Image subtraction and quantification in rest and acetazolamide stress brain SPECT using anatomic standardization for a one-day imaging protocol

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Image subtraction and quantification in rest and acetazolamide stress brain SPECT using anatomic standardization for a one-day imaging protocol

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ABSTRACT

The aim of this study was to develop and evaluate the method of image subtraction procedure and automated quantification of the subtracted images acquired consecutive injection of ^{99m}Tc-ethyl cysteinate dimer or ^{99m}Tc-hexamethyl propyleneamine oxime in rest and acetazolamide stress brain SPECT. Eleven patients with cerebrovascular disorders (6 female, 5 male ; mean age 58.2±19.5 yr) were studied. The first and the second SPECT images were standardized anatomically using statistical parametric mapping algorithm. The first SPECT images were corrected with decay factor, washout rate, and normalize factor. After these corrections, corrected first SPECT images were subtracted from the second SPECT corrected with acquisition time. Automated quantification was applied to the rest images and the subtracted images with standardized mask image for calculation of mean counts using Lassen's linearization algorithm. Subtraction procedure produced the images of only stress condition without significant high count area due to standardization error. Absolute regional CBF values using our automated procedure were comparable with those using the conventional manual procedure. This method combined the image subtraction and the automatic quantification of rCBF may be useful for evaluation of vascular reserve in patients with cerebrovascular disorders.

KEY WORDS

Cerebral blood flow, Acetazolamide, Vascular reserve, Image processing, Anatomic standardization

INTRODUCTION

For evaluation of vascular reserve in patients with cerebrovascular diseases, regional cerebral blood flow (rCBF) single photon emission computed tomography (SPECT) with acetazolamide stress has been performed. Because of little redistribution of ^{99m}Tc-labeled CBF agents in the brain[1, 2], the baseline (rest) study and the stress study with acetazolamide administration (the second SPECT) can be performed in the same day. Advantage of this method is that change of patient condition may be little, but disadvantage is that the second SPECT contains both the activity of the baseline and that of the stress. An appropriate subtraction procedure should be performed to obtain the image of only stress condition. Anatomic standardization algorithm such as statistical parametric mapping (SPM)[3] and three dimentional stereotactic surface projection (3D-SSP)[4] make it possible with correcting a position difference between two image sets of SPECT.

For interpretation of images in this study, the calculation of absolute CBF values are necessary. We

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preveously reported the method for quantification of rCBF with ^{99m}Tc-labeled tracer[5, 6], and this method has been widely accepted.

The aim of this study was to evaluate the method of image subtraction procedure and automated quantification of the subtracted images acquired consecutive injection of ^{99m}Tc-ethyl cysteinate dimer (^{99m}Tc-ECD) or ^{99m} Tc-hexamethyl propyleneamine oxime (^{99m}Tc-HMPAO) in rest and acetazolamide stress brain SPECT.

METHODS

1. Subjects :

Eleven patients with cerebrovascular disorder included five men and six women, aged 18-75 years (58.2 y ± 19.5 y, mean ± s.d.) were examined. The informations of these patients were listed in table 1.

2. Data acquisition :

Radionuclide angiography (RNA) was performed for calculation of mean cerebral blood flow value using a gamma camera of large field of view (Toshiba e-cam) by employing low energy high resolution parallel hole collimator, and SPECT was carried out after RNA using a three-head rotating gamma camera system (Toshiba GCA9300A/HG) with low energy high resolution fan beam collimators.

One-day protocol of rCBF SPECT study before and after acetazolamide administration is as follows. The first RNA was performed with intravenous bolus injection of 555 MBq of ^{99m}Tc-ECD or ^{99m}Tc-HMPAO into the right brachial vein, followed by the first SPECT. Data acquisition and analysis were performed using the same method described in the previous study[5]. While the acquisition of the first SPECT, 1g of acetazolamide (DIAMOX®) was administered intravenously. The second RNA was performed in the same manner as the first RNA except for backgound data acquisition before the second intravenous bolus injection of 740 MBq of ^{99m} Tc-ECD or ^{99m} Tc-HMPAO, followed by the second SPECT.

3. Data processing :

For exluding the effects of activity of the rest condition to the second SPECT, subtraction procedure was performed as follows. The program for data processing was coded using C++ Builder (Borland). This program consists of following four steps, 1) conversion of file format, 2) anatomical standardization, 3) subtraction, 4) correction of linearity between the pixel counts and the absolute CBF values.

