Fractal Analysis of Nuclear Medicine Images for the Diagnosis of Pulmonary Emphysema: Interpretations, Implications, and Limitations

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OBJECTIVE. The purpose of this study was to investigate, on images obtained in nuclear medicine examinations, the physical meanings and consequent implications of fractal analysis developed in a recent study that was reported to be effective in quantifying the heterogeneous distribution of carbon particle radioaerosol in the lungs.

MATERIALS AND METHODS. Fractal dimensions were computed for 108 sets of radionuclide imaging data from 28 patients according to the methods in a previous report, and were then correlated with the ratio of tissue areas segmented at two thresholds (15% and 35% of maximal radioactivity).

RESULTS. Fractal dimension was found to linearly correlate with the ratio natural logarithm of tissue areas segmented at two different threshold levels ($n = 108$, $r = 0.999$), with regression slope accurately predicted (error = 0.06%). Bland-Altman analysis showed that fractal dimensions ranging from 0.2 to 1.9 can be explained by this area ratio with disagreement of only 5.13% at two standard deviations; thus, fractal dimension seems to be an oversimplified parameter unrelated to spatial heterogeneity of radioaerosol distribution.

CONCLUSION. The analysis of this study suggested that the fractal dimension defined in a previous report was limited to the indication of the percentage area of low-radioactivity regions with respect to total tissue area in the image. Because the fractal dimension partially reflects, but is not specific to, a certain degree of focal spots of low radioactivity, we suggest using fractal analysis in clinical practice only with careful control and thorough understanding of the physical meanings.

Attempts have been made to quantify the spatial distribution of radioaerosol in the lungs during ventilation nuclear medicine examinations for the diagnosis of pulmonary diseases such as emphysema [1–3]. In pulmonary emphysema with functional impairments of the alveoli, ventilation images indicate focal areas of decreasing pixel intensity [4]. Such an image appearance is known to result from a relatively low radioactivity in the regions with nonfunctional alveoli, which are less reachable by the inhaled radioaerosol [5, 6]. In contrast, regions with functionally normal alveoli possess a relatively high pixel intensity, known as hot spots. The consequent heterogeneous appearance of ventilation nuclear medicine images has been used as a diagnostic index for emphysematous severity [1, 2, 4]; however, 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.

Recently, Nagao et al. [1] presented fractal analysis, an approach for obtaining a reproducible and sensitive quantification of emphysematous severity, and reported their analysis results of 40 patients. 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 using conventional Euclidean geometry [7]. In the work of Nagao et al., the heterogeneous distribution of a ^{99m}Tc -labeled ultrafine carbon particle radioaerosol, Technegas (Daiichi Radioisotope, Tokyo, Japan) [8], on single-photon emission computed tomography (SPECT) images was assessed using a parameter termed “fractal dimension.” Derived from the analysis method developed by Nagao et al., the fractal dimension was found to be significantly larger in emphysematous patients than in healthy volunteers ($p < 0.0005$) [1]. Furthermore, fractal dimension was reported to be sensitive in detecting mild impairments in the ventilation status in patients with suspected

Received July 8, 1999; accepted after revision September 8, 1999.

H. W. Chung is supported in part by the National Science Council grant NSC-87-2314-B002-330-M08.

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AJR 2000;174:1055–1059

0361–803X/00/1744–1055

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emphysema [1], indicating its clinical value in early diagnosis and in the monitoring of the progression of pulmonary emphysema.

Further investigation of the origin of the efficacy of the fractal analysis method, considering its promising diagnostic potential and easy implementation, seems worthwhile. Briefly, the theory is based on an equation relating a measure (M) to the scale (ϵ) of the ruler that measures M :

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

where k is a proportionality constant and D is a generalized extension of the concept of dimension called the fractal dimension. As equation 1 implies, the quantity M to be measured is a function of the ruler scale and can be a nonconstant. Such phenomena are seen, for example, when measuring the length of the British coastline [9]: as the ruler decreases in scale, small bays and peninsulas gradually become resolvable. The coastline thus becomes more "twisted" as the ruler scale decreases, thereby altering the measured length of the coastline. This property

for fractal objects is known as self-similarity at various scales [7, 9].

