

# Quantitative Analysis of Technegas SPECT: Evaluation of Regional Severity of Emphysema

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The purpose of this study was to quantify the regional severity of emphysema by 3-dimensional fractal analysis of technegas ( $^{99m}\text{Tc}$ -carbon particle radioaerosol) SPECT images. **Methods:** Technegas SPECT was performed on 22 patients with emphysema. The lungs were delineated using 4 cutoff levels (15%, 20%, 25%, and 30% of the maximal pixel radioactivity), and the total number of pixels was measured in the areas surrounded by the contours obtained with each cutoff level. We calculated fractal dimensions from the relationship between the total number of pixels and cutoff levels transformed into logarithms. Fractal dimension for total or regional lung was defined as the severity of emphysema. **Results:** Total lung fractal dimension (T-FD), upper lung fractal dimension (U-FD), and lower lung fractal dimension (L-FD) for patients with emphysema were  $1.84 \pm 0.46$  (mean  $\pm$  SD),  $2.22 \pm 0.61$ , and  $1.77 \pm 0.49$ , respectively. U-FD was significantly greater than was L-FD. Patients with the ratio of U-FD to L-FD of  $<1.16$  had a significantly greater percentage forced vital capacity (FVC) than did patients with the ratio of  $>1.16$ . Patients with an L-FD of  $<1.8$  had a significantly greater forced expiratory volume in 1 s ( $\text{FEV}_1$ )/FVC than did patients with that of  $>1.8$ . No significant difference was found between patient groups stratified by U-FD. **Conclusion:** The regional severity of emphysema was well shown by these fractal dimensions.

**Key Words:** technegas; fractal analysis; pulmonary emphysema; ventilation study; SPECT

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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. With the increasing application of lung volume reduction surgery during the past several years, the radiologic assessment of emphysema has gained additional clinical importance (1–6). Findings on chest radiography, CT scanning, and perfusion scintigraphy studies strongly influence patient selection for lung volume reduction surgery (7–9). Features considered favorable for lung volume reduction surgery include marked thoracic hyperinflation and a heterogeneous distribution of emphysema with the presence of severely affected surgical target areas amid areas

of more mildly emphysematous lung (1–3,7–9). On preoperative imaging studies, patients with evidence of great upper lobe emphysema, greater heterogeneity of severity of emphysema, and a larger percentage of mildly diseased lung have experienced the greatest clinical improvement after lung volume reduction surgery (7–9). Thus, evaluation of the regional severity of emphysema is the most important factor for determining the surgical target area and predicting clinical outcome after lung volume reduction surgery. However, visual estimation of the regional severity of emphysema on several radiologic studies is difficult, and these estimations are subject to inter- and intraobserver variations.

Ventilation scintigrams in conjunction with other radiologic studies serve to provide information about the distribution and overall severity of emphysema. Technegas ( $^{99m}\text{Tc}$ -carbon particle radioaerosol; Daiichi Radioisotope Co. Ltd., Tokyo, Japan) SPECT images reveal peripheral irregularity in mild emphysema and further hot spot formation and regional defects in severe emphysema (10–13). It is generally known that the distribution of technegas on SPECT images becomes more heterogeneous with the severity of emphysema. We developed 3-dimensional fractal analysis for quantitative analysis of the heterogeneity of technegas distribution in the lung (14). We reported that the fractal dimension increased as emphysematous change progressed and that a good correlation was found between the forced expiratory volume in 1 s ( $\text{FEV}_1$ )/forced vital capacity (FVC) and the fractal dimension (14). Thus, these findings suggested that the fractal dimension has useful quantitative parameters to evaluate the overall severity of emphysema. The purpose of this study was to quantify the regional severity of emphysema in 22 patients using fractal analysis of technegas SPECT images. The secondary purpose was to characterize pulmonary function test abnormalities according to the regional severity of emphysema.