1) Conversion of file from GMS format to SPM Analyze format : Toshiba GMS format has only one file containing image information header and image pixel data. Information of header size is described byte 4 and 5 from top of the file in fixed length header area (64 bytes) as 2-byte integer. Header size is usually 2 or 3 Kbytes (2048 or 3072 bytes). From byte 64, variable length header area started. In this area, image informations are described using ACR

Table 1. Findings in eleven patients with cerebrovascular disorders.

No.	Age	Sex	Diagnosis	tracer	mean CBF	
					rest	stress
1	67	F	right ICA occlusion	HMPAO	41.3	55.4
2	75	M	left ICA stenosis	ECD	34.3	45.2
3	73	M	right ICA stenosis	ECD	36.1	35.4
4	71	M	left ICA stenosis.	HMPAO	30.7	34.9
5	65	M	left ICA stenosis	HMPAO	36.2	46.1
6	62	F	bilateral ICA stenosis	ECD	46.3	52.2
7	60	F	TIA.	HMPAO	41.4	43.2
8	18	F	Moyamoya disease	ECD	43.9	69.5
9	22	F	Aortitis syndrome	ECD	50.6	35.9
10	60	F	left ICA occlusion	ECD	38.6	56.9
11	67	M	right ICA occlusion	HMPAO	37.9	34.0

ICA, intracarotid artery ; TIA, transient ischemic attack.

NEMA code. Necessary informations for data conversion are these items : image orientation (NEMA code group ID, element ID = 0x0020, 0x0020), matrix size (x : 0x0028, 0x0011 ; y : 0x0028, 0x0010), bit depth of each pixel (0x0028, 0x0100), pixel size (0x0028, 0x0030), slice number (=matrix size of z ; 0x6b01, 0x1001), slice thickness (=pixel size of z ; 0x6b01, 0x1016). These parameters are copyed and output as header file of Analyze format.

2) Anatomical standardization : The brain images of all cases were tranformed to standardized template image using algorithm of SPM99.

3) Subtracton to obtain the CBF image only stress condition : When subtraction was performed, following four parameters were considered, a) acquisition time, b) decay correction, c) washout of the tracer, d) normalizing factors of integer data files.

a) Acquisition time : Each scan mode is continuous, 5 minutes per each rotation with 4 or 5 rotations. If number of rotations is different, it should be corrected. Information of acquisition time can be read from GMS header with NEMA code (0x0018, 0x1242).

b) Decay correction : Difference of acquisition start time between the baseline and the stress studies was to be considered. At the time of the stress image acquisition, the activity of the rest fraction of the brain is reduced according to physical half life. When subtraction, this reduction of the rest fraction should be considered. Information of acquisition start time is written in GMS header with NEMA code (0x0008, 0x0030).

c) Washout of the tracer : In the case of ^{99m}Tc-HMPAO, washout of the tracer can be ignored, so that it was assumed to be zero. On the other hand, in the case of ^{99m}Tc-ECD, we use the value of 20%/h that is similar reported by Friberg et al[2]. This correction also needs information of acquisition start time of each scan.

d) Normalizing factor : GMS image file has three types of bit depth, 1) 8 bit unsigned integer, 2) 16 bit singed integer, 3) 32 bit float. In the clinical setting, latter two formats are usually used. When 16 bits singed integer format is selected, GMS system performes 9 bit normalize procedure to the image, which converts as max value of the image to 9 bits integer (value range from 256 to 511). And normalize factor are recorded as following equation (normalizing factor b is actually zero).

$$\text{normalized count} = \text{normalizing factor a} \times \text{actual count} + \text{normalizing factor b} \quad (1)$$

In order that actual count is calculated, pixel counts recorded in the image file should be devided by normalizing factor a. Information of normalizing factor a can also be read from GMS header with NEMA code (0x0028, 0x1053).

4) Correction of linearity between the pixel counts to the absolute CBF values using Lassen's correction equation :

For linear correction between SPECT counts and rCBF values, following Lassen's correction equation[1] were used :

$$F_i = F_r \cdot \frac{\alpha \cdot (C_i/C_r)}{[1+\alpha-(C_i/C_r)]} \quad (2)$$

where F_i and F_r represent CBF values for a region i and a reference region respectively, and C_i and C_r are the SPECT counts for the region i and the reference region, respectively. The cerebral hemisphere was used as the reference region. Mean CBF value calculated using graphical analysis[6] was applied to F_r. Mask images for excluding extracere-bral regions were made on MRI T1 template images and applied to Cr. Intracerebral structures such as lateral ventricles were not excluded.

