An Alternative to Kinevac

TO THE EDITOR: Our referring physicians have found hepatobiliary scanning with gallbladder stimulation by Kinevac (sincalide for injection; Bracco Diagnostics Inc., Princeton, NJ) to be useful in the management of their patients. With Kinevac no longer available (*1*), we sought to develop an alternative procedure to provide similar information.

On the basis of our review of fatty-meal gallbladder stimulation studies using ultrasonography (*2*,*3*) and cholescintigraphy (*4*,*5*), we developed a protocol using a standardized oral fatty meal to serve as the stimulus for gallbladder contraction. At 60 min after the intravenous administration of 185 MBq (5 mCi) of ^{99m}Tc-mebrofenin, and assuming normal visualization of the gallbladder, we give the patient 90 mL (3 oz) of heavy whipping cream sweetened with a teaspoon of sugar. This quantity contains 30 g of fat. Imaging is performed immediately after ingestion of the meal and at 15, 60, and 75 min after ingestion. The ejection fraction is calculated using the peak (baseline or, rarely, 15 min) and trough (75 or, rarely, 60 min) counts. On the basis of our previous experience and for simplicity's sake, background and decay correction are not performed.

We analyzed the data for the first 82 consecutive patients on whom the protocol could be successfully accomplished. The whipping cream was usually not given to patients with nasogastric tubes, and only 2 other patients could not tolerate the meal. When an ejection fraction of <40% was considered abnormal and 40%–49% was considered borderline, 11 (13%) of 82 patients had an abnormal ejection fraction and 21% had an abnormal or borderline ejection fraction. When the same parameters were used on our last 32 consecutive Kinevac-stimulated scans, 3 (9%) of 32 patients had abnormal ejection fractions and 5 (16%) of 32 had abnormal or borderline ejection fractions. For fatty-meal and Kinevac stimulation, the average ejection fractions of all patients were 70% and 71%, respectively.

We conclude that fatty-meal–stimulated cholescintigraphy is well tolerated and easy to perform and results in ejection fraction values similar to those obtained with Kinevac-stimulated cholescintigraphy. We are in the process of evaluating the clinical significance of the ejection fractions obtained with the fatty meal.

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Fractal Analysis of Cerebral Blood Flow Distribution in Alzheimer's Disease

TO THE EDITOR: We read with great interest the article of Nagao et al. (*1*). The authors applied 3-dimensional fractal analysis for quantifying cerebral blood flow (CBF) distribution in patients with probable Alzheimer's disease (AD) and in healthy volunteers. Imaging studies have shown spatial and temporal heterogeneity of brain structure and function whenever studied. A key question of these studies is how to differentiate abnormal alterations from normal perfusion heterogeneity. Postprocessing (such as fractal analysis) of the SPECT images may help with image interpretation when visual and traditional approaches fail.

Mandelbrot (*2*) introduced the word *fractal* from the Latin *fractus* ("to break") to describe the finer irregular fragments that appear when objects are viewed at higher and higher magnifications. Practically, the object or process is considered fractal if its small-scale form appears similar to its large-scale form (such as vermis of cerebellum, bronchial tree of lungs, and daily heart rate variability). Highly recursive and self-similar structures and processes without a well-defined shape can be characterized by fractal analysis. Fractal analysis of the image property is based on nonlinear equations and can be described by a power-law equation showing how a property $L(\varepsilon)$ of the system depends on the scale ε:

$$L(\varepsilon) = A \cdot \varepsilon^{\alpha}, \qquad \text{Eq. 1}$$

where A is the scaling constant and α is the exponent (*3*).

The authors concluded that the fractal dimension correlated well with cognitive impairment, as assessed by neuropsychologic tests (*1*). This conclusion is true. However, their decision that CBF distribution becomes more heterogeneous when AD progresses is wrong. The overall heterogeneity (or complexity) of CBF distribution lessens when disease progresses from the moderate to the end stages. This is a definitive question of the exponent α in Equation 1.

The power-law scaling describes how the property $L(\varepsilon)$ of the system depends on the scale ε at which it is measured (Eq. 1). The fractal dimension D describes how the total number of voxels $M(\varepsilon)$ of the brain SPECT data depends on the scale ε (cutoff level), namely:

$$M(\varepsilon) = k \cdot \varepsilon^{-D}, \qquad \text{Eq. 2}$$

where k is a constant. This cutoff threshold method is useful for determining the fractal dimension. However, to use this approach, we must derive the relationship between the fractal dimension D and the scaling exponent α (*3*). We equate these 2 powers of the scale ε (Eqs. 1 and 2) and then solve for the fractal dimension D (*3*). For 3-dimensional surface rendering of SPECT data, the solution of the fractal dimension is (*3*):

$$D = \alpha + 3. \qquad \text{Eq. 3}$$

The result is that the authors have reported the value of $-\alpha$ instead of D, leading to their conclusion that "... CBF distribution be-

comes more heterogeneous when AD progresses in the moderate and end stages" (*1*).

