Parametric Cerebrovascular Reserve Images Using Acetazolamide ^{99m}Tc -HMPAO SPECT: A Feasibility Study of Quantitative Assessment

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Abstract

Purpose Basal/acetazolamide stress ^{99m}Tc -HMPAO single-photon emission computed tomography (SPECT) has been widely used for evaluation of hemodynamics; however, qualitative and subjective visual assessment of cerebrovascular reserve (CVR) has been performed in clinical settings. The aim of this study was to generate parametric CVR images and evaluate its feasibility of quantification.

Methods Basal/acetazolamide stress ^{99m}Tc -HMPAO SPECT data from 17 patients who underwent bypass surgery or percutaneous transluminal angioplasty were used. Spatial normalization was performed and parametric CVR images were generated using relative CVR (rCVR) of each voxel proportional to CVR of the whole brain. Binary parametric maps to show area of relatively reduced CVR were generated also using threshold of rCVR < 90 %. We calculated rCVR of internal carotid artery (ICA) using the parametric CVR images and probabilistic maps for ICA territory. Pre- and postprocedural parametric CVR images were obtained and quantitative rCVRs were compared. The rCVRs were evaluated according to visual grades for regional decreased CVR.

Results Postprocedural rCVR obtained from parametric CVR images increased significantly from preprocedural rCVR. The rCVR was significantly correlated with visual grades of reduced CVR for each side of ICA territories.

Conclusions We generated parametric CVR images for basal/acetazolamide stress ^{99m}Tc -HMPAO SPECT. As a quantitative measurement, rCVR obtained from the parametric image was feasibly assessed hemodynamic abnormalities with preserved anatomical information.

Keywords ^{99m}Tc -HMPAO SPECT · Cerebrovascular reserve · Parametric images · Cerebral ischemia

Introduction

The evaluation of hemodynamic abnormalities is important for management of patients with cerebral ischemia [1]. Imaging studies including perfusion single-photon emission computed tomography (SPECT), positron emission tomography (PET) and magnetic resonance imaging (MRI) have been used for assessment of hemodynamics [2]. Among them, basal/acetazolamide stress perfusion SPECT is widely used because it can evaluate cerebrovascular reserve (CVR) as well as cerebral perfusion, which is highly sensitive for detecting flow abnormalities [3]. Furthermore, CVR is strongly associated with a risk of stroke in patients with carotid artery stenosis [4–6].

Visual analysis of basal/acetazolamide stress SPECT has been performed for evaluation of hemodynamics in clinical settings; however, visual assessment of SPECT is qualitative, subjective and hardly reproducible [7]. For quantitative evaluation of CVR, semi-quantitative methods using manually drawn region of interest (ROI) or statistical probabilistic anatomical mapping (SPAM) have been reported [8–10]. However, ROI-based analysis is also subjective and operator dependent. Quantification of CVR using SPAM has provided reliable descriptive parameters for hemodynamic abnormality, although limited for assessment of anatomical extent and spatial information.

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The purpose of this study was to develop and assess a method for generation of parametric CVR images using basal/acetazolamide stress ^{99m}Tc -HMPAO (^{99m}Tc -hexamethylpropyleneamineoxime) SPECT. To validate the parametric CVR images, patients with cerebral ischemia including carotid artery stenosis and middle cerebral artery stenosis who underwent bypass surgery or percutaneous transluminal angioplasty (PTA) were enrolled retrospectively. We compared parametric CVR images obtained from pre- and postprocedural scans and also analyzed quantitative CVR. We evaluated correlation between quantitative CVR using the parametric images and visual assessment of hemodynamic abnormalities.

Materials and Methods

Subjects

From January 2011 to June 2012, 17 patients with carotid artery stenosis or middle cerebral artery stenosis were retrospectively selected. Among them, 11 patients underwent endovascular carotid angioplasty including stenting and balloon angioplasty. Six patients underwent superficial temporal artery-middle cerebral artery (STA-MCA) anastomosis (Table 1). This study was approved by the Institutional Review Board.

