Heterogeneity of Cerebral Blood Flow in Alzheimer Disease and Vascular Dementia

Takuya Yoshikawa, Kenya Murase, Naohiko Oku, Masao Imaizumi, Masashi Takasawa, Piao Rishu, Yasuyuki Kimura, Yoshitaka Ikejiri, Kazuo Kitagawa, Masatsugu Hori and Jun Hatazawa

*AJNR Am J Neuroradiol* 2003, 24 (7) 1341-1347

http://www.ajnr.org/content/24/7/1341
Heterogeneity of Cerebral Blood Flow in Alzheimer Disease and Vascular Dementia

Takuya Yoshikawa, Kenya Murase, Naohiko Oku, Masao Imaizumi, Masashi Takasawa, Piao Rishu, Yasuyuki Kimura, Yoshitaka Ikejiri, Kazuo Kitagawa, Masatsugu Hori, and Jun Hatazawa

BACKGROUND AND PURPOSE: Alzheimer disease (AD) and vascular dementia (VaD) are the two major diseases that cause dementia, and early diagnosis is important. Single photon emission CT (SPECT) of cerebral blood flow (CBF) is used for the early detection of dementia and as an auxiliary method for follow-up. AD shows reduced posterior blood flow and VaD manifests reduced anterior blood flow on CBF SPECT images. We examined the usefulness of 3D fractal analysis of CBF SPECT images to objectively quantify the heterogeneity of CBF in patients with AD and VaD.

METHODS: Thirty-two patients with AD and 22 with VaD based on neuropsychologic tests and imaging findings, as well as 20 age-matched control subjects underwent technetium-99m hexamethyl propyleneamine oxime CBF SPECT. We then conducted statistical image processing by 3D fractal analysis on reconstructed data. Fractal dimension, an index of heterogeneity, was then calculated for the whole brain, as well as for the anterior and posterior regions of the brain. A higher fractal dimension indicates that the CBF SPECT image is uneven. The ratio of fractal dimension of the anterior region to fractal dimension of the posterior region (A/P ratio) was calculated. Heterogeneity of CBF was compared among the AD, VaD, and control groups.

RESULTS: Fractal dimensions of the AD, VaD, and control groups were 1.072 ± 0.179 (mean ± SD), 1.005 ± 0.156, and 0.806 ± 0.06, respectively. A significant difference of fractal dimension was noted between the control group and the two types of dementia (P < .0001); however, no significant difference was noted between the AD and VaD groups. The A/P ratios of the AD and VaD groups were significantly different (0.952 and 1.163, respectively; P < .01).

CONCLUSION: Analysis of CBF SPECT images quantitatively showed that the fractal dimension was significantly higher (indicating heterogeneity) in patients with AD and VaD when compared with age-matched control subjects. Comparison of the A/P ratio on CBF SPECT images between AD and VaD groups showed that the heterogeneity of CBF was posterior-dominant for AD and anterior-dominant for VaD. Thus, 3D fractal analysis enabled a simple and objective evaluation of the heterogeneity of CBF in patients with AD and VaD.
metabolism in the brain by means of PET has report-
edly shown that glucose metabolism is decreased in
the posterior cingulate gyrus before any other site in
the very early stage of AD (9). There have also been
many reports on the dynamics of the cerebral circu-
lation and metabolism in VaD. According to one
report on Binswanger disease, which is a clinical vari-
ant of VaD, PET has shown that CBF and the cere-
bral metabolic rate for oxygen are decreased in the
white matter as well as in the cortex (10). In addition,
a diffuse decrease of CBF was observed at SPECT
(11), and reduced blood flow was also commonly seen
in the frontal lobe (12, 13). In VaD, abnormalities
tend to be detected with cognitive function tests that
include parameters for evaluation of frontal lobe
function (14). Namely, AD tends to present with
posterior-predominant rather than anterior-predom-
inant blood flow reduction, whereas VaD tends to
conversely present with anterior-predominant rather
than posterior-predominant blood flow reduction.