Nagao et al. [1] used five cutoff levels, 15%, 20%, 25%, 30%, and 35% of the maximal pixel intensity in the ventilation SPECT images, to segment the lung tissue; therefore, the total apparent area occupied by the lung tissue varied as a function of the intensity thresholds. The five chosen thresholds were used as the ruler scale ϵ in equation 1, and the total numbers of pixels with intensity higher than the corresponding thresholds were used as $M(\epsilon)$. Clearly, $M(\epsilon)$ decreases as ϵ increases; hence a linear regression on the $M(\epsilon)$ 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 . Figure 1A shows a typical lung perfusion scintigraphy image, and Figure 1B is the corresponding intensity histogram, with dashed lines marking the five thresholds. The total number of pixels on the right side of these dashed lines is $M(\epsilon)$. The graph exemplifying the calculation of fractal dimension D for this image is shown in Figure 1C, but notice that the generation of Figure 1C,

and hence the computation of fractal dimension D , can be accomplished solely from the intensity histogram (Fig. 1B). Because the histogram simply plots the number of pixels in the entire field of view versus the gray level possessed by these pixels, the intensity histogram of a nuclear medicine image reflects only the radioactivity statistics and is thus totally unrelated to spatial heterogeneity. Likewise, the fractal dimension D derived from the histogram is also unrelated to spatial heterogeneity. The application of fractal dimension to the diagnosis of pulmonary emphysema may therefore face problems in interpretation because the fractal dimension does not convey any positional information required to indicate the extent of focal impairments of alveolar function.

The question that arises from these observations is, "What does fractal dimension mean if it is shown to be sensitive to the detection of mild alteration in the ventilation status, while being unrelated to spatial heterogeneity in a nuclear medicine image?" Taking a closer look at Figure 1C, note that the fractal dimension D was computed as the magnitude of the negative

Fig. 1.—54-year-old man with pulmonary embolism.

A. Lung perfusion scintigram shows typical technetium-99m uptake in lungs.

B. Corresponding intensity histogram shows five thresholds marked out as dashed lines. Note total numbers of pixels on right side of dashed lines, $M(\epsilon)$. M = measure. ϵ = scale.

C. Graph shows calculation of fractal dimension D . Calculation of D using five values of $M(\epsilon)$ requires use of information in **B** only. Fractal dimension, absolute slope of hypotenuse of right triangle, is equal to h/w . h = height, w = width.

slope, which is simply the ratio of the height (h) to its width (w), if the five data points fall exactly on the regression line. Because the five chosen cutoff thresholds were used as the abscissa ε , the width w is fixed at $\ln |35| - \ln |15| = \ln |35/15| = 0.84730$ (note that the natural logarithm was used here and in the work of Nagao et al. [1]). In other words, the fractal dimension D , or the absolute slope of the hypotenuse, is directly proportional to the height h in Figure 1C with proportionality constant $1/0.84730 = 1.18022$. The height h , being approximately equal to $(\ln |M(\varepsilon = 15)| - \ln |M(\varepsilon = 35)|)$, represents the natural logarithm of the ratio of lung tissue areas when segmenting at two different threshold levels (i.e., 15% and 35% of the maximal signal intensity). We therefore infer that the fractal dimension calculated by Nagao et al. is only an indicator of this area ratio completely unrelated to spatial heterogeneity, with a proportionality constant of 1.18022. In addition, because the inferences drawn from our observations were purely methodologic, we predict that such situations in nuclear medicine images are independent of the image technique and the anatomy being examined.

