Statistical Evaluation of Single-Photon Emission Computed Tomography Image Using Smoothed Bootstrap Method

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Many of the neurodegenerative diseases associated with a decrease in regional cerebral blood flow (rCBF) are untreatable, and the appropriate therapeutic strategy is to slow the progression of the disease. Therefore, it is important that a definitive diagnosis is made as soon as possible when such diseases are suspected. Diagnostic imaging methods, such as positron emission tomography (PET) and single-photon emission computed tomography (SPECT), play an important role in such a definitive diagnosis. Since several problems arise when evaluating these images visually, a procedure to evaluate them objectively is necessary, and studies of image analyses using statistical evaluations have been suggested. However, the assumed data distribution in a statistical procedure may occasionally be inappropriate. Therefore, to evaluate the decrease of rCBF, it is important to use a statistical procedure without assumptions about the data distribution. In this study, we propose a new procedure that uses nonparametric or smoothed bootstrap methods to calculate a standardized distribution of the Z-score without assumptions about the data distribution. To test whether the judgment of the proposed procedure is equivalent to that of an evaluation based on the Z-score with a fixed threshold, the procedure was applied to a sample data set whose size was large enough to be appropriate for the assumption of the Z-score. As a result, the evaluations of the proposed procedure were equivalent to that of an evaluation based on the Z-score.

Key words single-photon emission computed tomography; diagnostic imaging; bootstrap method

Diagnostic imaging methods, such as positron emission tomography (PET) and single-photon emission computed tomography (SPECT) imaging, are well established for assessing decreases in regional cerebral blood flow (rCBF). Many of the neurodegenerative diseases associated with a decrease of rCBF are untreatable, and the appropriate therapeutic strategy is to slow the progression of the disease. Therefore, when such diseases are suspected, it is important that a definitive diagnosis is made as soon as possible. Diagnostic imaging methods such as PET and SPECT play an important role in the definitive diagnosis of neurodegenerative diseases. Since several problems arise when evaluating these images visually, a procedure to evaluate them objectively is necessary, and studies of image analyses using statistical evaluations, such as statistical parametric mapping (SPM), three-dimensional stereotactic surface projection (3D-SSP), and the easy Z-score imaging system (eZIS), have been suggested.¹ For example, the Z-score is calculated for each pixel of an image and is then used as an index of the decrease of rCBF in each pixel. The Z-score is based on statistical significance, and the formula is

\[ Z\text{-score} = \frac{x_0 - x}{\sigma_0} \]

where \( x \) is the pixel value in the patient data, and \( x_0 \) and \( \sigma_0 \) are the average and the standard deviation of the pixel values in the control data set, respectively.

If a Z-score exceeds a threshold, \( T_0 \), which is based on the significance level, the decrease of rCBF at the pixel is statistically significant. A number of methods of statistical evaluations in image analysis require an assumption about the data distribution, such as the data being normally distributed. For example, \( T_0=2.0 \) is sometimes used as the Z-score threshold; that is, if the Z-score is greater than 2.0, the decrease of rCBF in the pixel is judged to be significant. The evaluation based on this threshold is nearly equivalent to the results of a statistical test at a significance level of 5% when the Z-score follows a standard normal distribution. In discriminating between images taken from a patient’s brain at an early stage of Alzheimer’s disease and those of a normal brain, statistical procedures were found to be superior to visual inspection.² This is because for the appropriate use of some statistical procedures, several assumptions must be satisfied. For example, to ensure statistical significance at a level of 5% when the Z-score is greater than 2.0, the control data set must follow a normal distribution. However, when the sample size is insufficiently large or contains biased data, the assumptions about the data distribution may be inappropriate. Therefore, it is important to have a statistical procedure that can evaluate a decrease in rCBF without requiring an assumption about the data distribution.

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One suggestion was to use nonparametric permutation testing for the statistical tests between two groups from functional neuroimaging.\(^{11}\) Commonly, the null hypothesis of a permutation test is that the data distributions (populations) are equivalent. The bootstrap method, which is a resampling method, enables us to evaluate the null hypothesis that the parameters are equivalent; thus the bootstrap method has a broader range of applications than does the permutation test.\(^{12,13}\) Accordingly, in this study, we suggest a new procedure that uses nonparametric or smoothed bootstrap methods to calculate a standardized distribution of the Z-score without any assumptions about the data distribution. To compare the evaluations of the decrease of rCBF using the proposed procedure and using the Z-score with a fixed threshold (hereinafter, referred to as ZFT), both procedures were applied to a control data set whose sample size was large enough to be appropriate for the assumption that the Z-score follows a standardized normal distribution. Iterative simulation trials were then carried out to compare the effectiveness of both procedures in a small data set.