α is a correction factor for the linearization. In case of ^{99m}Tc-HMPAO, the optimal value of α estimated from the following equations :

$$\alpha = \frac{k_3}{k_{2r}} \quad (3)$$

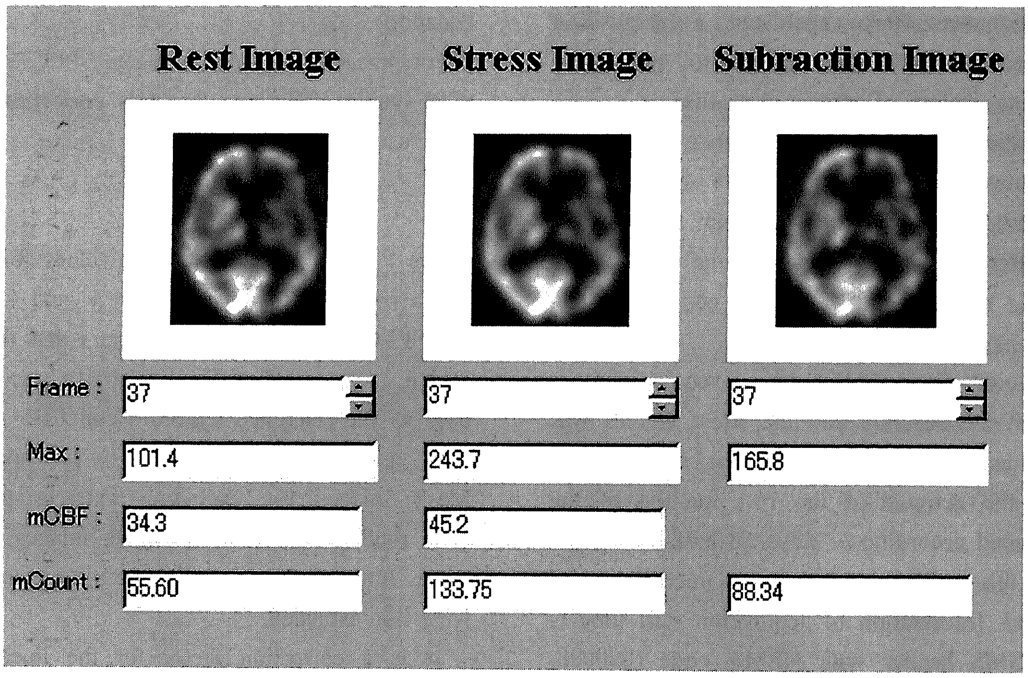
$$k_{2r} = \frac{K_{1r}}{\lambda} = \frac{E \cdot F_r}{\lambda} \quad (4)$$

Where k_3 is the conversion rate constant from lipophilic to hydrophilic tracer in the brain, k_{2r} is the rate constant of the back-diffusion from a reference region in the brain to the blood, K_{1r} is the clearance from the blood to a reference region in the brain, λ is the brain-blood partition coefficient of the lipophilic tracer and E describes the first-pass extraction of the lipophilic tracer across the blood-brain barrier. In case of ^{99m}Tc-ECD, fixed value of 2.59[2]

Table 2. Calculated values of α ratios, transfer constants, brain-to-blood partition coefficient (λ) and extraction for ^{99m}Tc-ECD and ^{99m}Tc-HMPAO.

	tracer	
	^{99m}Tc-ECD	^{99m}Tc-HMPAO
α	2.59	variable*6)
k3 (min^{-1})	0.57	0.80
λ (ml/g)	1.33	0.67
E	0.60	$-0.29F+0.90$8)

F, flow value of the reference region (mℓ/g/min)
*, α ratio was calculated from equation 3 and 4.



	Rest Image	Stress Image	Subraction Image
Frame :	37	37	37
Max :	101.4	243.7	165.8
mCBF :	34.3	45.2	
mCount :	55.60	133.75	88.34

Fig. 1. The processed images in a case of the left intracarotid artery stenosis at the level of the striatum. Low perfused area was demonstrated in the left frontotemporal region in the rest image, but no significant change of rCBF distribution in the subtraction image.

was used which also derived from equation 3 and 4. The parameters for calculation of α values of both tracers are listed in table 2[1,2].