Basal/Acetazolamide Stress Perfusion SPECT

Basal and acetazolamide brain SPECT was performed before (median 27 days, range 1–190 days) and after (median 23 days, range 1–263 days) angioplasty or anastomosis. For basal study, SPECT was obtained 5 min after intravenous injection of 555 MBq of ^{99m}Tc -HMPAO with the patient resting using a dedicated triple-head gamma-camera (Prism 3000; Picker International). Ten minutes before the end of the basal SPECT, 20 mg/kg of acetazolamide was injected intravenously, and another 1,110 MBq of ^{99m}Tc -HMPAO was injected. A second SPECT was performed 5 min after the end of basal SPECT. Acetazolamide stress SPECT images were obtained by decay-corrected subtraction of the basal images from the second SPECT images. SPECT images were acquired using a low-energy high-resolution fanbeam collimator. Forty step-and-shoot images were obtained with intervals of 3° for 20 s per step. SPECT images were reconstructed using filtered back projection with a Butterworth filter on a 128×128 matrix.

Parametric Cerebrovascular Reserve Images

Parametric cerebrovascular reserve maps were generated after spatial preprocessing using statistical parametric mapping software package (SPM2; University College London, London, England). Spatial normalization of SPECT images was performed using a standard ^{99m}Tc HMPAO SPECT template. Affine transformations followed by nonlinear

Table 1 Clinical characteristics of patients

Patient no.	Sex	Age	Procedure	Lesion of stenosis	Outcome
1	F	55	STA-MCA anastomosis	R ICA	Symptom improved
2	M	73	Stenting	L ICA	Symptom improved
3	M	77	Balloon angioplasty	R ICA	Further stent insertion
4	M	60	Stenting	L ICA	Underlying infarct; symptom improved
5	M	50	STA-MCA anastomosis	L ICA	Underlying infarct; symptom improved
6	M	55	Stenting	R ICA	Underlying infarct; not improved
7	F	70	Balloon angioplasty	R ICA	Symptom improved
8	M	68	STA-MCA anastomosis	R ICA	Underlying infarct; symptom improved
9	M	63	Stenting (ECA)	R ICA, ECA	Not improved
10	M	81	Stenting	L ICA	Symptom improved
11	M	57	STA-MCA anastomosis	L ICA	Symptom improved
12	F	61	Stenting	R MCA	Symptom improved
13	M	74	Stenting (ECA)	L ICA, ECA	Symptom improved
14	F	60	STA-MCA anastomosis	L MCA	Symptom improved
15	M	70	Stenting	R ICA	Symptom improved
16	M	44	STA-MCA anastomosis	R ICA	Symptom improved
17	M	58	Stenting	R ICA	Symptom improved

ICA internal carotid artery, ECA external carotid artery

transformations were used for spatial normalization. Parametric CVR maps were calculated using relative CVR (rCVR):

$$\text{rCVR} = \frac{C_{\text{voxel,acetazolamide}}/C_{\text{voxel,basal}}}{C_{\text{whole brain,acetazolamide}}/C_{\text{whole brain,basal}}} \times 100$$

where $C_{\text{voxel,acetazolamide}}$ and $C_{\text{voxel,basal}}$ represent counts of each voxel on acetazolamide stress SPECT and basal SPECT images. $C_{\text{whole brain, acetazolamide}}$ and $C_{\text{whole brain, basal}}$ represent mean counts of whole brain on acetazolamide stress SPECT and basal SPECT images. Thus, on parametric CVR maps, each voxel represents the relative value of cerebrovascular reserve proportional to whole-brain cerebrovascular reserve. To obtain counts for the whole brain from spatially normalized SPECT images, a binary mask for the whole brain was applied and the outer scalp removed.

We also generated the cerebrovascular reserve threshold maps. Binary images for $\text{rCVR} < 90$ were obtained for each basal/acetazolamide stress SPECT image, which represent the voxels less than 90 % of mean whole brain CVR. As previous studies defined hemodynamic deficit as a 10 % reduction of asymmetric index in patients with carotid stenosis, we generated 90 % rCVR threshold maps to highlight hemodynamic abnormalities [11, 12].