**MATERIALS AND METHODS**

**Bootstrap Method** The bootstrap method is a resampling procedure proposed by Efron in 1979.\(^{12}\) In a resampling procedure, sampling from a population is simulated by resampling an already observed sample from that population. Resampling procedures enable us to estimate not only the parameters but also their distributions. Since these procedures are applicable to various estimations and require few assumptions, they are especially effective when the distribution of parameters is unknown. Because of its simplicity, the bootstrap method has been applied in several fields.\(^{13–15}\) The basic algorithm of the bootstrap method with \(B\) resampling is as follows:

1. **Step-1.** Construct a data distribution from an observed sample.
2. **Step-2.** Generate a bootstrap sample from the data distribution constructed in Step-1. Here, the size of the bootstrap sample is the same as that of the observed sample.
3. **Step-3.** Calculate the parameters from the bootstrap sample.
4. **Step-4.** Repeat Step-2 and Step-3 \(B\) times.
5. **Step-5.** Construct the bootstrap distributions of the parameters by sorting.

The bootstrap distribution itself is directly utilized, or other parameters such as the variance are estimated from the distribution. To correctly simulate sampling from the population using the bootstrap method, the randomness involved in resampling the bootstrap samples from the observed sample is an important factor. Therefore, in the above algorithm, the construction of the data distribution from the observed sample in Step-1 is an important process. For the construction, a number of procedures are suggested, such as parametric and nonparametric bootstrap methods.

In the parametric bootstrap method, the data distribution is assumed to be a well-known distribution, such as a normal distribution, and then random numbers are generated based on the distribution. In the nonparametric bootstrap method, the distribution is constructed by assigning the same probability to each data point in the observed sample, and thus no assumptions about the data distribution are required. This procedure is the same as “sampling with replacement”; that is, a datum is resampled from the observed sample and then it is replaced. Although the smoothed bootstrap method has characteristics similar to the parametric method, it is included in the nonparametric methods. For example, instead of assuming a well-known distribution, the data distribution is provided based on the observed sample as in the nonparametric method, but the resampled data sets consist of random numbers based on the data distribution, as in the parametric method.

The parametric bootstrap method is a powerful procedure if the assumed data distribution is appropriate, but the estimation of a distribution or parameter becomes impaired if the assumptions are inappropriate. In contrast, since the nonparametric bootstrap method involves no assumed data distribution, it is widely applicable and is used more frequently. However, if the size of an observed sample is extremely small, the bootstrap sample tends to be biased due to resampling with replacement from the small data set, and thus the estimations from the bootstrap distribution are inadequate. In the smoothed bootstrap method, to avoid limiting the data distribution and the parameters, the data distribution function from which the bootstrap samples are taken is constructed by interpolating data points of the observed sample without any assumptions. The constructed distribution function enables a bootstrap sample to include points other than the data points of the observed sample, and therefore, the probability of generating an extremely biased bootstrap sample is lowered.

In this study, the nonparametric and smoothed bootstrap methods were applied to the statistical evaluation of the decrease of rCBF in a SPECT image. The parametric bootstrap method would only enable a similar evaluation to those by known statistical image analyses, such as the Z-score, even if the assumed data distribution were appropriate. Therefore, in this study, the parametric bootstrap method was not used. The nonparametric (case-resampling) bootstrap method was selected because of its simplicity, and the smoothed bootstrap method was also selected because the sample size is often too small to carry out the nonparametric bootstrap method after the segmentation of a control data set.

**Algorithm** In the proposed procedure, a standardized distribution of a statistical index, the Z-score, is constructed from a control data set by using two variations of the bootstrap method. The \(p\)-value of the statistics is calculated based on the constructed bootstrap distribution. The algorithm for the proposed procedure is described in the following. We used a SPECT image in a cross-sectional view vertical to the z-axis consisting of \(m_1 \times m_2\) pixels. The pixel values at coordinates \((k,l)\) in the control and patient data set are \(q_{ikl}\) and \(r_{ikl}\), respectively. The sample size of the control data set is \(n\) and the significance level is \(\alpha\).

