flow and metabolism in the living organ is measurable even with low spatial resolution techniques such as PET and SPECT. The coefficient of variation (COV) is often used to assess heterogeneity on lung ventilation and perfusion SPECT images.[13,16] In the present study, the total radioactivity of Technegas inhaled by patients differs according to the individual, and the number of voxels at 15% cut-off varied from 20802 to 132423, but the fractal dimension was not associated with the amount of Techneges inhaled. The COV is strongly influenced by the tissue sample size or size of the region of interest. As the computer automatically calculates the fractal dimension, 3D-FA may be more interobserver independent than the COV method.

Kuikka et al. described the fractal analysis of 2D SPECT images, which applies a box counting method of fractal analysis.[17,18] In 2D fractal analysis, the number of subregions (ROI size) and the COV in ROI was used as the ruler scale ε and as $M(\varepsilon)$ in equation (1). Two hundred and fifty-six symmetrical regions of interest (ROI) were drawn on each hemisphere of the reconstructed SPECT images when measuring the heterogeneity of cerebral blood flow.[19] The whole cortex on reconstructed SPECT images contains 512 subregions. The mean size of ROIs is 1 cm^3. A fractal relationship exists between the number of subregions (ROI size) and the COV in ROI. Special software is necessary to draw many symmetrical ROIs and to calculate the COV corresponding to ROI size in this analysis. As a simple method, 3D-FA is more applicable for routine clinical use than 2D-FA.

CLINICAL APPLICATION

Patient selection

This review is based on the result for 25 patients with pulmonary emphysema. Diagnosis was made on the basis of clinical symptoms, pulmonary function tests, and CT examinations according to the American Thoracic Society criteria.[20] 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. There were 22 males and 3 females, ranging in age from 59 to 80 years (mean age: 71 years). The forced expiratory volume in 1 second (FEV1)% and %Vital capacity (%VC) in pulmonary function tests for 25 patients were 50.5 ± 12.3 (mean ± SD) and 84.7 ± 19.7.

Statistical analysis

The significance of differences between U-FD and L-FD for patients with emphysema were determined by a paired t-test. The significance of differences in pulmonary function tests between patient groups stratified by the fractal dimension was determined with the Mann-Whitney's U test. In all tests, $p < 0.05$ was regarded as significant.

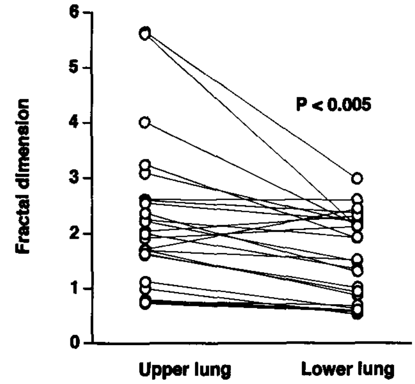

Fig. 5 Plot of upper and lower fractal dimensions in 25 patients with emphysema. Lines connect circles for each subject.

Evaluation of regional severity of emphysema by 3D-FA

Lung volume reduction surgery is emerging as a promising therapeutic option for the treatment of selected patients who have severe debilitating emphysema despite optimal medical management.[21] With the increasing application of lung volume reduction surgery in the past several years, the radiologic assessment of emphysema has gained additional clinical importance.[22] Patients with great upper lobe emphysema, greater heterogeneity and with a larger percentage of mildly diseased lung, on preoperative imaging studies, have experienced the greatest clinical improvement after lung volume reduction surgery.[23] Evaluation of the regional severity of emphysema is therefore the most important factor for determining the surgical target area and predicting the clinical outcome after lung volume reduction surgery.

Ventilation scintigrams in conjunction with other radiologic studies serve to provide information about the distribution of emphysema.[24–26] We defined T-FD, U-FD and L-FD as the severity of emphysema for the overall or regional lung. We assess the relationships between the fractal dimension and regional severity of emphysema and between the fractal dimension and pulmonary function.