Strictly speaking, the 3-dimensional fractal dimensions (Eq. 3) for patients with clinical dementia rates of 0, 1, 2, and 3 are 2.48, 2.37, 2.23, and 1.57, indicating more homogeneous CBF when disease progresses. The decrease in the fractal dimension is associated with impairment of the patient's condition, as was previously found in patients with dementia of the frontal lobe type using 2-dimensional fractal analysis of SPECT perfusion data (*4*).

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REPLY: My colleagues and I introduced 3-dimensional fractal analysis for lung ventilation and cerebral blood flow SPECT images in *The Journal of Nuclear Medicine* (*1*,*2*). Three-dimensional fractal analysis depends on the cutoff level of radioactivity and measures the irregular alterative form in 3 dimensions with changing of the cutoff level. Fractal geometry characterizes the relationship between a measure M and the scale ε and is expressed as:

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

where k is a scaling constant and D is termed the fractal dimension. The fractal dimension measures the spatial heterogeneity of the structure, which is expressed as M(ε). As the fractal dimension increases, the structure is more heterogeneous. In the modified fractal geometry of 3-dimensional fractal analysis, the cutoff level of radioactivity is used as ε, and D is a measurement of an irregular alterative form in 3 dimensions. In 3-dimensional fractal analysis, D is a negative quantity when calculated for an increasing cutoff level and a positive quantity when calculated for a decreasing cutoff level (Fig. 2 in (*2*)). Because fractal dimension serves as a measurement of scale independent of the irregularity of the object, D for increasing or decreasing cutoff levels must be the same value. We believe that fractal dimension should be the absolute value in our analysis.

In the letter to the editor, Dr. Kuikka describes fractal analysis of the image property as:

$$L(\varepsilon) = A \cdot \varepsilon^{\alpha}, \qquad \text{Eq. 2}$$

and mathematically solves for D:

$$D = \alpha + 3. \qquad \text{Eq. 3}$$

Kuikka points out that α may be a true fractal dimension. However, because D is an absolute value, D ± 3 in Equation 3 may be meaningless in our 3-dimensional fractal analysis. Kuikka and Hartikainen (*3*) described fractal analysis of 2-dimensional SPECT images using the number of subregions (size of region of interest). Their method, which applies box counting, is interesting. We believe that the fractal dimension obtained from 3-dimensional fractal analysis differs entirely from that obtained from their 2-dimensional fractal analysis. Both analyses show spatial heterogeneity on SPECT images. Fractal analysis of SPECT images may help to assess anatomic and physiologic changes in living organs.

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Clinical Impact of ^{18}F-FDG PET in Thyroid Carcinoma Patients with Elevated Thyroglobulin Levels and Negative ^{131}I Scanning Results After Therapy

TO THE EDITOR: The report by Helal et al. (*1*) provides convincing evidence of the superiority of ^{18}F-FDG PET for localization of residual thyroid carcinoma in a small patient cohort presenting with a difficult problem in the management of this disease. However, their conclusions about therapeutic and patient outcome efficacy raise some questions (*2*). Although PET was said to have initiated surgery for removal of a residual tumor in 23 patients, implicitly 5 of these had had some abnormality on conventional imaging (Tables 1 and 2 in (*1*)). It would have been helpful if the authors had gone into more detail on the process whereby PET was decisive, especially as this bears on the significance of the disease-free status achieved by 14 patients. Might not additional cervical lymph nodes, for example, have been identified in a conventionally initiated surgical exploration? Assuming, however, that without PET 14 more patients would have continued with occult residual disease, the real question is of the net benefit achieved by the extra interventions for the group as a whole. From an oncologist's perspective, this benefit needs to be expressed in terms of patients' length and quality of life and ideally offset against the expenditure involved. A figure of $50,000 per quality-adjusted life-year is often quoted, and some analysis of this nature is required to support conclusions about "undeniable clinical value" of imaging technologies (*3*). We hope Helal et al. will take this next step in putting numeric flesh on the sense of improved patient outcome that their report provides.

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REPLY: ^{18}F-FDG PET in differentiated thyroid carcinoma concerns only a few patients with metastases that do not concentrate ^{131}I, and the benefit of ^{18}F-FDG PET expressed in terms of "patients' length and quality of life and ideally offset against the expenditure involved" is difficult to determine without undertaking a multicenter study involving large groups of patients. Differentiated thyroid carcinoma represents less than 1% of all cases of cancer and has, above all, a generally good prognosis: 80%–95% survival to 10 y (*1*).

However, it is important to underline 2 points. First, most patients with thyroid carcinoma are cured from the first treatment and are then followed up with long-term monitoring, based on the relatively low cost of the thyroglobulin assay. However, recurrence will develop in 5%–20%, and their long-term prognosis will then depend on how soon the recurrence is detected and treated (*2*). Furthermore, recurrent disease that does not concentrate radioactive iodine has a negative outcome, and so it is important to detect recurrence by whatever means, as soon as possible, allowing a treatment other than ^{131}I.

The second point to underline is that in our group of 37 patients who could have been expected to have a negative outcome, ^{18}F-FDG PET detected recurrence in 19 of the 27 patients who had a negative morphologic assessment, leading to a cure in 10 patients and to a change in treatment in 4 others. Of the other 10 patients, ^{18}F-FDG PET made it possible to stick to the proposed surgery for 5, whereas a change of treatment was envisaged for the other 5.

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