The proposed procedure is presented below and shown in Fig. 1:

1. **Step-1.** Generate a bootstrap sample \(q_{i_kl}^* (i=1, \cdots, n)\) and \(r_{i_kl}^*\) from the control data set \(q_{ikl} (i = 1, \cdots, n)\) at coordinates \((k,l)\).
2. **Step-2.** Calculate a Z-score of the bootstrap sample, \(z_{ikl}^*=(mq_{ikl}^*−r_{ikl}^*)/σ_{q_{ikl}}^*\), where \(mq_{ikl}^*\) and \(σ_{q_{ikl}}^*\) are the average and standard deviation of a bootstrap sample, respectively.
3. **Step-3.** Repeat Step-1 and Step-2 \(B\) times, \(z_{ikl}^* (j=1, \cdots, B)\)
Step-4. Construct a bootstrap null distribution of the Z-score at the coordinates \((k, l)\) by sorting the Z-scores, \(z_{kl}^* (j=1, \cdots, B)\), calculated in Step-3.

Step-5. Calculate the \(p\)-value, \(p_{kl}\), of the Z-score, \(z_{kl}\), of the patient data at coordinates \((k, l)\), \(r_{kl}\), based on the bootstrap distribution.

Step-6. If \(p_{kl} < \alpha/2\), the decrease of rCBF at coordinates \((k, l)\) in the patient is significant.

Step-7. Repeat Step-1 through Step-6 for all coordinates, \(p_{kl} (k=1, \cdots, m, \ l=1, \cdots, M)\).

The process of resampling a data set is included in Step-1 of the proposed procedure. The processes of the nonparametric and smoothed bootstrap methods are described in the following. Hereinafter, the sample size of a data set is \(n\), and the data set consists of \(x_i (i=1, \cdots, n)\).

The process of resampling a data set by using the nonparametric bootstrap method in Step-1 of the proposed procedure is presented below and shown in Fig. 2.

Step-1-1. Sort a data set, \(x_i (i=1, \cdots, n)\), in ascending order.

Step-1-2. Interpolate the data set using a step function.

Step-1-3. Generate a bootstrap sample.

Step-1-4. Construct a step function as the inverse function of the cumulative distribution function based on the plotted points.

Step-1-5. Generate a bootstrap sample.

Step-1-6. Repeat Step-1-5 \(n\) times to obtain a bootstrap sample, \(x_i^* (i=1, \cdots, n)\).

A simple smoothed bootstrap method was proposed by Hutson in 2002, and it was used with a slight modification in this study. The process of resampling a data set by using the
smoothed bootstrap method in Step-1 of the proposed procedure is presented below and shown in Fig. 3.

Step-1-1. Sort a data set, $x_i$ (i=1, ⋯, n), in ascending order.

Step-1-2. Assign the data set, $x_i$ (i=1, ⋯, n), to cumulative probabilities, $1/(n+1), \ldots, n/(n+1), \ (i)/(n+1)$, $x_i$ (i=1, ⋯, n).

Step-1-3. Plot $(i/(n+1), x_i)$ (i=1, ⋯, n) on a graph in which the horizontal axis indicates the cumulative probability and the vertical axis indicates $x$.

Step-1-4. Construct an inverse function of the cumulative distribution function by interpolating the plotted points with a linear function. Both ends between $0$ and $1/(n+1)$ and between $n/(n+1)$ and 1 are constructed by the extrapolations of nonlinear functions.

Step-1-5. Generate a random number, $\xi$, satisfying $0 \leq \xi < 1$ by using a uniform random number generator, and then calculate a value of the bootstrap sample, $x^*_i$, by applying $\xi$ to the function constructed in Step-1-4.

Step-1-6. Repeat Step-1-5 n times to obtain a bootstrap sample, $x^*_i$ (i=1, ⋯, n).