## MATERIALS AND METHODS

### Patient Selection

The subjects consisted of 22 patients with pulmonary emphysema (20 men, 2 women; age range, 49–83 y; mean age, 69 y). Their ventilation studies using technegas were performed in 1993 and 1994 at Ehime University and Ehime Prefectural Niihama Hospital. Diagnosis was made on the basis of clinical symptoms,

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pulmonary function tests, and CT examinations according to the American Thoracic Society criteria (15). We selected patients who had a heterogeneous distribution of emphysema in the entire lung and excluded patients who had the bullous type and localized emphysema only in the upper lung. Most patients had smoking-related emphysema. One patient had documented  $\alpha_1$ -antitrypsin deficiency, but not all patients were tested for this disorder. Four patients required continuous oxygen supplementation. Table 1 shows physiologic indices for patients with emphysema.

### Control Population

Eleven healthy volunteers (9 men, 2 women; age range, 32–74 y; mean age, 48 y) were recruited from our hospital staff. All volunteers were nonsmokers who had no evidence of lung disease on the basis of their history and the results of physical examination, chest radiography, and pulmonary function tests. Informed consent was obtained from each subject after he or she received a detailed explanation of the purpose of this study and the scanning procedures.

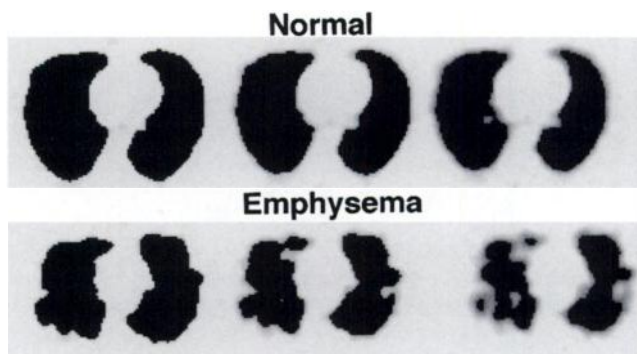
### Data Acquisition

Technegas was prepared as described (14). Technegas was administered through a mouthpiece, with a nose clip in situ, to subjects in the sitting position. The subjects slowly inhaled technegas and then held their breath for 5 s at the maximal point of inspiration. This procedure was repeated 3–5 times. The dose of technegas in the lung was estimated as 85–192 MBq from the data of Komatani et al. (16).

SPECT imaging was performed using a 3-head 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 using 5° angle intervals on a 128 × 128 matrix over 360° by rotating each detector head 120°. The acquisition time was 40 s/projection, corresponding to a total acquisition time of 16 min. The voxel size was 3.2 × 3.2 × 3.2 mm. Reconstruction of images was performed using the filtered backprojection method with a ramp backprojection filter and a Butterworth filter (order, 8; cutoff frequency, 0.15 cycle/pixel). Attenuation correction was not performed.

### Fractal Analysis

Fractal analysis is a mathematic tool for dealing with complex systems that have no characteristic length scale (scale invariant). A



**FIGURE 1.** Comparison of areas surrounded by contours obtained with each cutoff level between healthy volunteer (normal) and patient with emphysema. Cutoff levels of left, center, and right images are 15%, 20%, and 25%, respectively. Contours of lung for patient with emphysema become more irregular with increasing cutoff level than for healthy volunteer.

well-known example is the finely branched bronchial tree (17,18). Scale-invariant systems are usually characterized by noninteger dimensions termed fractal dimensions. 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 (19–21). The observed variance increases with the increasing number of subregions in the organ studied (21). This resolution-dependent variance can be described by fractal analysis (21).

As described earlier (14), 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 ( $\epsilon$ ) is expressed as:

$$M(\epsilon) = k \times \epsilon^{-D}, \quad \text{Eq. 1}$$

where k is a scaling constant and D is the fractal dimension (17).