The subtraction images were evaluated visually from the point of the artifacts such as high-count area generated from the deviation between two images due to standardization error. Comparison of rCBF values was performed between automated calculation with mask image and conventional manual setting of region of interest (ROI) for mean count value. The values of rCBF were calculated using three dimentional stereotaxic ROI template (3D-SRT)[7].

RESULTS

The subtraction images of 10 patients out of eleven demonstrate no significant high count area due to standardization error or other artifacts with visual evaluation. The vascular reserve of the lesion can be

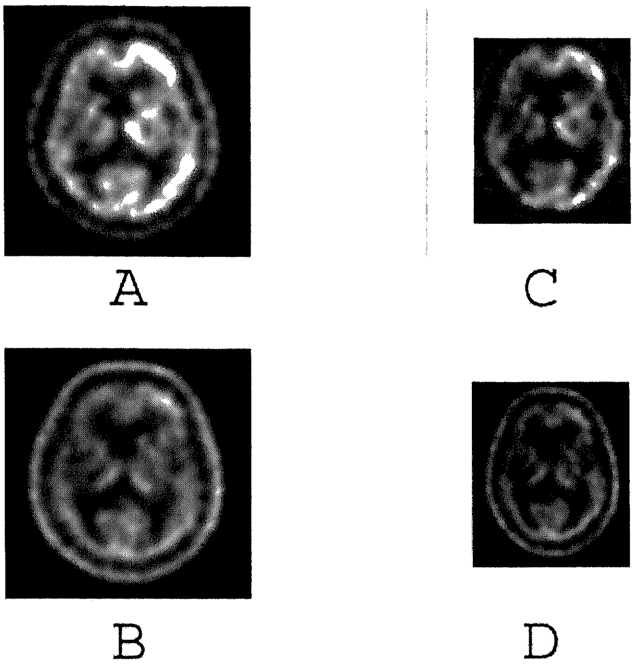


Fig. 2. A case in which anatomic standardization was failed. A, The rest image of before standardization ; B, The second image of before standardization ; C, The rest image of after standardization ; D, The second image of after standardization. Because of high activity of the scalp in image B, standardization algorithm mistook the scalp for the brain. Standardized image (D) was reduced in size and mispositioned.

Table 3. Comparison of rCBF values calculated with manual procedure and with autocalculation.

	CBF values (ml/100g/min)				%difference	
	manual procedure		autocalculation			
	right	left	right	left	right	left
Anterior	51.14	51.80	52.52	53.03	2.63	2.32
PreCentral	49.24	51.34	50.29	51.47	2.09	0.25
Central	46.60	44.33	46.53	44.67	0.15	0.76
Parietal	38.83	38.31	38.48	37.65	0.91	1.75
Angular	49.62	50.65	48.91	50.29	1.45	0.72
Temporal	48.57	47.94	48.56	48.66	0.02	1.48
Occipital	41.42	41.88	41.38	42.17	0.10	0.69
PeriCallosal	44.27	45.97	45.89	48.95	3.53	6.09
LenticularNuc	45.85	46.16	47.43	47.37	3.33	2.55
Thalamus	41.64	40.74	43.74	42.94	4.80	5.12
Hippocampus	32.00	33.21	33.19	34.86	3.59	4.73
Cerebellum	52.83	49.30	54.20	49.52	2.53	0.44
Average	45.17	45.14	45.93	45.97	2.09	2.24

more easily evaluated by comparing the rest image and the subtracted image than by comparing the rest image and the second SPECT image. Figure 1 showed the processed images in a case of the left intracarotid artery stenosis at the level of the striatum (case 2). Low perfused area was demonstrated in the left frontotemporal region in the rest image, but no significant change of rCBF distribution in the subtraction image. This case was indicated that the perfusion reserve was preserved.

In only one case out of eleven, anatomic standardization was failed of the second SPECT image, so subtraction procedure was not able to perform (case 11). Figure 2 demonstrated mispositioned standardization of the image. SPM algorithm recognized the scalp of the image as the brain because its activity was very high.