In Hutson's method, if $x$ is always positive, the functions for extrapolations are the following:

$$Q_{\text{hl}}(\phi) = \phi x_i, \quad 0 < \phi \leq 1/(n+1)$$

$$Q_{\text{hl}}(\phi) = x_i - (x_i - x_{i-1}) \log \left\{ (n+1) \times (1 - \phi) \right\}, \quad n/(n+1) \leq \phi < 1$$

where $x_i$ (i=1, ⋯, n) are in ascending order, and $\xi = (n+1)\phi$. In Eqs. 1 and 2, if $\xi \to 0$ then $Q_{\text{hl}}(\xi) \to 0$, and if $\xi \to 1$ then $Q_{\text{hl}}(\xi) \to +\infty$. In the proposed procedure, $Q_{\text{hl}}(\xi)$ of Eq. 2 is used when $n/(n+1) \leq \xi < 1$, and a concave function is used instead of the linear function of Eq. 1 when $0 < \xi \leq 1/(n+1)$. The function for extrapolations in $0 < \xi \leq 1/(n+1)$ is the following:

$$Q_{\text{lt}}(\phi) = b/a, \quad 0 < \phi \leq 1/(n+1)$$

where $(a, b)$ are parameters. If we let $Q_{\text{lt}}(\xi)$ be a monotonically increasing function that passes through the two points (0, 0) and $(x_1, 1/(n+1))$, then $Q_{\text{lt}}(\xi)$ and the first derivative of $Q_{\text{lt}}(\xi)$, $Q_{\text{lt}}'(\xi)$, must be positive. Therefore, $a/b > 0$ and $b > 0$, that is $a, b > 0$. Additionally, $(a, b)$ are calculated along with the following conditions if $Q_{\text{lt}}(\xi)$ is continuous at $1/(n+1)$,

$$Q_{\text{lt}}(1/(n+1)) = b/a \times 1/(n+1)^a = x_i \quad (4)$$

$$Q_{\text{lt}}(1/(n+1))' = b \times 1/(n+1)^{a-1}$$

The two Eqs. 4 and 5 are solved for $a$ and $b$,

$$a = 1 - (x_2 - x_1) \times 2/(n+1 - 1/(n+1)) \times 1/(n+1)/x_1 \quad (6)$$

$$b = (x_2 - x_1) \times 2/(n+1 - 1/(n+1)) \times 1/(n+1)/x_1 \quad (7)$$

However, as shown in Fig. 4, if $a > 1$, $Q_{\text{lt}}(\xi)$ is a convex function, and in that case, a linear function, Eq. 1, is used as $Q_{\text{lt}}(\xi)$ instead.

Data Set

The reconstructed three-dimensional SPECT images were obtained from a public data set in eZIS. The original images that SPM used were stored in a left-handed coordinate system, which means the $X$-axis increases from right to left, the $Y$-axis increases from front to back, and the $Z$-axis increases from bottom to top. All images were spatially normalized to the Talairach atlas, and each coordinate indicated the same location through all images. After spatial normalization, the images were stored in a right-handed coordinate system, which means the $X$-axis increases from left to right, the $Y$-axis increases from back to front, and the $Z$-axis increases from bottom to top. The right-handed coordinate system is consistent with the Talairach atlas. The origin (0, 0, 0) was placed at the center of gravity of a brain, and coordinates were placed every 2 mm from −78 mm to 78 mm on the $X$-axis, from −112 mm to 76 mm on the $Y$-axis, and from −50 mm to 84 mm on the $Z$-axis. A slice of the $XY$ plane at every point on the $Z$-axis consisted of 7505 (=79×95) pixels. In this study, the image slices at Z=0 in each three-dimensional SPECT image were used. There were 4413 pixels as the evaluated coordinates in the image slice at Z=0.

Based on the explanation for the sample data set in eZIS, the control data set was images from subjects who satisfied the following conditions.

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Fig. 4. Overview of the $Q_{\text{lt}}$ Function
1. In the Mini Mental State Examination (MMSE) and the Hasegawa’s Dementia Scale Revision (HDS-R), their results were normal.
2. In the Wechsler Memory Scale-Revised (WMSR) and the Wechsler Adult Intelligence Scale-Revised (WAIS-R), their results were normal.
3. High signal intensities consistent with age were observed only in T2-weighted images in their white matter.
4. They have no risk factors for cerebrovascular accidents, such as hypertension or diabetes.

The patient data set consisted of images from a subject who was diagnosed as having Alzheimer’s disease.