Materials and Methods

To strengthen our reasoning, we combined nuclear medicine scans acquired from different anatomic locations. A total of 108 sets of image data obtained from 28 subjects were retrospectively reviewed, including 40 lung perfusion scintigrams from 20 patients, four liver scintigrams from two patients, 15 sets of three-dimensional ^{99m}Tc -hexamethylpropyleneamine oxime brain SPECT images from five patients, and three sets of ^{99m}Tc -RBC liver SPECT images from one patient. Two additional sets of three-dimensional brain SPECT images from two patients were included but treated as multiple sets of two-dimensional images (total: 46 slices). Selection of patients for entry in the study was double-blinded and randomized. All scintigrams and SPECT images were obtained from a dual-head gamma camera (Prism 2000 Odyssey VP; Picker, Cleveland, OH) and digitally transferred to a PC for further analysis using Matlab software (MathWorks, Natick, MA). Fractal analysis was performed according to the method described by Nagao et al. [1]: images were segmented at five threshold levels—15%, 20%, 25%, 30%, and 35% of highest pixel intensity—and the total area was computed as a function of the threshold values. The fractal dimension D was calculated as the absolute value of the regression slope of the $\ln |M(\varepsilon)|$ versus $\ln |\varepsilon|$ plot. Note that for the three-dimensional data sets, the highest pixel intensity in the entire volume was used, whereas in the two-dimensional images, such as the projection scintigrams, D was calculated on a slice-by-slice basis.

The apparent tissue areas obtained at 15% and 35% threshold values were then computed. The ratio (area ratio) of these two values for each set of images was derived and its natural logarithm correlated with the fractal dimension D . Bland-Altman analysis [10] was used for a rigorous assessment of the agreement between these two parameters. This was accomplished by calculating, for all data points, the percentage of difference between D and its predicted value using the area ratio. The difference in D obtained with two methods was then plotted versus the average of D computed using the two methods.

To assess the degree of self-similarity, the $\ln |M(\varepsilon)|$ versus $\ln |\varepsilon|$ plot of each set of image data was also obtained with a larger range of threshold values, namely 5–60% of maximal pixel intensity with 5% increments. The linearity of such curves was visually examined.

Results

The $\ln$ - $\ln$ plot obtained using a large range of thresholds for three typical sets of images shows that all these curves are highly nonlinear (Fig. 2). Such nonlinearity has a direct implication: the calculation of fractal dimension D as the slope of the regression line highly depends on the selected range of threshold values, regardless of the possible existence of fractal nature. In other words, the measurement of apparent tissue area, $M(\varepsilon)$, is not self-similar over the range of 5–60% threshold values. In contrast, the data in Figure 2 seem to be highly linear within the range of 15–35% thresholds, as shown by the fitted lines.

This observation may lead one to conclude that the range of 15–35% thresholds is a proper choice for using fractal analysis as

done in the work of Nagao et al. [1]. Indeed, the linearity within this limited range was found to be excellent for all images in our study; however, this also implies that the inference we have described seems to be valid; that is, fractal dimension may be only an indicator of the area ratio, with a proportionality constant of 1.18022. Our prediction is corroborated by the experimental data shown in Figure 3, in which the fractal dimension, computed using the five threshold values, was plotted versus area ratio. Notice that regardless of the image technique or the anatomy examined, the combination of data from different imaging techniques shows a significant correlation, with $r = 0.999$. Furthermore, the regression equation in Figure 3 shows that the fractal dimension and logarithm of the area ratio are linearly related with a proportionality constant of 1.181, only a 0.06% deviation from the predicted value of 1.18022 plus a negligible intercept of -0.0082 .

If one uses the equation in Figure 3 and the area ratio to predict fractal dimension, a Bland-Altman analysis [10] can be performed to assess the agreement between this prediction and that obtained using the method of Nagao et al. [1]. Figure 4 shows the result of Bland-Altman analysis, which indicates that the percentage of disagreement in D at two standard deviations is only 5.13% (D ranging from 0.2 to 1.9). Because the disagreement is minor ($<8\%$ in all cases), we concluded that the fractal dimension as defined in the work of Nagao et al. is effectively equivalent to the ratio of apparent

Fig. 2.— $\ln$ - $\ln$ plot of $M(\varepsilon)$ versus ε shows large range of thresholds (5–60% of maximal pixel intensity with 5% increments) for three typical sets of images. All curves are highly nonlinear, leading to ambiguous determination of fractal dimension. In contrast, data within small range of 15–35% thresholds are highly linear as shown by dotted lines. + = patient 7, o = patient 12, x = patient 14. M = measure, ε = scale.