Absolute rCBF values in a case calculated using 3D-SRT showed in Table 3 (case 7). The rCBF values of absolute image made with our automated procedure were comparable to that with the conventional manual ROI setting. The difference of rCBF was 0.98±0.79mℓ/100 g/min absolutely, and 2.17% ±1.77% relatively (mean±s.d.).

DISCUSSION

There are two protocols of stress study of CBF SPECT. An advantage of two-day protocol is to obtain absolute rCBF values of rest and stress conditions separately, but a disadvantage of this method is that patient condition may change. On the other hand, one-day protocol has an advantage that patient condition change may be little. Although the method has a disadvantage that the second SPECT image contains both activity of the rest and the stress conditions, if an appropriate image subtraction were performed, calculated rCBF values are more suitable for evaluation of vascular reserve of the patients. The positioning error of patient head between the first and the second SPECT has been prevened such subtraction procedure. Anatomic standardization makes it possible by means of correcting a position difference between two image sets of SPECT. We used the algorithm of SPM99[3] for anatomic standardization. Whereas 3D-SSP[4] can be also selected for this purpose.

Only one case out of eleven showed standardized error because of its high activity of the scalp. SPM algorithm recognized the high active scalp as the brain, so whole brain size was reduced and mispositioning occurred. This was not subtraction error. High activity of other extra-cerebral activity may also cause standardization error.

When subtraction, the washout of the tracer should be considered. Andersen et al. reported that count rate loss from compartment Ⅲ (hydrophilic fraction in the brain) found to be <0.4%/h, so this parameter can be ignored[8]. On the other hand, if the tracer is ^{99m}Tc-ECD, Friberg et al[2]. found the k_5 (rate constant from hydrophilic fraction in the brain to the blood) value is 0.0038/min, which is two times of the radioactive decay rate of ^{99m}Tc.

For linear correction between SPECT counts and rCBF values, Lassen's correction algorithm 1) were used. For this correction, CBF value of a reference region (C_r in equation 2) is necessary. We preveously reported the method that mean CBF value calculated using graphical analysis[9,10] applied to the CBF value of a reference region[6]. For calculating mean CBF value of the stress condition using the second RNA, background subraction procedure is needed. Reproducibility of this subtraction procedure was good and offered reliable mean CBF even with significant amount of background activity[11].

The parameters of equation 3 and 4 for α value calculation of Lassen's correction equation are listed in the table1[1,2]. This value is influenced by CBF. But, in case of ^{99m}Tc-ECD, α value of 2.59 is so high that fixed value can be available. On the other hand, in case of ^{99m}Tc-HMPAO, α is relatively low so that it should be calculated from CBF of reference region.

We compared two methods of generating images of absolute rCBF values using Lassen's algorithm. The conventional method for mean count calculation needs manual ROI setting to an added image at the level of the striatum. This process produces an operation error. The method we developed in this study used a standardized mask image that covers whole cerebral region. This procedure makes it possible to calculate mean count automatically and produces no operation error.

CONCLUSION

We developed a method for image subtraction and producing absolute rCBF images. This procedure makes it easy to compare the rest condition and the stress conditions. It is also possible to minimize operation error when mean count values are calculated. It is considerd to be useful in the clinical setting.

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アセタゾラミド負荷脳血流一日法における解剖学的標準化を用いたSPECT画像減算および自動定量画像算出法の開発

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要 旨

本研究の目的は^{99m}Tc標識製剤を用いたアセタゾラミド負荷脳血流SPECT一日法において，画像減算と自動定量法を開発し評価することである。11例の脳血管障害患者（男性５名，女性６名；平均年齢±標準偏差 58.2歳±19.5歳）に対して脳血流SPECTを施行し，安静時および負荷後のSPECT像に解剖学的標準化を施した。安静時SPECTに減衰補正，洗い出し補正，normalizing factorの補正を施した上で，収集時間補正を施した負荷後SPECTから減算し，負荷時の血流のみを示すサブトラクション画像を作成した。次に標準化したマスク像を用いて平均カウント算出を自動化し，負荷前およびサブトラクション像の定量化をLassenの補正式を用いて行なった。得られたサブトラクション像が視覚的に評価可能か検討し，局所脳血流値においては信頼性を比較した。サブトラクション像は定性的な判断をするのに十分な画像表示ができ，核医学専用機による表示も可能であった。自動算出した血流値においても信頼性が高く，臨床での有用性が期待できる。