T-FD, U-FD and L-FD for all patients with emphysema were 1.72 ± 0.77 (mean ± SD), 2.23 ± 1.31 and 1.59 ± 0.76. U-FD was significantly greater than L-FD ($p = 0.0017$) (Fig. 5). These results suggested that Technegas distribution in the upper lung was more heterogeneous than that in the lower lung and major cases in this study were centrilobular emphysema, because centrilobular emphysema was the most common type of emphysema among cigarette smokers and was more frequent in the upper lung zones,[27] but L-FD is greater than U-FD in 3 patients. This suggested that a few patients have more severe

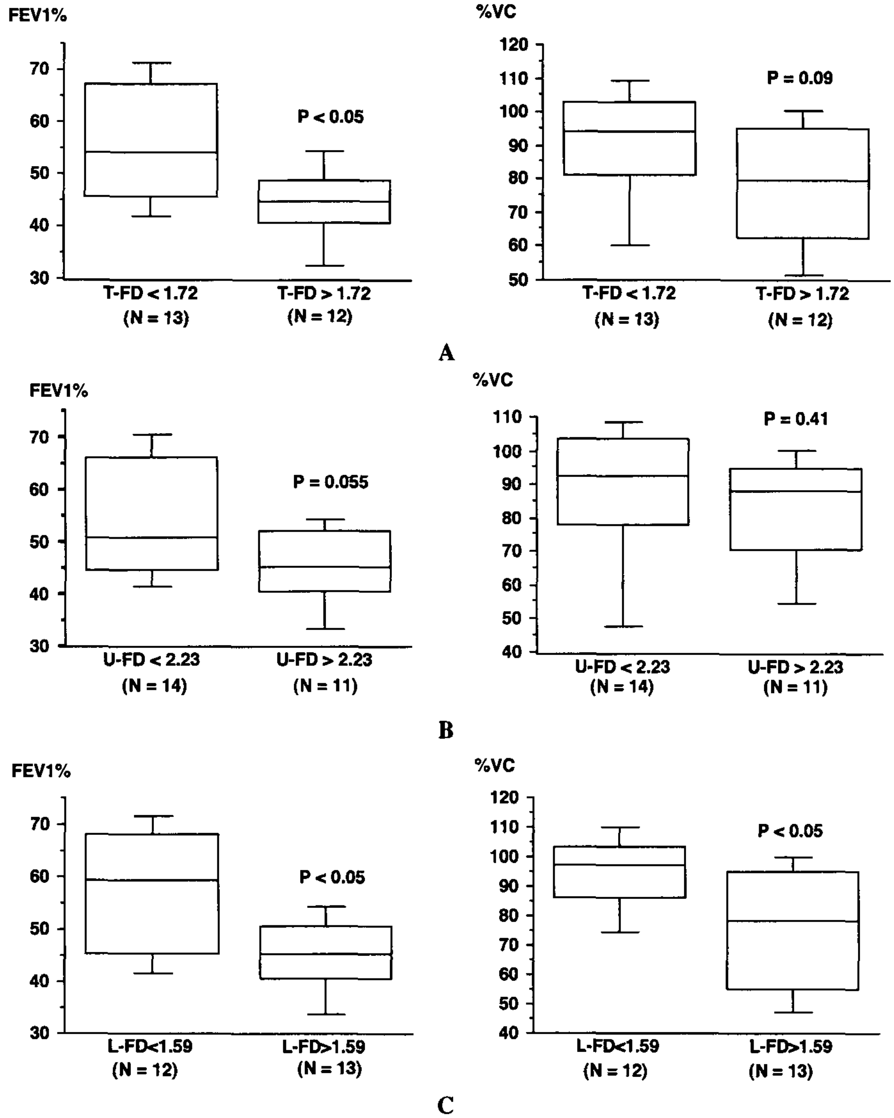

Fig. 6 A: Box-and-whisker plot shows comparison of $FEV_1\%$ and %VC between two patients group stratified by T-FD. B: Box-and-whisker plot shows comparison of $FEV_1\%$ and %VC between two patients group stratified by U-FD. C: Box-and-whisker plot shows comparison of $FEV_1\%$ and %VC between two patients group stratified by L-FD.

emphysematous change in the lower lung than in the upper lung.

Correlation with pulmonary function

To characterize pulmonary function test abnormalities according to the regional severity of emphysema, we examined whether there was a difference in pulmonary function tests between two patient groups stratified by mean T-FD, U-FD and L-FD. As we previously indicated that T-FD strongly correlated with $FEV_1\%$, the patients with T-FD less than 1.72 had a significantly greater $FEV_1\%$ than the patients with T-FD greater than 1.72 (56 vs. 43, $p = 0.019$) (Fig. 6A). Since the $FEV_1\%$ was the most important index in pulmonary function tests for airflow obstruction,[20] this result suggested that T-FD was a useful quantitative parameter to evaluate the obstructive impairment of emphysema. There was no significant difference between patient groups stratified by T-FD in %VC (Fig. 6A).