Fig. 3.—Graph shows fractal dimension computed using five threshold values and plotted versus logarithm of ratio of apparent tissue areas segmented at 15% and 35% of maximal pixel intensity. Note high correlation coefficient of $r = 0.999$ regardless of imaging technique or anatomy examined. Also note regression equation shows that fractal dimension and logarithm of area ratio are linearly related with proportionality constant at 1.181, which is only 0.06% deviation from theoretic predicted value of 1.180 plus negligible intercept of -0.0082 . $y = 1.181x - 0.0082$, $n = 108$, y = fractal dimension, $x = \ln$ (area ratio).

Fig. 4.—Graph shows Bland-Altman [10] analysis plotting percentage of disagreement in D computed using two methods versus their average. Note that disagreement at two standard deviations (dashed lines) is only 5.13% (average of D ranging from 0.2 to 1.9), indicating that fractal dimension as defined in work of Nagao et al. [1] is effectively equivalent to area ratio.

tissue areas segmented at two threshold levels, 15% and 35% of maximal pixel intensity.

Discussion

Our results have several implications regarding the effectiveness of fractal dimension, as defined by Nagao et al. [1], when used as a diagnostic index for pulmonary emphysema. First of all, the nonlinearity of data (Fig. 2) indicates that the measurement of apparent tissue area, $M(\epsilon)$, does not exhibit self-similarity over a wide range of scales. Because self-similarity (usually required over several orders of magnitude [11]) is a prerequisite for a justification of fractal properties, the absence of self-similarity may lead to questionable value of the application of fractal analysis on nuclear medicine images. On the other hand, because the decrease of apparent tissue area with the increase of threshold values is a natural trend in all digital images, the decreasing trend of the data shown in Figure 1C is not related to fractal properties. In our opinion, the highly linear behavior of this data set may be because the small amount of the five data points comes only from a very limited range of values, namely 15–35% of maximal pixel intensity, which is only a magnitude of 2.33 compared with several orders of magnitude used in more rigorous fractal analyses [7, 9, 11]. Furthermore, because a logarithm was taken for both variables in Figure 1C, any curved trend that can be described by the power law would tend to be linearized, giving what

was observed as an apparent fractal property described in the work of Nagao et al.

Regardless of its origin, the linearity of the area–threshold curve, that is, the “ $\ln |M(\epsilon)|$ versus $\ln |\epsilon|$ ” plot, showed that this fractal dimension can at least be computed with high reproducibility in an objective manner. In such a case, however, our theoretic analysis and the experimental results in Figures 3 and 4 show that this parameter can also be precisely predicted using the ratio of apparent tissue areas at two intensity thresholds (15% and 35% of maximal pixel intensity) in a nuclear medicine scan. If one denotes the apparent tissue area greater than 15% radioactivity as A_{15} , and that greater than 35% radioactivity as A_{35} , a simple equation: can further relate the

$$1 - \left(\frac{A_{15}}{A_{35}} \right)^{-1} = \frac{A_{15} - A_{35}}{A_{15}} \quad (2)$$

area ratio to the percentage of area of tissue with low radioactivity (15–35% of maximal radioactivity as shown on the right side of equation 2, if one roughly segments the entire tissue area as that $>15\%$ radioactivity). The fractal dimension as defined in the work of Nagao et al. [1] is, therefore, only an indicator of the percentage of area of low radioactivity. This consequence would also imply that the same information can be obtained visually by producing a postprocessed nuclear medicine image with only three gray levels, that is, an image dual-segmented at