Although visual evaluation of normal tomograms is
the primary method currently used for SPECT in the
area of general clinical testing, this method lacks
objectivity because it is heavily influenced by differ-
ences in image quality and the image display method,
as well as by the judgment of the interpreter. It is
difficult to establish a region of interest (ROI) in
exactly the same location for all subjects in semiquan-
titative analysis methods that employ the ROI, which
are frequently used for nuclear medicine as more
objective indexes, because of differences in brain
morphology. In addition, the territory of the ROI is
limited, but evaluation of locations other than the
ROI is impossible, and a subjective influence cannot
be avoided during establishment of the ROI. Recent
statistical methods for the analysis of functional im-
ages have allowed changes that were missed with
conventional ROI analysis to be more easily detected.
CBF can now be evaluated three-dimensionally by
using 3D stereotactic surface projections (15) for the
diagnosis of disease that involves dementia. One of
the advantages of evaluation by statistical image analysis of
3D stereotactic surface projections is that sites of abnor-
mal CBF and metabolism can be detected more objec-
tively, since correction can be done for anatomic
differences among patients, and patient data can be
statistically compared with a normal data base on a
voxel-by-voxel basis. In this study, we quantified the
heterogeneity of CBF in patients with AD or
with VaD due to small-vessel disease.

The heterogeneity of the distribution of a tracer
can provide us with useful information on the func-
tional status of organs and tissues. Fractal analysis is
a mathemetic tool for dealing with complex systems
that have no characteristic length scale (scale invari-
ant) (16). Scale-invariant systems are usually charac-
terized by noninteger dimensions, which are termed
fractal dimensions. Fractal geometry allows structures
to be quantitatively characterized in geometric terms,
even if their forms are irregular and fragmented,
because it deals with the geometry of hierarchies and
random processes. In this study, fractal analysis was
used to assess the heterogeneity of SPECT images.
This type of analysis is most useful for characterizing
branching structures, such as the pulmonary airways
and blood vessels (17, 18). Spatial changes of regional
blood flow and metabolism in living organs are mea-
surable by using fractal analysis with PET and SPECT
(16, 19–20). The observed variance increases along
with the number of subregions studied in an organ
(16), and such resolution-dependent variance can be
described with fractal analysis (16, 20–21). Biologic
systems show considerable spatial and temporal het-
erogeneity, such as CBF, myocardial blood flow, and
pulmonary blood flow (21–23). VaD due to small-
vessel disease is fairly common and is hard to distin-
guish from AD (24, 25). In this study, we examined
the use of 3D fractal analysis for objective evaluation
of the heterogeneity of CBF in patients with AD or
with VaD due to small-vessel disease.

Methods

Subjects

The subjects consisted of 32 patients (15 men, 17 women)
with AD (AD group), 22 patients (12 men, 10 women) with
VaD (VaD group), and 20 age-matched controls (nine men, 11
women) (control group). The clinical characteristics of these
three groups are shown in the Table. All of the subjects were
right-handed. CBF SPECT was performed from June 2000 to
June 2002. The National Institute of Neurologic and Commu-
nicative Disorders and Stroke–Alzheimer Disease and Related
Disorders Association, or NINCDS-ADRDA, diagnostic crite-
ria (26) were used to diagnose probable AD. A diagnosis of
VaD was made in a comprehensive manner based on the
diagnostic criteria proposed by the National Institute of Neu-
rologic Disorders and Stroke–Association International pour la
Recherche et l’Enseignement en Neurosciences (NINDS-
AIREN) (27), and the criteria for subcortical VaD proposed by
Erkinjuntti et al (28). The 22 patients with VaD were classified
as having small-vessel disease based on head MR images that
revealed small infarcts ranging from 3 to 15 mm in diameter
(seen as low signal intensity on T1-weighted images and as high
signal intensity on T2-weighted images) in the basal ganglia,
thalamus, pons, and deep white matter. The control group
consisted of 20 age-matched individuals who attended our
outpatient clinic for investigation of headache or dizziness and
underwent CBF SPECT, but who had no neuropsychiatric
abnormalities and no abnormalities at CT or MR imaging.
The Mini-Mental State Examination (MMSE) (29) was performed
within 3 months of CBF SPECT for evaluation of cognitive
function. Patients who could not undergo the intellectual func-
tion test because of conditions such as aphasia were excluded.
Informed consent was obtained from all of the subjects and
from family members when a subject could not fully understand the details of the study.

Data Acquisition

Technetium-99m hexamethyl propyleneamine oxime (99mTc-HMPAO) was created by reconstituting HMPAO with 20 mCi (740 MBq) of fresh 99mTc pertechnetate. 99mTc-HMPAO was injected intravenously while the subject rested supine on the scanning bed with the eyes closed in a quiet examination room. SPECT scanning was performed with a four-headed gamma camera (Gamma View SPECT 2000H; Hitachi Medical Corp., Tokyo, Japan), by using a low-energy thin-section parallel-hole collimator (30). The in-plane and axial resolution after reconstruction was 10.0 mm in full-width at half-maximum. SPECT acquisition was performed at 8 seconds per step, with 128 collections over 360°, and data were recorded in a 64 × 64 matrix.