The patients with L-FD less than 1.59 had a significantly greater $FEV_1\%$ than the patients with L-FD greater than 1.59 (57 vs. 44, $p = 0.03$) (Fig. 6C). The patients with L-FD less than 1.59 had significantly greater %VC than the patients with L-FD greater than 1.59 (94 vs. 76, $p = 0.02$). On the other hand, there was no significant difference between two groups stratified by U-FD in $FEV_1\%$ and %VC (Fig. 6B). The contribution of lower lung severity to decrease $FEV_1\%$ and %VC is greater than that of upper lung severity. As several studies have shown, predominant emphysema in the lower lung affected pulmonary function more than that in the upper lung.[27,28]

The fractal dimension closely correlates $FEV_1\%$ and

%VC in pulmonary function tests and characterizes pulmonary function abnormalities according to the regional severity of emphysema. $FEV_1\%$ and %VC are most important factors for predicting the prognosis of emphysema.[29,30] The fractal dimension, which can demonstrate the overall and regional severity of emphysema might be useful for making a prognosis of emphysema.

CONCLUSION

The fractal dimension derived from 3D-FA is the relative and objective measurement which can assess the heterogeneous distribution on Technegas SPECT images. The fractal dimension well documented the overall and regional severity of emphysema and might provide useful information about the surgical target area of lung volume reduction surgery and the clinical outcome of emphysema.

3D-FA is applicable for routine clinical use because it is simple and because the computer automatically calculates the fractal dimension without using special software.

ACKNOWLEDGEMENTS

We gratefully acknowledge Assistant Prof. Teruhito Mochizuki, and Prof. Junpei Ikezoe in the Department of Radiology, Ehime University Medical School for their assistance to prepare the manuscript.