Visual Analysis and Quantitative Evaluation Using Parametric CVR Images

Visual analysis of 34 basal/acetazolamide stress SPECT images from 17 patients, including pre- and postprocedural scans, were performed by two nuclear medicine physicians independently. Reduced regional CVR, defined as abnormal cerebral perfusion that lower in acetazolamide stress SPECT than basal SPECT, was assessed and visually graded. Regions of known cerebral infarct with cerebral perfusion defect were not assessed for visual grading. The visual grade of reduced CVR was classified into mild, moderate and severe grades (0, no reduced CVR; 1, mild; 2, moderate; 3, severe grade of reduced CVR). Severe grade was defined as definite perfusion decrease in acetazolamide stress SPECT compared with basal SPECT over more than two-thirds of the internal carotid artery (ICA) territory. Mild grade was defined as perfusion decrease in acetazolamide stress SPECT compared with basal SPECT with less than one-third of the ICA territory. Moderate grade was defined as decreased perfusion in acetazolamide stress SPECT definitely, not classified as mild or severe grades. Visual grading was performed on each side of hemispheres, considered ICA perfusion territories. The discordant cases were reevaluated to reach an agreement on visual grades between two readers and final concordant visual grades were included in the latter analysis.

Quantitative CVR was calculated using parametric CVR maps and statistical probabilistic maps of blood supply from ICA [13]. Mean rCVR of ICA was obtained using rCVR maps were calculated:

$$\text{Mean rCVR}_{\text{ICA}} = \frac{\sum_{i,j,k} \text{rCVR}_{i,j,k} \times P_{i,j,k}}{\sum_{i,j,k} P_{i,j,k}}$$

where $P_{i,j,k}$ is the probabilistic value of each voxel for ICA territory and $\text{rCVR}_{i,j,k}$ is the voxel-based rCVR values on the parametric maps.

The method for acquisition of parametric CVR images, threshold maps, and mean CVR_{ICA} calculation are summarized in Fig. 1.

Statistical Analyses

The interobserver concordance regarding visual grading was evaluated using kappa statistics. Wilcoxon signed rank tests were performed for comparison between pre- and postprocedural mean rCVR_{ICA} . We compared quantitative rCVR_{ICA} derived from parametric images according to visual grades using Kruskal-Wallis nonparametric test. Additionally, Mann-Whitney tests between different visual grades were performed. A p value < 0.05 was considered significant.

Results

Parametric CVR Images for Pre- and Postprocedural Basal/Acetazolamide Stress SPECT

Using preoperative parametric CVR maps, the area of relatively decreased CVR was identified and the CVR threshold map showed an asymmetric pattern of decreased CVR. The postoperative parametric CVR map and CVR threshold map showed symmetric distribution. Figure 2 shows representative pre- and postprocedural SPECT images and parametric CVR maps.

Quantitative analysis using statistical probabilistic map of the ICA reveals significantly increased mean rCVR_{ICA} of affected side on postprocedural scans compared with preprocedural scans ($p=0.007$) (Fig. 3).

While rCVR_{ICA} of 14 patients recovered, those of three patients decreased in postprocedural scans. A patient (no. 3) underwent further stent insertion after balloon angioplasty and postprocedural SPECT, another patient (no. 6) had chronic infarct lesion involving the ICA territory, and the other (no. 11, Fig. 4) showed improved CVR identified on the parametric CVR images in spite of decreased rCVR_{ICA} in postprocedural scan. Among the 14 patients who showed

Fig. 1 Schematic workflow for generation of parametric CVR map and CVR threshold map. Firstly, basal and acetazolamide stress ^{99m}Tc -HMPAO SPECT images were spatially normalized and relative CVR

was calculated for each voxel. Using probabilistic map, mean rCVR for internal carotid artery was measured

improved $rCVR_{ICA}$, clinical symptoms were improved in 13 patients after PTA or bypass surgery.