Applicaiton The proposed procedure with the nonparametric or smoothed bootstrap methods was applied to the above control data set which consisted of 95 images and the patient data set. Those results were compared with the evaluations based on ZFT when the sample size of the data set was large enough; that is, the assumed data distribution for the Z-score was appropriate. To compare the evaluations using the proposed procedure and those using ZFT with respect to the decrease of rCBF in an image taken from a subject who had no neurodegenerative disease, each control image was evaluated as having a significant decrease by ZFT, by the proposed procedure, and by both ZFT and the proposed procedure; and max(a, b) is the maximum of the values in the parentheses. The ARs were 0.943 and 0.936 in the proposed procedure with the nonparametric and smoothed bootstrap method, respectively.

Table 1 shows the results where the decreases of rCBF were evaluated as decreases, according to the proposed procedure and with \( \alpha = 0.05 \). The shaded areas in the three images of Fig. 5 were almost the same. In fact, the number of coordinates included in the shaded areas was 576, 564, and 559 in Figs. 5a–c, respectively. The agreement rate of the coordinates included in the shaded areas was calculated by Eq. 8,

\[
AR = \frac{N_{sc\text{Ag}}}{\max(N_{sc\text{ZFT}}, N_{sc\text{PP}})}
\]

where \( AR \) is the agreement rate; \( N_{sc\text{ZFT}}, N_{sc\text{PP}}, \) and \( N_{sc\text{Ag}} \) are respectively the number of coordinates in which the rCBF was evaluated as having a significant decrease by ZFT, by the proposed procedure, and by both ZFT and the proposed procedure; and \( \max(a, b) \) is the maximum of the values in the parentheses. The ARs were 0.943 and 0.936 in the proposed procedure with the nonparametric and smoothed bootstrap method, respectively.

Figure 6 shows the scatter plot of the agreement rates (ARs) in the proposed procedure with the smoothed bootstrap method against the number of coordinates evaluated as a decrease of rCBF by ZFT \((N_{sc\text{ZFT}})\) in control images. When both \( N_{sc\text{ZFT}} \) and \( N_{sc\text{PP}} \) were 0 in Eq. 8, the \( AR \) was set to 0. The scatter plot of the \( AR \) in the proposed procedure with the nonparametric bootstrap method is not shown because it is almost the same as Fig. 6. As \( N_{sc\text{ZFT}} \) increased, \( AR \) was higher and came close to 1.0 in Fig. 6. Since ZFT and the proposed procedure are the statistical evaluations with a significance level,
there is a possibility that some false positives, also called Type I errors, are included in the evaluations by each procedure. When evaluating the image in which it was unclear if rCBF had decreased, both the $N_{sc_{ZFT}}$ and $N_{sc_{PP}}$ were low and probably tended to be influenced by false positives. To confirm the equivalence between ZFT and the proposed procedure while avoiding the influence from false positives, in the control image that had the largest $N_{sc_{ZFT}}$, the evaluation by the proposed procedure was compared with that of ZFT.

Figure 7 shows the evaluation of rCBF for the control image that had the largest shaded area in the evaluations based on ZFT. Figure 7 is the same as Fig. 5 except for the evaluation being of the image of the control instead of that of the patient. The number of coordinates included in the shaded pattern areas was 1019, 999, and 1001 in Figs. 7a–c, respectively. As in Fig. 5, the evaluations of significant decrease in the control’s rCBF using the proposed procedure was almost the same as those of ZFT.

Figure 8 shows the averages (“$Tr$” in Fig. 8) of the number of coordinates in which decreases of rCBF were judged as being significant at the small sample simulations using ZFT and the proposed procedure with the nonparametric or smoothed bootstrap methods (“NB” and “SB” in Fig. 8). Figure 8a shows the results of the simulations in the evaluation of the patient’s data. In the simulations with a sufficiently large sample size ($n_s=30, 40$), the results of the patient’s rCBF were similar for the three procedures. However, in the results using ZFT and a small sample size ($n_s=5, 10$), there were too many coordinates in which the patient’s Z-scores were greater than 2.0 compared to the results of the simulations with a sufficiently large sample size. On the other hand, the results using the proposed procedure and the small sample size were slightly decreased in comparison with that of the simulations with the sufficiently large sample size. The results of the evaluations for the control data set are shown in Fig. 8b. As with the simulation results with the patient data, the coordinates in which the decrease of rCBF was judged to be significant were
increased in the case of ZFT, but scarcely varied in the proposed procedure at the small sample size (n=5, 10).

