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Interobserver variability of cerebral blood flow measurements obtained using spectral analysis and technetium-99m labeled compounds

Masashi TAKASAWA,* Kenya MURASE,** Naohiko OKU,*** Minoru KAWAMATA,** Makoto NAGAYOSHI,** Yasuhiro OSAKI,*** Masao IMAIZUMI,* Takuya YOSHIKAWA,* Kazuo KITAGAWA,* Masatsugu HORI* and Jun HATAZAWA***

*Division of Strokology, Department of Internal Medicine and Therapeutics, Osaka University Graduate School of Medicine
**Department of Allied Health Sciences, Osaka University Graduate School of Medicine
***Department of Nuclear Medicine and Tracer Kinetics, Osaka University Graduate School of Medicine

Radionuclide angiography with technetium-99m hexamethylpropylene amine oxime (^{99m}Tc-HMPAO) or technetium-99m ethyl cysteinate dimer (^{99m}Tc-ECD) enables the non-invasive estimation of absolute cerebral blood flow (CBF) to be determined by using spectral analysis (SA). We previously demonstrated the clinical use of SA; however, this method involves a few manual steps. The aim of this study was to evaluate the interobserver variability of CBF estimations made using SA and compare these results with those obtained by using graphical analysis (GA). In twenty patients with various brain diseases (27–74 years old), radionuclide angiography examinations were performed using ^{99m}Tc-labeled compounds (10 patients, ^{99m}Tc-HMPAO; 10 patients, ^{99m}Tc-ECD). Bilateral cerebral hemispheres were studied in all patients, and the brain perfusion index (BPI) values were estimated using SA and GA. The interobserver variability between two observers was then assessed. A good correlation between the BPI values assessed using both SA (BPI^S) and GA (BPI^G) was obtained. The correlation coefficient for BPI^S ($r = 0.987$) was almost the same as that for BPI^G ($r = 0.982$). The degree of interobserver variability was not affected by the measurement of elevated BPI values. Measurements carried out by two observers using both SA and GA exhibited a similar degree of interobserver variability. SA appears to have a satisfactory interobserver variability and may be more suitable for clinical applications.

Key words: brain perfusion index, cerebral blood flow, spectral analysis, graphical analysis, single-photon emission tomography

INTRODUCTION

THE QUANTIFICATION of cerebral blood flow (CBF) is very important for patient management, especially in the presence of cerebrovascular disease.[1,2] In particular, either determining the infarct and symptomatic blood flow thresholds of the cerebral cortex or measuring the residual flow in ischemic brain tissue have not only a considerable impact upon prognosis and also therapeutic planning. The absolute quantification of CBF is critical to the above processes.

Matsuda et al. developed a simple, non-invasive method for the quantification of brain perfusion using technetium-99m hexamethylpropylene amine oxime (^{99m}Tc-HMPAO)[3] or technetium-99m ethyl cysteinate dimer (^{99m}Tc-ECD).[4] They measured the brain perfusion index (BPI) using radionuclide angiographic data and graphical analysis (GA). Recently, Murase et al.[5] developed an alternative approach for estimating the BPI using spectral analysis (SA) and investigated its usefulness in comparison to the conventional method using GA. They showed that the BPI measured using SA (BPI^S) provides a more accurate measurement of absolute CBF than BPI measurements using GA (BPI^G).

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For reprint contact: Masashi Takasawa, M.D., Division of Strokology, Department of Internal Medicine and Therapeutics, Osaka University Graduate School of Medicine, 2–2, Yamadaoka, Suita, Osaka 565–0871, JAPAN.

E-mail: tkswm@medone.med.osaka-u.ac.jp

In routine clinical settings, the reproducibility or interobserver variability must be established to ensure precise CBF measurements. Murase et al.[6] demonstrated a good reproducibility of BPI^S values using a double injection of ^{99m}Tc-ECD. However, the SA method involves a few manual steps that must be performed on a workstation; these manual steps introduce a possibility of error into the estimation of BPI values.

The aim of this study was to investigate the interobserver variability of BPI values obtained using SA, and compare these results with those obtained using GA for both ^{99m}Tc-HMPAO and ^{99m}Tc-ECD radionuclide data.