REFERENCES

1. Burch WM, Sullivan PJ, McLaren CJ. Technegas: a new ventilation agent for lung scanning. *Nucl Med Commun* 1986; 7: 865–871.
2. Pelitier P, Rimkus DS, Ashburn WL. Lung ventilation scanning with a new carbon particle radioaerosol (Technegas). Preliminary patients studies. *Clin Nucl Med* 1990; 15: 222–226.
3. Satoh K, Tanabe M, Takahashi K, Kobayashi T, Nishiyama Y, Yamamoto Y, et al. Assessment of technetium-99m Technegas scintigraphy for ventilatory impairment in pulmonary emphysema: comparison of planar and SPECT images. *Ann Nucl Med* 1997; 11: 109–113.
4. Satoh K, Takahashi K, Sasaki M, Kobayashi T, Honjo N, Ohkawa M, et al. Comparison of ^{99m}Tc-Technegas SPECT with ^{133}Xe dynamic SPECT in pulmonary emphysema. *Ann Nucl Med* 1997; 11: 201–206.
5. Nagao M, Murase K, Yasuhara Y, Ikezoe J. Quantitative analysis of pulmonary emphysema: three-dimensional fractal analysis of single-photon emission computed tomography images obtained with a carbon particle radioaerosol. *AJR* 1998; 171: 1657–1663.
6. Nagao M, Murase K, Ichiki T, Sakai S, Yasuhara Y, Ikezoe J. Quantitative analysis of Technegas SPECT: evaluation of regional severity of emphysema. *J Nucl Med* 2000; 41: 590–595.
7. Mandelbrot B. How long is the coast of Britain? Statistical self-similarity and fractal dimension. *Science* 1967; 156: 636–638.
8. Mandelbrot B. *Fractal Geometry of Nature*. San Francisco; Freeman, 1982.
9. Sirr SA, Junenemann PJ, Tom H, Boudreau RJ, Chandler RP, Loken MK. Effect of ethanol on droplet size, efficiency of delivery, and clearance characteristics of technetium-99m DTPA aerosol. *J Nucl Med* 1985; 26: 643–646.
10. Peltier P, Bardies M, Chetanneau A, Chatal JF. Comparison of technetium-99m C and phytate aerosol in ventilation studies. *Eur J Nucl Med* 1992; 19: 349–354.
11. Peltier P, Faucal P, Chetanneau A, Chatal JF. Comparison of technetium-99m aerosol and krypton-81m in ventilation studies for the diagnosis of pulmonary embolism. *Nucl Med Commun* 1990; 11: 631–638.
12. Nelson T. Fractal physiologic complexity, scaling, and opportunities for imaging. *Invest Radiol* 1990; 25: 1140–1148.
13. Zhang X, Hirano H, Yamamoto K, Kusaka Y, Sugimoto K, Kimoto T. Technegas ventilation SPECT for evaluating silicosis in comparison with computed tomography. *Ann Nucl Med* 1996; 10: 165–170.
14. Chung HW, Huang YH. Fractal analysis of nuclear medicine images for the diagnosis of pulmonary emphysema: interpretations, implications, and limitations. *AJR* 2000; 174: 1055–1059.
15. Nagao M, Murase K, Kikuchi T, Ikeda M, Nebu A, Fukuhara R, et al. Fractal analysis of cerebral blood flow distribution in Alzheimer's disease. *J Nucl Med* 2001; 42: 1446–1450.
16. Xu J, Moonen M, Johansson A, Gustafsson A, Bake B. Quantitative analysis of inhomogeneity in ventilation SPET. *Eur J Nucl Med* 2001; 28: 1795–1800.
17. Kuikka JT, Bassingthwaighte JB, Henrich MM. Mathematical modeling in nuclear medicine. *Eur J Nucl Med* 1991; 18: 351–361.
18. Kuikka JT. Effect of tissue heterogeneity on quantification in positron emission tomography. *Eur J Nucl Med* 1995; 22: 1457–1458.
19. Kuikka JT, Hartikainen P. Heterogeneity of cerebral blood flow: a fractal approach. *Nuklearmedizin* 2000; 39: 37–42.
20. American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease (COPD) and asthma. *Am Rev Respir Dis* 1987; 136: 225–244.
21. Cooper J, Trulock E, Triantafillou A, Patterson G, Pohl M, Deloney P, et al. Bilateral pneumonectomy (volume reduction) for chronic obstructive pulmonary disease. *J Thorac Cardiovasc Surg* 1995; 109: 106–119.
22. Daniel TM, Chan BB, Bhaskar V, Parekh JS, Walters PE, Reeder J, et al. Lung volume reduction surgery, case selection, operative technique, and clinical results. *Ann Surg* 1996; 223: 526–531.
23. Slone RM, Pilgram TK, Gierada DS, Sagel SS, Glazer HS, Yusen RD, et al. Lung volume reduction surgery: comparison of preoperative radiographic features and clinical outcome. *Radiology* 1997; 205: 685–693.
24. Suga K, Kume N, Matsunaga N, Ogasawara N, Motoyama K, Hara A, et al. Relative preservation of peripheral lung function in smoking-related pulmonary emphysema: assessment with ^{99m}Tc-MAA perfusion and dynamic ^{133}Xe SPET. *Eur J Nucl Med* 2000; 27: 800–806.
25. Suga K, Tsukuda T, Awaya H, Matsunaga N, Sugi K, Esato K, et al. Interactions of regional respiratory mechanics and

pulmonary ventilatory impairment in pulmonary emphysema: assessment with dynamic MRI and xenon-133 single-photon emission CT. *Chest* 2000; 117: 1646–1655.
26. Imai T, Sasaki Y, Shinkai T, Ohishi H, Nezu K, Nishimoto Y, et al. Clinical evaluation of ^{99m}Tc-Technegas SPECT in thoracoscopic lung volume reduction surgery in patients with pulmonary emphysema. *Ann Nucl Med* 2000; 14: 263–269.
27. Thurlbeck WM, Muller NL. Emphysema: Definition, imaging, and quantitation. *AJR* 1994; 163: 1017–1025.
28. Stern EJ, Frank MS. CT of the lung in patients with pulmonary emphysema: diagnosis, quantitation, and correlation with pathologic and physiologic findings. *AJR* 1994; 162: 791–798.
29. Postma DS, Sluiter HJ. Prognosis of chronic pulmonary disease: the Dutch experience. *Am Rev Respir Dis* 1989; 140: 100–105.
30. Nagao M, Murase K, Ichiki T, Sakai S, Yasuhara Y, Ikezoe J. Relationship between regional severity of emphysema and coronary heart disease. *Ann Nucl Med* 2000; 14: 369–372.