DISCUSSION

When the Z-score is less than 2.0, the patient’s rCBF lies within a 95.5% confidence interval of rCBF in the control data set. Since the shaded area in Fig. 5a indicates that the Z-score in the area was greater than 2.0, the decrease of the patient’s rCBF in the area was significant at the level of α=0.05. The shaded area in Figs. 5b and c show that the decrease of the patient’s rCBF was significant at the level of α=0.05 in the proposed procedure with the nonparametric and smoothed bootstrap methods. Accordingly, the shaded areas in all images in Figs. 5 indicate the nearly equal evaluations for the decrease of rCBF. Since the shaded areas in the three images were almost the same size, the evaluations of a significant decrease in the patient’s rCBF using the proposed procedures with both bootstrap methods should be approximately equivalent to those of ZFT.

Furthermore, each control image was regarded as a patient image and evaluated by using both ZFT and the proposed procedure. The AR was then calculated for each image. Figure 6 shows the scatter plot of the ARs against the NscZFT in the control images. Some ARs were low when the NscZFT was low. When evaluating the image in which it was unclear if rCBF had decreased, both the NscZFT and Nscpp would tend to be influenced by false positives. Thus the evaluation by the proposed procedure might have been different from that of ZFT when the NscZFT was low. On the other hand, when the NscZFT was high the ARs came close to 1.0. If the proposed procedure is not equivalent to ZFT, the AR should never come close to 1.0 even when the NscZFT is high. Therefore, the results displayed in Fig. 6 indicate that ZFT and the proposed procedure are equivalent.

Figure 7 shows the evaluations of rCBF in the control image where the shaded area was largest in the control data set. The shaded areas of each image in Fig. 7 were almost the same. Therefore, the proposed procedure with either bootstrap method is nearly equivalent with the evaluations based on ZFT, even if the control image was evaluated as a patient image.

Figure 8 shows the results of the simulations for evaluating the behaviors of ZFT and the proposed procedure in a small control data set. In the results of ZFT at n = 5 and 10, the number of coordinates in which rCBF decreased significantly was compared with the results in the original control data set (n=95). When the sample size of the control data set was sufficiently large, the Z-score followed a standard normal distribution, and the threshold for statistical judgment worked adequately. But when the sample size was very small, the Z-score was not expected to follow a standard normal distribution, and the decrease of rCBF was evaluated as excessive. On the other hand, the results of the proposed procedure with either bootstrap method were comparatively stable even if the sample size of a control data set was small. In the proposed procedure, since the Z-score was evaluated based on the bootstrap distribution of the Z-score in a control data set, the decrease of rCBF was evaluated adequately compared with using a fixed threshold regardless of the sample size of the control data set. There were few differences between the above results of the proposed procedures with the two bootstrap methods, but some bootstrap samples in a small control data set consisted of only one observation, and the Z-scores were not calculated from such bootstrap samples because a nonparametric bootstrap resample comes from sampling with replacement from the original data set. Therefore, when the sample size of a control data set is too small, the smoothed bootstrap method, in which the same value is not resampled, is often more suitable for the proposed procedure than is the nonparametric bootstrap method.

CONCLUSION

In this paper, we proposed a procedure for statistically evaluating the decrease of rCBF in brain SPECT images using bootstrap methods without any assumed data distribution. By using a sample data set whose size is large enough for the assumption of the Z-score to be appropriate, the evaluations of the proposed procedure with two bootstrap methods were compared with that of ZFT. As a result, the evaluations of the proposed procedure were equivalent to that of the evaluation based on ZFT. Furthermore, to evaluate the effects of a sample size for the judgment of ZFT and the proposed procedure, simulations in which the subsamples from the original data set were regarded as the control data set were carried out. Consequently, when the sample size of the control data set was small, the decrease of rCBF tended to be overestimated in the evaluations based on ZFT. On the other hand, in the evaluations using the proposed procedure, such a tendency was not seen even if the sample size of the control data set was 5. Thus, when a small control data set is used for the evaluation of a decrease in rCBF, the proposed procedure with a bootstrap method will be more suitable than ZFT.

REFERENCES