Visual Assessment

Degree of reduced CVR was visually assessed for pre- and postprocedural SPECT images and graded each side of ICA territories. In preprocedural scans, visual grades of 34 ICA territories were classified into 17 of grade 0, 4 of grade 1, 7 of grade 2 and 6 of grade 3. In postprocedural scans, visual grades were classified into 24 of grade 0, 7 of grade 1, 2 of grade 2 and 1 of grade 3. Among 68 ICA territories of pre- and postprocedural scans, 54 (79.4 %) were in agreement on visual grades and 14 (20.6) showed discordant visual grades (Table 2). The agreements of visual grades according to the two readers were good ($\kappa=0.76$; 95 % confidence interval 0.64–0.89) to evaluation of decreased CVR.

Comparison of Visual Grade and Quantification Using Parametric CVR Images

Mean $rCVR_{ICA}$ obtained using parametric CVR images was significantly different according to the visual grades (mean $\pm$ SD of $rCVR_{ICA}$ 101.40 ± 2.86 , 98.04 ± 1.87 ,

94.69 ± 4.99 , 91.71 ± 2.50 , respectively; $p < 0.0001$). Post hoc analysis revealed mean $rCVR_{ICA}$ of visual grade 0 was significantly higher than mean $rCVR_{ICA}$ of grade 1, 2 and 3. Mean $rCVR_{ICA}$ of visual grade 3 group showed significantly higher than grade 1 also (Fig. 5a). Figure 5b represents the mean $rCVR_{ICA}$ of discordant visual grades. A $rCVR_{ICA}$ of visual grade 0–1, decreased CVR for which a reader graded 1 and another reader graded 0, was significantly lower than that of visual grade 0 (101.70 ± 2.78 and 97.58 ± 1.13 for grade 0 and grade 0–1; $p < 0.001$) (Fig. 5b).

Discussion

In the current study, a method for generating parametric CVR images from basal and acetazolamide stress ^{99m}Tc -HMPAO SPECT images was developed and evaluated. The parametric CVR images provide semi-quantitative value for CVR and show the brain regions of reduced CVR. Parametric CVR threshold maps could show asymmetric perfusion reserve effectively. Postprocedural parametric CVR images showed visually improved CVR compared with preprocedural images and quantitative $rCVR_{ICA}$ recovered

Fig. 2 A representative case for pre- and postprocedural parametric CVR images. Pre-procedural basal (a) and acetazolamide stress (b) ^{99m}Tc -HMPAO SPECT images showed reduced CVR in right fronto-temporal cortex. c Parametric CVR image revealed reduced rCVR. d Parametric

CVR threshold map showed regions with relatively reduced CVR asymmetrically. e, f Postprocedural basal/acetazolamide ^{99m}Tc -HMPAO SPECT images showed recovered CVR visually. Recovered rCVR was found in parametric CVR image (g) and CVR threshold map (h)

Fig. 3 Changes in rCVR of the ICA measured on parametric CVR images. Postprocedural rCVR_{ICA} increased significantly compared with preprocedural scans ($p=0.007$)

significantly also. Furthermore, mean rCVR_{ICA} was significantly different according to visual grades.

CVR evaluation is clinically used for determining whether patients will benefit from interventions or surgical treatment for chronic cerebral ischemia [14]. As CVR abnormality is strongly associated with clinical outcome in patients with chronic ischemia, CVR tests are performed in evaluation of treatment response or estimation of collateral flow [6, 15]. Furthermore, CVR evaluation is important for patients with moyamoya disease or dementia work-up to assess vascular factors as well as chronic ischemia [15]. However, CVR measurement using direct cerebral blood flow (CBF) from ^{99m}Tc -HMPAO SPECT is hardly used in clinical settings in spite of kinetic studies for CBF [16, 17]. Instead, visual assessment for basal/acetazolamide stress SPECT is used in spite of interobserver variation [7].