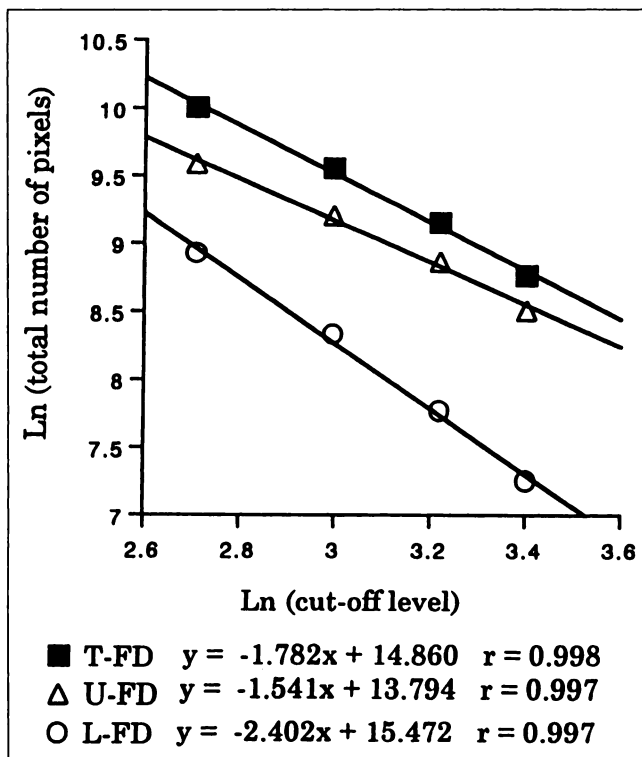
We delineated the lung at 15%, 20%, 25%, and 30% cutoff levels of the maximal pixel radioactivity in all slices of SPECT images and measured the total number of pixels in the areas surrounded by the contours obtained with each cutoff level (Fig. 1). The total number of pixels was automatically determined by a computer. In this study, the cutoff level of the maximal pixel radioactivity was used as  $\epsilon$  and the total number of pixels measured was used as M( $\epsilon$ ) in Equation 1. In practice, we calculated a linear regression equation from the total number of pixels and cutoff levels transformed into natural logarithms and obtained the fractal dimension from the slope of the linear regression equation. In all cases, the relationship between the cutoff level and the total number of pixels transformed into logarithms became linear and the correlation coefficient between them was >0.988.

We calculated fractal dimension for total lung, upper lung, and lower lung and defined total lung fractal dimension (T-FD), upper lung fractal dimension (U-FD), and lower lung fractal dimension (L-FD) as severity of emphysema for the overall or regional lung (Fig. 2; Table 2). 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 the subject underwent chest radiography, and then a small quantity of  $^{99m}\text{TcO}_4^-$  was placed on this marked point when the SPECT

**TABLE 1**  
Physiologic Indices in 22 Patients with Emphysema

Physiologic index	Mean $\pm$ SD	Range
FEV <sub>1</sub> (% predicted)	38.8 $\pm$ 13.7	21.8–69.2
FVC (% predicted)	74.6 $\pm$ 22.2	36.6–106
FEV <sub>1</sub> /FVC	35.6 $\pm$ 9.3	18.3–57.6
RV (% predicted)	187.8 $\pm$ 39.9	134.6–334.5
RV/total lung capacity	57.3 $\pm$ 7.5	40.3–75.9
Diffusing capacity of lung for CO (mL/min/mm Hg)	7.7 $\pm$ 2.1	2.5–11.2
Pao <sub>2</sub> (mm Hg)	75.2 $\pm$ 10.3	65.6–88.2
Paco <sub>2</sub> (mm Hg)	47.8 $\pm$ 7.6	39.7–56.4

RV = residual volume; CO = carbon monoxide; Pao<sub>2</sub> = partial pressure of oxygen, arterial; Paco<sub>2</sub> = partial pressure of carbon dioxide, arterial.



**FIGURE 2.** Calculation of fractal dimension in total lung (■), upper lung (△), and lower lung (○) regions of patient with emphysema. Ln denotes natural logarithm.

study was performed. The number of the axial SPECT slices for both the upper and the lower lung zones was the same. In addition, we calculated the ratio of U-FD to L-FD for heterogeneity of the severity of emphysema between upper and lower lungs.

