The Severity of Pulmonary Emphysema Investigated with Fractal Analysis: Regional Dependence

TO THE EDITOR: In the April 2000 issue of *The Journal of Nuclear Medicine*, Nagao et al. (*1*) presented a fractal analysis method to evaluate the regional severity of pulmonary emphysema in patients examined using SPECT with inhalation of a ^{99m}Tc carbon particle radioaerosol. This article was preceded by their original work, published in *The American Journal of Roentgenology* in 1998 (*2*), reporting the effectiveness of their fractal analysis algorithm. With great interest, we repeated the 1998 study by Nagao et al. but reached very different conclusions (*3*). Our major findings are summarized in the following:

1. To our best knowledge, no report in the literature has defined fractal dimension in a way analogous to that reported by Nagao et al. In our opinion, nuclear medicine images of the airway in a ventilation study do not exhibit sufficient self-similarity to be qualified for non-Euclidean fractal analyses.
2. The fractal dimension defined in the work by Nagao et al. can be derived solely from the image intensity histogram, which contains no information on the spatial heterogeneity of radioaerosol. The fractal dimension thus could be entirely unrelated to focal functional impairments of the alveoli.
3. Nagao et al. measured the number of pixels delineated using four cutoff levels; that is, 15%–30% of maximal pixel intensity, to derive the fractal dimension. We demonstrated, however, that the number of pixels versus the cutoff level plotted in logarithmic scale showed a highly curvy behavior. Two implications can be deduced. First, the measurement of the number of pixels does not exhibit self-similarity and is thus nonfractal; and, second, the fractal dimension calculated from a linear regression would strongly depend on the range of cutoff levels chosen. Nagao et al. observed a linear behavior simply because the cutoff range of 15%–30% was small compared with the scale of curve nonlinearity.
4. We have shown that the fractal dimension defined by Nagao et al. was equivalent to the ratio of tissue areas segmented at two different intensity levels; that is, 15% and 30% of maximal pixel intensity, respectively. This phenomenon is true regardless of the image modality and the anatomy to be examined.
5. We recognized that fractal dimension used by Nagao et al. to indicate the "percentage area of tissue with low radioactivity" is partially related to the heterogeneity of radioaerosol distribution. However, it may be an oversimplified parameter that, without combining with visual diagnosis, is insufficient to reflect the severity of emphysema.
6. Even if the fractal dimension is of some diagnostic value for pulmonary emphysema in clinical practice, we would prefer a direct use of the "percentage area of tissue with low radioactivity" for its self-explanatory nature.

In addition to the above pitfalls, another confusing result was found in the 2000 article. In this study, fractal dimension was reported to be significantly greater in the upper lung (2.22 ± 0.61) than in the lower lung (1.77 ± 0.49) for patients with pulmonary emphysema and for healthy volunteers (0.56 ± 0.05 versus 0.49 ± 0.05) (*1*). If the regional severity of pulmonary emphysema could be indicated reliably by the fractal dimension, one would conclude that emphysema tends to result in impaired alveolar functions more in the upper airway than in the lower. This is clearly counterintuitive, particularly because Nagao et al. had explicitly stated that they excluded patients with localized emphysema only in the upper lung. Even though Nagao et al. provided a valid explanation that the majority of patients with emphysema are of centriacinar type and, hence, upper lung impairments prevail, their finding of greater fractal dimension in the upper lung, in our opinion, is another pitfall of the use of fractal dimension. One must first recognize that the fractal dimension as defined by Nagao et al. is equivalent to the ratio of tissue area segmented at 15% and 30% of maximal pixel intensity (*3*). Because the tissue area segmented at 30% of maximal pixel intensity is to be placed at the denominator, the ratio derived would tend to be large when the denominator is small; that is, when the tissue area is small. By nature, the human lung has a smaller cross-section area in the upper part than in the lower part. Therefore the "percentage area of tissue with low radioactivity;" that is, the fractal dimension of Nagao et al., would tend to be larger in the upper lung than in the lower lung and unrelated to the actual regional distribution of the severity of emphysema. In other words, the fractal dimension is not an unbiased estimator. Another example is seen in Figure 2 of the article by Nagao et al. (*1*), in which the patient with emphysema had larger fractal dimension in the lower lung and also showed smaller volume in the lower lung than in the upper. Consequently, the explanation of normal gravitational effects for upper/lower lung difference proposed by Nagao et al. was not too convincing. It should be noted that the above criticism is not meant to discredit fractal analysis in nuclear medicine examinations. The purpose of our investigation, rather, is to strongly suggest that fractal analysis in clinical practice should be performed only under careful interpretation and with a thorough understanding of its physical meanings.