Quantification of CVR using basal/acetazolamide stress SPECT has been reported previously using ROI or SPAM [8, 10]. Moreover, objective image quantification using SPAM has been widely studied in PET data such as ^{18}F -FP-CIT PET for dopamine transporter imaging [18, 19]. Although SPAM-based quantification provided the objective parameters, the

Fig. 4 A representative case of regional reduced rCVR identified on the parametric CVR image. Preprocedural rCVR_{ICA} using probabilistic map for ICA was not significantly reduced despite left ICA stenosis (a). Postprocedural rCVR_{ICA} using probabilistic map was not increased (b). Regional decreased rCVR was found on left frontal lobe and manual ROI-based measurement revealed that rCVR increase in the postprocedural scan (c, d)

previous methods were descriptive and did not preserve anatomical information [8, 10]. Furthermore, a relatively small sized regional decreased CVR could not be assessed using a SPAM-based descriptive parameter. As shown in Fig. 5, visually decreased CVR was found in the parametric CVR map; however, SPAM-based quantification reveals rCVR_{ICA} was not far off the mean CVR for the whole brain, probably due to the relatively small extent of decreased CVR. Parametric CVR images could be applied not only to SPAM-based quantification but also ROI-based quantification. Figure 4c and d represents rCVR quantification using a manually drawn ROI,

which revealed reduced CVR in preprocedural scans. As an image-based approach, the parametric CVR images could enable quantitative assessment even in relatively small regional CVR abnormalities.

The parametric CVR maps could provide semi-quantitative CVR as an objective grade for disease severity. The parameter rCVR, an objective quantification using parametric CVR map was sensitive for subtle hemodynamic abnormalities particularly in borderline cases. Mean rCVR_{ICA} of visual grade 0–1, obtained from visually discordant cases of borderline hemodynamic abnormalities, was significantly lower than that of visual grade 0. The result suggest quantification using parametric CVR maps help to determine the significance of reduced CVR objectively, even in subtle changes. For diagnostic application in clinical settings, further studies regarding the diagnostic accuracy of parametric CVR maps according to clinical outcome are warranted.

We obtained rCVR, quantitative regional CVR relative to mean CVR of the whole brain, instead of absolute CVR. In the context of relative rather than absolute value, the rCVR has limitations despite reliable parameter to assess CVR as the results of present study. It could underestimate regional CVR changes in patients with bilateral ICA stenosis which

Table 2 Agreement of visual grades between two readers

Agreement		Disagreement	
Visual grade	No. of patients	Visual grade	No. of patients
Grade 0	38	Grade 0–1	7
Grade 1	5	Grade 0–2	2
Grade 2	4	Grade 1–2	2
Grade 3	7	Grade 1–3	1
		Grade 2–3	2
	54 (79.4 %)		14 (20.6 %)

Fig. 5 Relative CVR_{ICA} and visual grades. Relative CVR_{ICA} was significantly different according to visual grading for decreased CVR (a). Considering the cases of discordant visual grades, a pattern of

inverse correlation between rCVR_{ICA} and grades were found also (b). An rCVR_{ICA} of visual grade 0–1 was significantly lower than that of visual grade 0 (** $p < 0.001$ and *** $p < 0.0001$)

affect mean CVR of the whole brain, like so-called “balanced ischemia” in myocardial SPECT [20]. To overcome relative quantification, comprehensive assessment with anatomical imaging such as MR angiography to reduce false-negative results will be needed. Relative CVR acquisition using specific reference region, such as cerebellum, is a possible method to overcome bilateral ischemia.

This study has some limitations. We used nonlinear transformation to obtain spatially normalized images and apply uniform brain mask and probabilistic maps. However, perfusion defects in patients with underlying infarct lesions could affect registration accuracy and to increase noise for parametric CVR images. As a pilot study for development of image-based CVR estimation, we did not analyze clinical outcome of the patients. In the future, the evaluation of the correlation between clinical outcome and rCVR measured on parametric CVR images is warranted. As a sensitive image-based method, the parametric CVR images promises to evaluate hemodynamic abnormalities sensitively without loss of anatomical information not only in patients with cerebral ischemia but also in various pathologic processes from microangiopathy to moyamoya disease.

Conclusions

In this study, we successfully generated parametric CVR images for basal/acetazolamide stress ^{99m}Tc -HMPAO SPECT for objective assessment of cerebral hemodynamic abnormalities. As a quantitative measurement, rCVR from the parametric image was well correlated with visual grades for decreased CVR and assessed properly postprocedural recovered CVR. The parametric CVR images could be a potentially useful imaging tool for patients with cerebrovascular disorders.

Conflicts of Interest None.

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