The raw SPECT data were transferred to a nuclear medicine computer (HARP 3; Hitachi Medical Corp.). The projection data were prefiltered with a Butterworth filter (cutoff frequency 0.20 cycles/pixel, order 10) and reconstructed into transaxial sections of 4.0-mm-thick images in planes parallel to the orbitomeatal line. Chang’s attenuation correction was applied to the reconstructed data by using an attenuation coefficient of 0.08 cm⁻¹.

Anatomic Standardization

Anatomic standardization involves fitting individual brains of different sizes and shapes into the configuration of a standard brain with a fixed coordinate system. We used Neurologic Statistical Image Analysis Software (NEUROSTAT) developed by Minoshima et al (15) at the University of Washington to perform anatomic standardization of our SPECT data. First, the midsagittal plane was determined, and the brain angle was corrected for x plane, y plane, and z plane, since the original images obtained with SPECT are angled depending on the position at the time of imaging. Next, the anterior commissure–posterior commissure line, which is the reference line, was fixed based on four reference points (the polus frontalis, the base of the anterior aspect of the corpus callosum, the base of the thalamus, and the polus occipitalis) within the dimension and was matched to the standard brain coordinate system of Talairach and Tournoux (31). Then, linear transformation and nonlinear transformation were performed, and the brain surface was fitted to the contours of the standard brain by deformation. Since NEUROSTAT performs conversion three-dimensionally along the nerve fibers, atrophic brains could also be appropriately converted to the standard brain (32).

Three-Dimensional Fractal Analysis

In fractal geometry, the relationship between a measure (M) and the scale (a) is expressed as follows:

\[ M(a) = k \cdot a^{-D} \]

where k is a scaling constant and D is called the fractal dimension (17). As Equation 1 implies, the quantity \( M(a) \) to be measured is a function of the ruler scale and can be a nonconstant. D is one parameter that is useful for this purpose in characterizing organizationally complex structures (33).

CBF SPECT was performed by using 99mTc-HMPAO, and the cutoff value for the maximal voxel radioactivity on reconstructed images was established by dividing it from 35% to 50% at 11 equal intervals. The number of voxels with radioactivity equal to or above the established cutoff values was calculated. The cutoff value of the maximal radioactivity was defined as \( M(a) \), and the total number of voxels measured was defined as \( M(a) \), as shown in Equation 1. The cutoff values were changed in sequential order as this process was repeated, and the number of voxels with radioactivity equal to or above the established cutoff values was calculated. Then, the relationship between the number of voxels with a radioactivity equal to or greater than the established cutoff values and each cutoff value was determined. Finally, the relationship between the number of voxels and the cutoff values was converted into natural logarithms and plotted as a linear relationship. The logarithmic cutoff values were plotted on the horizontal axis of a graph, and the logarithmic value of the number of voxels was plotted on the vertical axis. The slope of this line corresponded to the fractal dimension (Fig 1). A higher fractal dimension indicates that the CBF SPECT image is uneven. As shown in Figure 1, one representative CBF SPECT image each was selected from the AD group, the VaD group, and the control group, after which 3D fractal analysis was performed and the fractal dimension was calculated. The fractal dimensions for the AD case, the VaD case, and the control case were 1.320, 1.112, and 0.767, respectively.

Items Examined

The fractal dimension of the whole brain was compared among the AD, VaD, and control groups. To examine the differences in CBF between the AD and VaD groups, the cerebrum was divided into anterior and posterior regions by a line connecting the central sulcus on the left and right sides, and the fractal dimension of each region was calculated. The border between the anterior region and the posterior region was determined by performing anatomic standardization so that the location did not vary from case to case. The ratio of fractal dimension of the anterior region to fractal dimension of the posterior region was calculated as an anterior-posterior ratio (A/P ratio) and was compared between the AD group and the VaD group.

Statistical Analysis

For comparison of the fractal dimension among the AD, VaD, and control groups, statistical analysis was performed by using the Mann-Whitney U test. The significance of differences in the clinical characteristics of these three groups was assessed with the Mann-Whitney U test. Statistical analysis was performed with the Wilcoxon signed rank test for comparison of the fractal dimension after the data for the AD group and the
VaD group were divided into anterior and posterior regions. Results are expressed as mean ± standard deviation (SD), and statistical significance was defined as a P value less than .01.

Results

There were no marked differences in age or sex among the three groups. The MMSE score of the AD group was 19.1 ± 5.8 (mean ± SD), which was lower compared with 23.6 ± 3.4 in the VaD group (Table). However, the result showed no significant difference.