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REPLY: Technegas has a small particle size and can reach the peripheral parts of the lung. The distribution of technegas on SPECT images becomes more hetergeneous with the severity of emphysema. We applied fractal analysis to quantify the heterogeneity of technegas distribution in the lung (*1*,*2*). The important

factor for calculating the fractal dimension is the range of cut-off levels. In our study (*1,2*), when a cut-off less than about 10% is used, regions outside the lung also tend to be delineated, especially in emphysema. Furthermore, hot spots formation in the central airway in emphysema had a high radioactivity. We considered the ventilatory impairment of the peripheral airway in emphysema as a main target and selected a 15%–35% cut-off as the maximal pixel radioactivity. We consider the cut-off range used in our study to be reasonable for fractal analysis, because the ln-ln plots obtained using this cut-off range are highly linear. As Chung and Huang (*3*) reported, the ln-ln spot obtained using a cut-off range of less than about 10% and more than about 35% are nonlinear. However, a cut-off range of less than about 10% and more than about 35% may correspond to regions with hot spots outside the lung and central airway. Thus, these cut-off ranges are not suitable to quantify the peripheral airway in emphysema. Because patients with emphysema inhale a small amount of technegas, maximal pixel radioactivity in patients with emphysema is much smaller than that with normal subjects. Although the cut-off range used in this study is small, the area with this range (15%–35%) accounts for most of the ventilatory volume in patients with emphysema.

A cut-off range of 15%–35%, used by Chung and Huang (*3*) for lung perfusion scintigram, may be too small to quantify lung perfusion distribution. The area surrounded by this cut-off range is only the peripheral zone around the lung contour. The area surrounded by this cut-off range is only the peripheral zone around the lung contour, and tends to decrease regularly with increasing cut-off. If we attempt fractal analysis of a lung perfusion scintigram, the wide perfusion area should be covered by the wide range of cut-off. Because the lung perfusion scintigram shows segmental perfusion defects in pulmonary embolism, the quantitation of the heterogenous distribution of the radioisotope in the lung may be unrelated to the progression of the disease.

As Chung and Huang reported (*3*), the fractal dimension calculated from the area at four or five cut-off (15%, 20%, 25%, 30%, and 35%) may be related to the ratio of the area at two cut-off (15% and 35%). However, I don't know what this relationship signifies in clinical practice. Chung and Huang (*3*) suggest that fractal dimension tends to be large when the tissue area at low cut-off (15%) is small. Because of air-trapping and thoracic hyperinflation, the tissue area at low cut-off in patients with emphysema is often larger than that in normal controls. The fractal dimension is not influenced by the tissue area at low cut-off.

We use fractal analysis and SPECT to quantify the heterogeneous distribution of the radioisotope. For much of the SPECT data such as lung, brain, and liver, it is necessary to analyze the heterogeneous distribution in three-dimension. The cut-off range should be established objectively to cover a target organ or region. The disease that shows the heterogeneous distribution on SPECT is suitable for objective study. For example, pulmonary embolism imaged on lung perfusion shows homogeneous distribution except for perfusion defects. Thus we consider that the area with this range may decrease regularly as the cut-off increases and may be, for the most part, unrelated to the progression of the disease. If we attempt fractal analysis of a lung perfusion scintigram, the wide perfusion area should be covered by the wide range of cut-off.

The closer relationship between the fractal dimension, which quantifies the spatial heterogeneity, and the ratio of the area at two cut-off (15%–35%) is a natural result. I do not know what the relationship between the fractal dimension and logarithms of the ratio of apparent tissue area at two cut-off (15%–35%) means (*3*). Chung and Huang (*3*) suggest that fractal dimension tends to be large when the tissue area at low cut-off (15%) is small. Because of air-trapping and thoracic hyperinflation, the tissue area at low cut-off in patients with emphysema is often larger than that in healthy individuals. The fractal dimension becomes greater with the progression of emphysema and is not influenced only by the tissue area at low cut-off .

We use fractal analysis and SPECT to quantify the heterogeneous distribution of the radioisotopes. Much SPECT data, such as lung, brain, and liver, must analyze the heterogeneous distribution in three dimensions. The cut-off range should be established objectively to cover a target organ or region. The disease which show the heterogeneous distribution on SPECT is suitable for the objective disease. Vascular diseases, such as pulmonary embolism and infarction, are not suitable for this analysis. We interest in that the heterogeneous distribution on SPECT shows fractal form. If the appropriate disease and cut-off range could be selected, it is possible to quantify the heterogeneity on SPECT in the various diseases.

REFERENCES

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