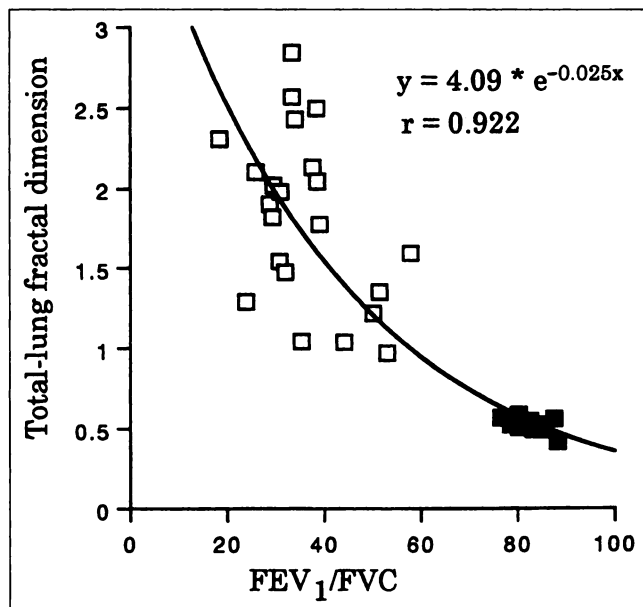
### Physiologic Indices

Pulmonary function tests were performed according to the standards of the American Thoracic Society (15). Lung volumes were measured by the closed circuit, helium dilution technique. The carbon monoxide diffusing capacity was measured with the single-breath technique. Arterial blood samples were obtained with subjects at rest breathing room air. All physiologic testing was performed within 2 wk before the technegas ventilation study.

**TABLE 2**  
Calculation of FD in Total Lung, Upper Lung, and Lower Lung Regions of 1 Patient with Emphysema

Cutoff level (%)	No. of pixels		
	Total lung	Upper lung	Lower lung
15 (2.71)	22,185 (10.01)	14,650 (9.59)	7,535 (8.93)
20 (3.00)	14,143 (9.56)	9,979 (9.21)	4,164 (8.33)
25 (3.22)	9,465 (9.16)	7,095 (8.87)	2,370 (7.77)
30 (3.40)	6,398 (8.76)	4,978 (8.51)	1,420 (7.26)
FD	1.78	1.54	2.40

Patient is same patient as that indicated in Figure 2. Number in parenthesis represents that transformed into natural logarithm.



**FIGURE 3.** Scatter plot of T-FD and  $FEV_1/FVC$  for patients with emphysema (□) and healthy volunteers (■). Best-fit curve is shown by solid line ( $r = 0.922$ ).

### Statistical Analysis

The significance of differences between U-FD and L-FD for healthy volunteers or patients with emphysema was determined using a paired *t* test. The significance of the difference in U-FD or L-FD between healthy volunteers and patients with emphysema was determined using the Mann-Whitney U test. The significance of differences in pulmonary function tests between patient groups stratified by quantitative technegas values was determined using the Mann-Whitney U test. In all tests,  $P < 0.05$  was regarded as significant.

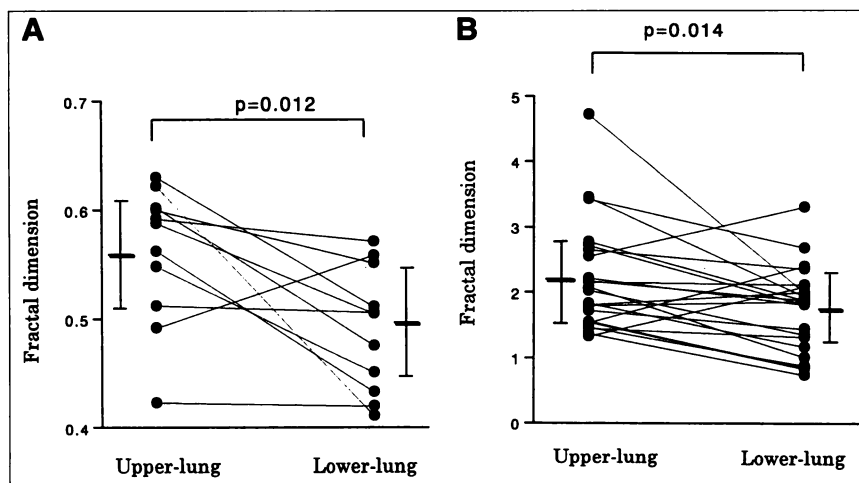
### RESULTS

There was a strong correlation ( $r = 0.922$ ) between T-FD and the  $FEV_1/FVC$  value for patients with emphysema and healthy volunteers (Fig. 3).