15% and 35% of maximal pixel intensity (Fig. 5). Clearly, the diagnostic information provided by Figure 5B may not be sufficient for monitoring pulmonary emphysema. In our opinion, the fractal dimension is likely to be an oversimplified parameter entirely unrelated to the spatial heterogeneity of radioaerosol distribution. Its value in terms of objectiveness might not be too different from defining a subjective threshold of, for example, -910 H in CT studies of pulmonary emphysema [12]. Even if this parameter is of some diagnostic value, we would prefer a direct use of the percentage of area of tissue with low radioactivity, because it has a clearer, more self-explanatory physical meaning than that of fractal dimension; therefore, it is not surprising that, to our knowledge, no fractal dimension in the literature has been defined in a way analogous to that reported by Nagao et al. [1]. In fact, in our opinion, nuclear medicine images of the airway in a ventilation study do not exhibit any sort of self-similarity, a prerequisite for non-Euclidean analyses such as those used in the calculation of fractal dimension.

One property of the area ratio or fractal dimension mentioned earlier is that this parameter is able to sense the portion of tissues with intensity values falling between 15% ($\approx 1/6$) and 35% ($\approx 1/3$) of maximal pixel intensity; therefore, this parameter indeed seems to be sensitive to mild to moderate alveolar impairments resulting in a decrease of signal to one third to

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Fig. 5.—47-year-old man with suspected pulmonary embolism.

A. Lung perfusion scintigram shows typical technetium-99m uptake in lungs. **B.** Corresponding postprocessed image obtained with dual-threshold segmentation at 15% and 35% of maximal pixel intensity shows three gray levels only. Diagnostic information provided by fractal dimension alone, which can be derived solely from image in **B**, may not be sufficient for monitoring pulmonary emphysema.

one sixth of the normal tissues. Such characteristics may explain the finding of Nagao et al. [1] in the sensitivity of fractal dimension in detecting suspected pulmonary emphysema. On the other hand, in special cases of severe emphysema with substantial functional impairments of the alveoli leading to signal reduction to less than one sixth of its expected value, the computational algorithm of Nagao et al. might treat these areas as being part of the background, possibly underestimating emphysematous severity.

In addition to these pitfalls of fractal analysis, because the fractal dimension defined by Nagao et al. [1] was derived using five cutoff levels of intensity thresholds, fractal dimension is a parameter that can be determined solely by the image-intensity histogram. As a consequence, any pre- or postprocessing for improvements of image quality, such as median filtering [13], histogram equalization [13], or the reconstruction routinely used in SPECT [14], would alter the measured fractal dimension, unless the intensity histogram is preserved by the processing algorithms. Furthermore, any inherent or artifactual presence of a single hot spot (single pixel with very high intensity) could affect the automatic selection of threshold values used for a calculation of fractal dimension. Such phenomena, however, may not be associated with pulmonary function to any extent. Under such circumstances, it is inferred that the method of fractal analysis proposed by Nagao et al. may be of questionable diagnostic value.

Finally, this study should not be regarded as a criticism to discredit fractal analysis as a potential morphometric tool in nuclear medicine examinations. In the work by Nagao et al. [1], although our study showed that the fractal di-

mension seemed unrelated to the spatial heterogeneity of radioaerosol distribution, fractal dimension does partially reflect the existence of a certain degree of focal spots of high and low radioactivity by showing increased percentage of area of low radioactivity in patients with pulmonary emphysema. In particular, on thin-slice SPECT images where partial volume effects are less severe than in projection scintigrams, the fractal dimension may be sensitive to disease severity. Therefore, the fractal analysis, when appropriately combined with conventional visual diagnosis, could be of some value by providing an objective quantity to serve as an index for diagnostic reference. Because the fractal dimension as defined herein has been shown in this study to be nonspecific to spatial heterogeneity and actually unrelated to the nature of fractal objects, we cite *Lancet*, "Since fractal analysis is essentially mathematical, as with all mathematical models, there must be a close link with the biological event, if the model is to be useful," [15] and strongly suggest usage of such an analysis in clinical practice only with rigorous control, careful interpretation, and thorough understanding of its physical meanings.

Acknowledgments

We thank Soo-Chang Pei (Department of Electrical Engineering, National Taiwan University, Taipei) and Cheng-Yu Chen (Department of Radiology, Tri-Service General Hospital, Taipei) for helpful discussions.

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