T2-weighted MR images and SPECT images of a representative patient from each group are shown in Figure 2. Although the AD group did not show any clear abnormalities on the T2-weighted MR images, a decrease of CBF in the bilateral temporoparietal lobes was noted on SPECT images. In the VaD group, multiple small infarcts were observed in the bilateral basal ganglia on the T2-weighted MR images, and a frontal region decrease of CBF was noted on SPECT images. The representative cases in Figure 2 are the same as those displayed in Figure 1.

The fractal dimensions in the AD, VaD, and control groups were 1.072 ± 0.179 (mean ± SD), 1.005 ± 0.156, and 0.806 ± 0.06, respectively (Fig 3). The fractal dimension of the whole brain showed a statistically significant difference between the control group and the AD group, as well as between the control group and the VaD group. However, no significant difference (NS) was noted between the AD group and the VaD group.

In contrast, the VaD group showed a significantly higher fractal dimension in the anterior region than in the posterior region (P < .01), which suggested the presence of anterior-predominant heterogeneity of CBF. The A/P ratios of the AD group and the VaD group were 0.952 and 1.163, respectively.

Next, the A/P ratios and fractal dimension of the whole brain were plotted on the horizontal axis and vertical axis, respectively, and each patient in the AD group and the VaD group was examined (Fig 5). A horizontal line was drawn where the mean fractal dimension of the whole brain in the control group was 0.806, and a vertical line was drawn where the A/P ratio was 1 (ie, when the heterogeneity of the anterior region and the posterior region was comparable). Although there was some spread of the data, most points were above the above-mentioned horizontal line in both the AD group and the VaD group. In addition, the two diseases tended to be separated by the A/P ratio of 1, since the AD group tended to have a ratio of 1 or less, whereas the VaD group had a ratio of 1 or more.

Discussion

CBF SPECT may not have much diagnostic significance for VaD compared with degenerative dementia, since VaD is diagnosed with MR imaging in most cases. Although a decrease of CBF and metabolism is naturally observed at sites of infarcts and hemorrhage sites in VaD, a decrease of CBF and metabolism in the cortex that is not limited to such locations can also be seen in diaschisis, and this is why CBF SPECT might have some significance. In a CT study, Loeb et al (34) found no difference in the location or size of
infarcts between a group with dementia and a group without dementia, and they concluded that the morphologic findings on images should be evaluated cautiously. The properties, locations, and clinical features of brain lesions that cause VaD vary markedly from case to case. Therefore, when clinical studies are performed, results may not necessarily be uniform whatever diagnostic criteria are used. For the VaD group in this study, we selected patients with subcortical ischemia, which is relatively common and difficult to differentiate from AD by visual evaluation (24, 25). The primary brain lesions in this pathologic condition are lacunar infarcts due to the small-vessel disease and ischemic white matter lesions. The criteria for subcortical VaD proposed by Erkinjuntti et al (28) were used as the diagnostic criteria. These criteria were established by correcting the subcortical section of the NINDS-AIREN diagnostic criteria for VaD. The reason why blood flow reduction was observed in VaD due to small-vessel disease, even in the cortex where there were no morphologic abnormalities, seemed to be because cerebral circulation and metabolism were decreased as a secondary effect due to disconnection between the deep cerebrum and the cortex (35).

We performed 3D fractal analysis in the AD, VaD, and control groups and compared fractal dimensions for the whole brain. Our results quantitatively showed that there was heterogeneity of CBF in the AD group and the VaD group compared with the control group, whereas there was no quantitative difference in the heterogeneity of CBF between the AD group and the VaD group. When the whole brain was divided into an anterior region and a posterior region in these two groups and the fractal dimensions were calculated for each region, there was posterior-predominant heterogeneity of CBF in the AD group and there was anterior-predominant heterogeneity of CBF in the VaD group. This is a quantitative confirmation of previous reports suggesting that there is posterior-predominant blood flow reduction in AD versus anterior-predominant blood flow reduction in VaD (1, 2). However, we must be careful, as the fractal dimension is an index of the heterogeneity of CBF and not an index of the extent of blood flow reduction. For example, if blood flow and metabolism are maintained and the CBF distribution is uneven on normal visual evaluation, the fractal dimension will be high even if there is no reduction of blood flow.