T-FD, U-FD, L-FD, and the ratio of U-FD to L-FD for healthy volunteers were  $0.52 \pm 0.04$  (mean  $\pm$  SD),  $0.56 \pm 0.05$ ,  $0.49 \pm 0.05$ , and  $1.16 \pm 0.14$ , respectively (Table 3). U-FD was significantly greater than was L-FD in healthy

**TABLE 3**  
Values of Quantitative Technegas in 22 Patients with Emphysema and in 11 Healthy Volunteers

Index	Mean $\pm$ SD	Range
<b>Patients with emphysema</b>		
T-FD	$1.84 \pm 0.46$	0.98–2.91
U-FD	$2.22 \pm 0.61$	1.34–4.73
L-FD	$1.77 \pm 0.49$	0.74–3.31
U-FD/L-FD	$1.34 \pm 0.38$	0.64–2.36
<b>Healthy volunteers</b>		
T-FD	$0.52 \pm 0.04$	0.42–0.59
U-FD	$0.56 \pm 0.05$	0.42–0.63
L-FD	$0.49 \pm 0.05$	0.42–0.57
U-FD/L-FD	$1.16 \pm 0.14$	0.88–1.51



**FIGURE 4.** Plot of U-FD and L-FD in 11 healthy volunteers (A) and in 22 patients with emphysema (B). Lines connect solid circles for each subject.

volunteers ( $P = 0.012$ ; Fig. 4A). T-FD, U-FD, L-FD, and the ratio of U-FD to L-FD for patients with emphysema were  $1.84 \pm 0.46$ ,  $2.22 \pm 0.61$ ,  $1.77 \pm 0.49$ , and  $1.34 \pm 0.38$ , respectively (Table 3). U-FD was significantly greater than was L-FD in patients with emphysema ( $P = 0.014$ ; Fig. 4B). The ratio of U-FD to L-FD for patients with emphysema covered a wider range (0.64–2.36) than did that for healthy volunteers (0.88–1.51) (Table 3). Both U-FD and L-FD for patients with emphysema were significantly greater than were those for healthy volunteers ( $P < 0.001$ ; Table 3).

Significant differences in pulmonary function tests were found between patient groups with emphysema stratified using quantitative technegas values (Table 4). Patients with emphysema were stratified by the ratio of U-FD to L-FD of 1.16 because the average (1.16) of the ratio of U-FD to L-FD for healthy volunteers was considered a standard value between upper and lower lungs influenced by the normal gravitational effect. Patients with the ratio of U-FD to L-FD of  $<1.16$  had a significantly greater percentage FVC than did patients with a ratio of  $>1.16$  (81.8 versus 59;  $P = 0.011$ ). Because the mean of L-FD for patients was 1.8, patients with an L-FD of  $<1.8$  had a significantly greater FEV<sub>1</sub>/FVC than did patients with a mean of  $>1.8$  (43.4

versus 31.9;  $P = 0.029$ ). No significant difference was found between patient groups stratified by U-FD in pulmonary function tests.

## DISCUSSION

We previously developed 3-dimensional fractal analysis for quantitative analysis of the heterogeneity of technegas distribution in the lung (14). T-FD for the overall severity of emphysema strongly correlated with the FEV<sub>1</sub>/FVC (Fig. 3). Because the FEV<sub>1</sub>/FVC was the most important index in pulmonary function tests for airflow obstruction (15), it suggested that T-FD was a useful quantitative parameter to evaluate the overall severity of emphysema. We calculated fractal dimensions for regional lung and tried to evaluate the regional severity of emphysema.

U-FD was significantly greater than was L-FD in the group of healthy volunteers (Fig. 4A). This result suggested that the heterogeneity of technegas distribution was different between the upper and lower lungs for healthy volunteers. The distribution of technegas in the lung is influenced by gravitational effects on the intrapleural pressure, which in the upright position leads to an increase in ventilation per unit volume of the lung by 1.5–2 times between the upper and lower zones (22–24). The presence of an increased basal deposition of technegas compared with <sup>81m</sup>Kr images has been reported (25). In this study the distribution of technegas in the upper lung was compared with that in the lower lung, resulting in a U-FD that was greater than was the L-FD for healthy volunteers. This phenomenon was considered to be reasonable for reflecting the normal gravitational effects in the physiologic characteristics of the lung. Thus, we considered the average (1.16) of the ratio of U-FD to L-FD for healthy volunteers as a standard value of the difference of heterogeneity between upper and lower lungs.