SUBJECTS AND METHODS

Theory

Spectral analysis

The radioactivity level of ^{99m}Tc-labeled compounds in the brain at a given time $t[C^S(t)]$ was modeled as a convolution of the blood input function $[C_a(t)]$ with a sum of k exponential terms, as shown by the following equation[5]:

$$C^S(t) = \sum_{i=0}^{k} \alpha_i \cdot \int_0^t C_a(u) e^{-\beta i(t-u)} du \qquad \text{(Eq. 1)},$$

where α_i and β_i were assumed to be positive or zero. The upper limit, k, represents the maximum number of terms to be included in the model and was set at 1000. The α_i values were determined from Eq. 1 using the level of brain radioactivity measured by radionuclide angiography and the non-negative least-squares method for β_i, ranging from 0 to 2 min^{-1} with an increment of 0.002 min^{-1}. In the present study, the amount of radioactivity in the aortic arch was taken as $C_a(t)$ in Eq. 1 to maximize the non-invasiveness of the procedure and eliminate the need for blood sampling. When $C_a(t)$ was replaced by Dirac's delta function in Eq. 1, the tissue impulse response function $[IRF^S(t)]$ was given by the following equation:

$$IRF^S(t) = \sum_{i=0}^{k} \alpha_i \cdot e^{-\beta_i t} \qquad \text{(Eq. 2)}.$$

The BPI^S was calculated from $IRF^S(0)$ as follows:

$$BPI^S = \sum_{i=0}^{k} \alpha_i \qquad \text{(Eq. 3)},$$

where BPI^S is expressed in units of min^{-1}.

Graphical analysis

The BPI^G was calculated as follows:

$$BPI^G = 100 \cdot k_u \cdot \frac{10 \cdot ROI_{aorta}}{ROI_{brain}} \qquad \text{(Eq. 4)},$$

where ROI_{aorta} and ROI_{brain} represent the size of the aortic arch and cerebral hemisphere ROIs, respectively, and k_u is the unidirectional influx rate of the tracer from the blood to the brain, determined by the slope of the line in the GA within the first 30 seconds post-injection. To compare BPI^G with BPI^S, we multiplied the result of Eq. 4 by 0.06 so that both BPI^G and BPI^S would be expressed in the same units (min^{-1}).

Subjects

Twenty patients (13 males, 7 females; age 61.5 ± 10.8 years [mean ± SD]) with various brain diseases (12 cerebral infarcts; 4 transient ischemic attacks; 3 vertigo; 1 brain tumor) participated in this study. Informed consent was obtained from each participant after a detailed explanation of the study's purpose and the scanning procedures.

Measurement of BPI

Data acquisition

After the intravenous injection of a bolus of 370–740 MBq ^{99m}Tc-HMPAO or ^{99m}Tc-ECD, sequential imaging was performed while the patient was in a supine position using a gamma camera (RC-2600i; Hitachi Medical Co., Tokyo, Japan) equipped with a low-energy, high-resolution collimator. The passage of tracer from the aortic arch to the brain was monitored. A total of 90 sequential frames, each 1 second in duration, were collected in a 128 × 128 image matrix.[3,4]

Calculation of BPI value

To calculate BPI^S, the raw planar dynamic data were transferred to a workstation (Indigo 2; Silicon Graphics, Mountain View, CA, USA). Regions of interest (ROIs) were hand-drawn over the left and right cerebral hemispheres and the aortic arch using the workstation and a software package (Dr. View; Asahi Kasei Joho System Co., Ltd., Tokyo, Japan), as described by Matsuda et al.[3,4] The BPI^S calculations for the ROIs were performed on the workstation using a software package for BPI analysis developed by Murase.[5]

To measure BPI^G, the raw planar dynamic data were transferred to a Hitachi workstation (RW-3000; Hitachi Medical Co., Tokyo, Japan), and the BPI^G calculations were performed using a software package for Patlak plot analysis (RW-3000; Hitachi Medical Co., Tokyo, Japan) with no filter, as previously described by Matsuda et al.[3,4]

Interobserver Agreement

Twenty patients, for a total of 40 hemispheres, were examined, and the BPI values were calculated by two operators (Observer 1, M.K.; Observer 2, M.T.) with varying degrees of experience and on different days. The two operators were unaware of the other's BPI estimations. Both operators were instructed to follow the BPI^G and BPI^S estimation protocols described above.