In the AD group, some patients had higher fractal dimensions in the anterior region than in the posterior region when individual cases were examined. Reduced anterior blood flow is also seen in frontotemporal dementia (36), care must be taken to differentiate between these diseases. Although the data are not presented here particularly, the A/P ratio for six cases of frontotemporal dementia was 1.482 ± 0.201 (mean ± SD) and was much higher than the A/P ratio for VaD, suggesting the presence of anterior-predominant rather than posterior-predominant heterogeneity of CBF. Some patients with a frontal lobe–predominant reduction on PET scans and who receive a clinical diagnosis of AD may receive a di-
agnosis of frontotemporal dementia several years later. Blood flow reduction in the frontal lobe due to physiologic aging may also be a problem. The VaD group also had patients with a higher fractal dimension in the posterior region than in the anterior region. Since there are also mixed types of AD, it is not rare for AD to be associated with cerebrovascular disease. Examination of autopsy cases has shown that 35–39% of patients with AD also had brain infarction (37). Diagnosis of dementia at the level of MMSE score 20–25 is relatively difficult. The line separating deterioration of cognitive function due to so-called physiologic aging (age-related cognitive impairment) from mild cognitive impairment, which is thought to be a transitional stage toward early dementia, and the line separating mild cognitive impairment from dementia are still unclear (38, 39). Three-dimensional fractal analysis has limited the clinical application owing to the significant overlap in the fractal dimension and the A/P ratio by using fractal analysis in the AD group and the VaD group.

In this study, we performed 3D fractal analysis of CBF SPECT images to quantify the heterogeneity of CBF. Compared with SPECT, PET has superior sensitivity and resolution. Since images obtained by means of fluorine-18–2-fluoro-2-deoxy-D-glucose (\(^{18}\text{F}-\text{FDG}\)) have a better resolution than images obtained by using \(^{15}\text{O}\) gas and \(\text{H}_2^{15}\text{O}\), this method is widely used for investigation of AD. When correlation of the fractal dimension calculated from CBF SPECT images and \(^{18}\text{F}-\text{FDG}\) PET images was examined before 3D fractal analysis was applied to CBF SPECT images, there was a significant correlation among the fractal dimensions obtained from each type of image, suggesting that heterogeneity of accumulation on CBF SPECT images was comparable to that on \(^{18}\text{F}-\text{FDG}\) PET images (40, 41). On the basis of such findings, it seemed that the fractal dimension obtained with CBF SPECT might also reflect CBF and metabolism, and that PET can be used instead of PET at institutions that do not have a PET apparatus.

Kuikka et al (16, 42) calculated the fractal dimension as a measure of heterogeneity from the relationship between the relative dispersion (ie, the SD divided by the mean count) and the number of subregions. Although they determined the subregions semiautomatically, this does not appear to be a straightforward method, especially in 3D analysis. However, the 3D fractal analysis method is simple to perform in a 3D manner, does not need special software, and is objective. The most important factor in calculating the fractal dimension from SPECT images is the cutoff value. In this study, the cutoff value for the maximum radioactivity was set at 11 levels from 35% to 50% at equal intervals, and the number of voxels with radioactivity exceeding the cutoff value was calculated in each case. In all cases, the relationship between the cutoff value and the number of voxels (converted to a natural logarithm) was linear, and the correlation coefficient between them was 0.99, which suggested that the CBF SPECT image appeared to have a fractal form for this range of cutoff values and that the cutoff values used in this analysis were reasonable.

Since the shape of the brain varies from patient to patient, it is difficult to divide the brain into an anterior region and a posterior region at the same site in all cases. Also, there is a serious issue of how to divide the brain into an anterior region and a posterior region. Although the central sulcus might have been more accurately identified by placing a thin-section MR image with its extensive anatomic information over a CBF SPECT image, it has now become possible to solve this problem by standardizing the brain shape through conversion of a patient’s SPECT images into the standard brain coordinate system of Talairach and Tournoux (31), after which the brain is divided into an anterior region and a posterior region at the line connecting the right and left central sulcus, which is easy to identify anatomically. Recently, statistical imaging has been used to assist in the diagnosis of dementia. Anatomic standardization is performed during this process. Since a common problem for statistical image analysis is the morphologic changes of a patient’s brain, particularly the effects of cerebral atrophy, this must be taken into consideration. Because statistical methods can easily detect systemic differences of images, such as those due to imaging equipment and imaging conditions, unity of imaging methods is important.

**Conclusion**

The 3D fractal analysis method of statistical image analysis allows heterogeneity of CBF in AD and VaD to be quantified and may also allow a simpler and more objective evaluation.

**Acknowledgments**

We thank Messrs. Yukio Nakamura, Hiroaki Matsuzawa, Kouichi Fujino and Miss Tomoko Fukunaga for helping us to perform the nuclear medicine examinations and for evaluating cognitive function.

**References**