Both U-FD and L-FD for patients with emphysema were significantly greater than were those for healthy volunteers (Table 3). These indices were increased by 3–4 times between patients with emphysema and healthy volunteers. These findings suggested that emphysema progressed in

**TABLE 4**  
Pulmonary Function Tests of 22 Patients Stratified by FD

Stratification	Mean pulmonary function tests	
	FEV <sub>1</sub> /FVC	FVC (% predicted)
<b>U-FD</b>		
≥2.2 (n = 8)	31.6	72.7
<2.2 (n = 14)	38.7	73.9
P	0.26	0.972
<b>L-FD</b>		
≥1.8 (n = 14)	31.9	71.3
<1.8 (n = 8)	43.4	77.3
P	0.029	0.452
<b>U-FD/L-FD</b>		
≥1.16 (n = 14)	36.5	81.8
<1.16 (n = 8)	35.4	59
P	0.811	0.011

both upper and lower lungs in patients. Patient selection for overall heterogeneous emphysema, except for the bullous type and upper lung localized emphysema, was proven. U-FD was significantly greater than was L-FD for patients with emphysema (Fig. 4B). In addition, the mean of the ratio of U-FD to L-FD for patients with emphysema was greater than was the mean for healthy volunteers (Table 3). This finding suggested that the severity of emphysema in the upper lung was more dominant than was the severity in the lower lung, and the 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 (26). Furthermore, the ratio of U-FD to L-FD for patients with emphysema covered a wider range than did that for healthy volunteers (Table 3). For example, in the healthy volunteer group, only 1 individual had a ratio of U-FD to L-FD of <1.0; on the other hand, in the patient group, 4 patients had a ratio of <1.0. These 4 patients might have more severe emphysematous change in the lower lung than the normal gravitational effects. Their emphysema type might be the panlobular type that was more frequent in the lower lung zones (26).  $\alpha_1$ -Antitrypsin deficiency that was seen in panlobular emphysema was documented in 1 case (26). When emphysema became severe, it was difficult to classify. Severe emphysema may be confused with centrilobular and panlobular emphysema (26,27), suggesting that the heterogeneity of severity of emphysema differs in each patient. This appears to result in a wide range of the ratio of U-FD to L-FD.

To characterize the pulmonary function test abnormalities according to the regional severity of emphysema, we compared stratified quantitative technegas values with pulmonary function tests. Patients with the ratio of U-FD to L-FD of >1.16 had a significantly greater percentage FVC than did patients with <1.16 (Table 4). Patients with more severe lower lung emphysema had a more decreased FVC than did those with upper lung emphysema. Patients who had an L-FD of >1.8 (average of L-FD for patients) had significantly smaller FEV<sub>1</sub>/FVC values than did patients with <1.8 (Table 4). On the other hand, no significant difference was evident between patient groups stratified by U-FD in pulmonary function tests. The contribution of lower lung severity to decreased FEV<sub>1</sub> is greater compared with the contribution of upper lung severity. As several studies have shown, predominant emphysema in the lower lung affected pulmonary function compared with that in the upper lung (26–28).

In this study, the strong correlation between quantitative technegas values and pulmonary function tests may reflect the closer relationship between pulmonary function, such as FEV<sub>1</sub> or FVC, and the prognosis that has been observed in patients with emphysema (29–32). It is possible that quantitative technegas values will be useful for predicting the prognosis of emphysema.

## CONCLUSION

The regional severity of emphysema was well documented by this quantitative technegas analysis. Technegas quantitative values might be able to provide useful information about the surgical target area and the prediction of clinical outcome when lung volume reduction surgery is performed. The quantitative parameters correlated strongly with decreased pulmonary function. Furthermore, this analysis is applicable for routine clinical use because it is simple, does not need special software, and is a purely objective method.

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