Calculation of Differences in BPI

We calculated the difference in BPI values determined by the two operators to study the degree of variation in BPI values calculated by two different observers. The BPI values (BPI^S and BPI^G) calculated by Observer 1 were defined as BPI_1. Likewise, the BPI values calculated by

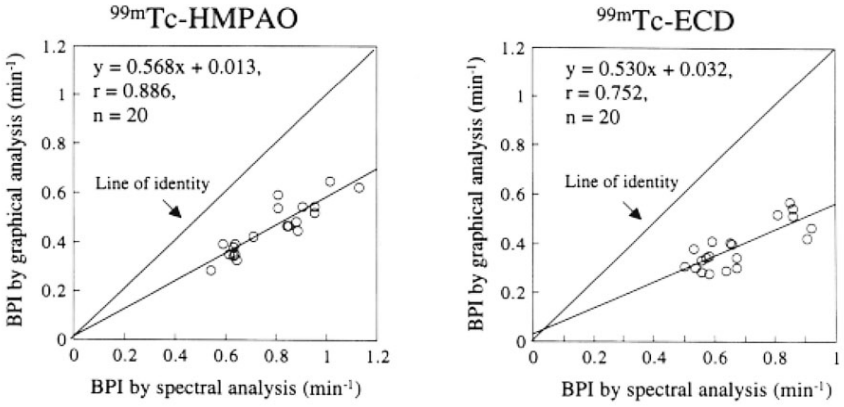

Fig. 1 Relationship between BPI^S and BPI^G by Observer 1. For both ^{99m}Tc-HMPAO and ^{99m}Tc-ECD measurements, the relationship between BPI^S and BPI^G was significant. The correlation coefficient for ^{99m}Tc-HMPAO was slightly higher than that for ^{99m}Tc-ECD.

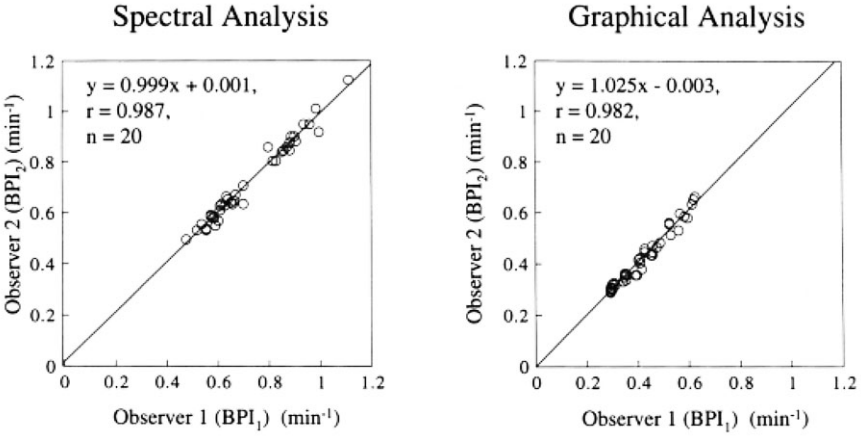

Fig. 2 Relationship between BPI_1 and BPI_2. The BPI values calculated by Observer 1 were defined as BPI_1. Likewise, the BPI values calculated by Observer 2 were defined as BPI_2. The BPI values calculated by the two different operators are similar. The correlation coefficient for spectral analysis (SA) was almost the same as that for graphical analysis (GA).

Observer 2 were defined as BPI_2. The difference between the BPI calculations of the two different operators was determined as follows:

$$\text{BPI Difference (\%)} = 100 \cdot \frac{[BPI_2] - [BPI_1]}{[BPI_1]}$$

Statistical Analysis

Either correlations between the BPI^S and BPI^G values or correlations between the BPI_1 and BPI_2 values were assessed using linear regression analysis. The degree of difference in BPI values between the two observers was compared using the paired t-test. A p value of less than 0.05 was considered significant.

RESULTS

Figure 1 shows the comparison between BPI^G and BPI^S. Although significant correlations were found for both ^{99m}Tc-HMPAO (Fig. 1, left) and ^{99m}Tc-ECD (Fig. 1, right), the correlation coefficient for ^{99m}Tc-HMPAO (r = 0.886) was slightly higher than that for ^{99m}Tc-ECD (r = 0.752).

Figure 2 shows the interobserver variability for the two different observers. Good correlations between both the BPI^S and BPI^G values calculated by Observer 1 (M.K.) (x) and those calculated by Observer 2 (M.T.) (y) were recognized. The correlation coefficient for SA (r = 0.987, $y = 0.999x + 0.001$) was similar to that for GA (r = 0.982, $y = 1.025x - 0.003$).

The differences between the two observers were −0.056 ± 3.640% for BPI^S and 1.909 ± 4.686% for BPI^G (mean ± SD), respectively. The degree of difference in BPI^S values was smaller than that for BPI^G, but was not statistically significant (p = 0.0722). Figure 3 shows a scatter plot of the mean BPI value against the difference in BPI values

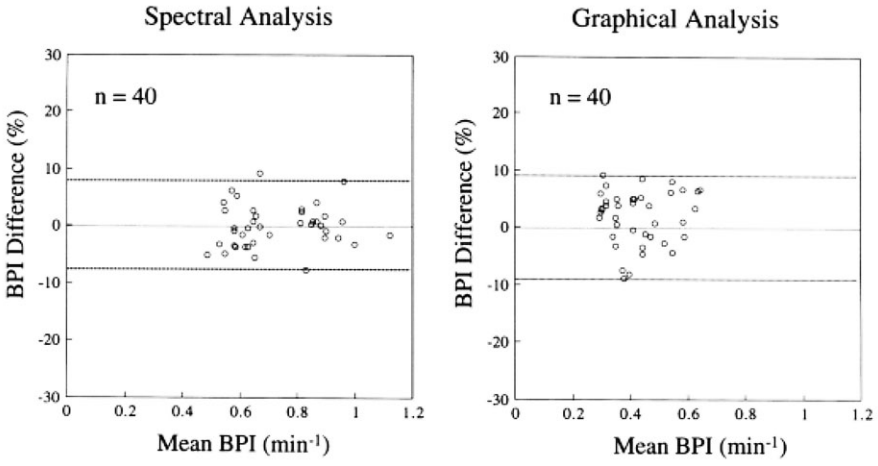

Fig. 3 Scatter plot of the mean BPI value against the difference between BPI_1 and BPI_2. The dynamic range of BPI^G was almost as much as that of BPI^S, and the interobserver variability for BPI^S and BPI^G did not increase for elevated BPI values. The broken line indicates the 2 standard deviations value (SD) of the difference in BPI values.

calculated by the two observers for each BPI value. The dynamic range of BPI^G was almost as much as that of BPI^S, and the difference in BPI values calculated by the two observers did not increase as the mean BPI value increased.

DISCUSSION

SA has been used to analyze dynamic PET scans in humans; this technique provides data representing the time course of activity in tissue regions of interest and in arterial blood following the administration of a radiolabeled tracer.[7] SA provides a simple spectrum of kinetic components that relates the tissue's response to the blood activity curve, facilitating the interpretation of dynamic PET data and simplifying comparisons between regions and subjects.

Murase et al.[5] first presented the non-invasive SA method for the quantification of CBF using technetium-99m compounds. They suggested that BPI^S reflected the CBF more truly than BPI^G and that BPI^S was less dependent on the first-pass extraction fraction of the tracer. Furthermore, BPI^S was insensitive to the rapid conversion of a lipophilic, diffusible component to a hydrophilic, non-diffusible type in arterial blood. In our study, BPI^G was underestimated, compared with BPI^S as shown in Figure 1. The extent of the underestimation was greater when using ^{99m}Tc-ECD than for ^{99m}Tc-HMPAO, suggesting that the first-pass extraction fraction of ^{99m}Tc-ECD is lower than that of ^{99m}Tc-HMPAO. These findings agree with those of previous reports.[5,8,9]

The reproducibility or interobserver variability of CBF measurements must be established to enable routine clinical application. The SA method involves a few manual procedures that must be performed using computer workstations.[5] First, the ROIs must be manually set on the images of the brain hemispheres and the aortic arch. Second, the radioactivity curve for the aortic arch must be manually fitted to that for the brain to calculate BPI^S. These manual procedures introduce potential sources of error into the estimation of BPI values.

Murase et al. demonstrated that the reproducibility of SA is satisfactory for observations using a double injection of ^{99m}Tc-compounds.[6] They also suggested that this double injection method using SA could be useful for activation studies involving pharmacological intervention within one day. We investigated the interobserver variability of BPI estimations made by two different observers. A good correlation between the BPI^S values by the two different observers was shown as was also shown between the BPI^G values. Furthermore, we analyzed a scatter plot of the mean BPI value against the difference in BPI values calculated by the two observers. The dynamic range of BPI^G was almost as much as that of BPI^S, and the scatter of the difference in BPI^S was, apparently, the same as that in BPI^G within 2 SD. This finding indicates that the interobserver variability of BPI^S and BPI^G does not increase for elevated BPI values.

In conclusion, the interobserver variability of SA is satisfactory and sufficient for this method to be applied in clinical assessments of CBF.

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