alterations observed during the early post-traumatic study. In particular, frontal localizations and more extended lesions appear to have a worse prognosis.

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Reproducibility of Regional Brain Metabolic Responses to Lorazepam

Gene-Jack Wang, Nora D. Volkow, John Overall, Robert J. Hitzemann, Naomi Pappas, Kathy Pascani and Joanna S. Fowler

Medical and Chemistry Departments, Brookhaven National Laboratory, Upton, New York; Departments of Radiology and Psychiatry, SUNY, Stony Brook, New York; Department of Psychiatry and Behavioral Sciences, University of Texas, Houston, Texas; and Psychiatry Service, VA Medical Center, Northport, New York

Changes in regional brain glucose metabolism in response to benzodiazepine agonists have been used as indicators of benzodiazepine-GABA receptor function. The purpose of this study was to assess the reproducibility of these responses. **Methods:** Sixteen healthy right-handed men underwent scanning with PET and [^{18}F]fluorodeoxyglucose (FDG) twice: before placebo and before lorazepam (30 μg/kg). The same double FDG procedure was repeated 6–8 wk later on the men to assess test-retest reproducibility. **Results:** The regional absolute brain metabolic values obtained during the second evaluation were significantly lower than those obtained from the first evaluation regardless of condition ($p \leq 0.001$). Lorazepam significantly and consistently decreased both whole-brain metabolism and the magnitude. The regional pattern of the changes were comparable for both studies (12.3% ± 6.9% and 13.7% ± 7.4%). Lorazepam effects were the largest in the thalamus (22.2% ± 8.6% and 22.4% ± 6.9%) and occipital cortex (19% ± 8.9% and 21.8% ± 8.9%). Relative metabolic measures were highly reproducible both for pharmacolgic and replication condition. **Conclusion:** This study measured the test-retest reproducibility in regional brain metabolic responses, and although the global and regional metabolic values were significantly lower for the repeated evaluation, the response to lorazepam was highly reproducible.

Key Words: cerebral glucose metabolism; lorazepam; pharmacological challenge

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The measurements of regional brain glucose metabolism with PET and 2-deoxy-2[^{18}F]fluoro-D-glucose (FDG) has been used to assess cerebral dysfunction in neuropsychiatric disorders (*1*) and disease progression (*2*) and to evaluate the effects of treatment (*3,4*). This is feasible because baseline regional brain metabolism has been reported to be reproducible (*5,6*).

PET-FDG has been used to assess effects of acute drug interventions on regional brain metabolism. This allows physicians to identify those areas of the brain that are most sensitive to the drug and thus provides some direction in understanding the mechanisms of drug action (*7,8*). It also enables researchers to assess if there are differences in drug response between subjects groups indicative of specific neurotransmitter involvement (*7*). The brain metabolic responses to benzodiazepine agonists have been one of the most widely investigated. Benzodiazepine agonists, which facilitate GABA induced chloride flux at the GABA-benzodiazepine receptor complex (*9*) decrease regional brain glucose metabolism (*8,10,11*). These decrements are reverted by benzodiazepine antagonists indicating that they involve interaction with benzodiazepine receptors (*12*). Regional metabolic decreases, induced by benzodiazepine agonists, have been found to be blunted in alcoholics (*11*) and in subjects at risk for alcoholism (*13*). Because these differences could reflect the subject's state when the drug is given it is important to evaluate the reproducibility of these responses.

This study evaluates the reproducibility of the regional brain metabolic responses to benzodiazepine agonists in 16 healthy controls. We evaluated their responses to lorazepam twice at 6–8-wk intervals.

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For correspondence or reprints contact: Gene-Jack Wang, MD, Medical Department, Brookhaven National Laboratory, Upton, NY 11973.

TABLE 1
Comparison of Cognitive Measures and Behavior Measures (0–10) Obtained after Lorazepam in Studies 1 and 2

	Study 1			Study 2			Study 1 (placebo-lorazepam) versus Study 2(placebo-lorazepam)* p
	Baseline	Lorazepam	p	Baseline	Lorazepam	p	
Stroop-read	103 ± 23	89 ± 16	ns	113 ± 17	91 ± 15	0.0001	ns
Stroop-xxx	77 ± 9	63 ± 13	0.0003	82 ± 10	67 ± 10	0.0001	ns
Stroop-color	51 ± 9	40 ± 11	0.0003	56 ± 11*	45 ± 10	0.0001	ns
SDMT	53 ± 11	38 ± 6	0.0001	54 ± 7	41 ± 7	0.0001	ns
Word association	14 ± 3	10 ± 4	0.0006	15 ± 4	9 ± 4	0.0001	ns
Calculation (errors)	0.6 ± 0.6	0.9 ± 0.8	ns	0.9 ± 0.7	0.7 ± 0.6	ns	ns
Desire	0.3 ± 1.3	0.4 ± 1.5	ns	0	0	ns	ns
Intoxication	0	1.9 ± 2.0	0.002	0	1.6 ± 1.8	0.003	ns
Sleepiness	0.7 ± 0.9	3.8 ± 2.4	0.001	2.3 ± 2.1	3.8 ± 2.6	ns	ns
Dizziness	0.1 ± 0.3	1.4 ± 2.0	ns	0	2.3 ± 2.0	0.004	ns
High	0	0.7 ± 0.1	ns	0.1 ± 0.5	1.3 ± 2.6	ns	ns
Anxiety	1.1 ± 1.7	0.1 ± 0.3	ns	0.3 ± 0.8	0.1 ± 0.3	ns	ns
Tiredness	1.0 ± 0.9	3.2 ± 2.9	0.001	1.5 ± 1.6	3.4 ± 2.4	0.004	ns

*Compared between studies 1 and 2: $p < 0.005$.
The Stroops include three sections:reading color names [read], describing the color [xxx] and reading color names colored with discrepant colors [color].
SDMT = single-digit matching test.

MATERIALS AND METHODS

Subjects

Sixteen healthy, right-handed men (aged 23–58 yr, mean 38.3 ± 11.2 yr) who consumed less than five alcohol drinks per week were selected for the study. All subjects underwent complete physical, neurological and psychiatric examination as well as routine laboratory tests including urine toxicology tests to exclude subjects with medical and/or neuropsychiatric illnesses. Subjects were instructed to refrain from drinking alcohol and to discontinue any over-the-counter medications 1 wk before the scan. Informed consent was obtained from each participant.

Experimental Design

Two sets of identical studies were performed in each subject 6–8 wk apart. Each study consisted of two PET scans performed with FDG, which were done on two separate days within 1 wk of each other. On the first day, subjects were injected with a placebo (3 cc of saline solution) given 40–50 min before FDG administration (baseline-FDG scan). On the second day, they were injected with lorazepam (30 μg/kg) given 40–50 min before to FDG (lorazepam-FDG scan). The subjects were blind to the drug received. To avoid circadian variability (*6*), the four scans for a given subject were obtained at the same time of day (±1 hr). Lorazepam concentration in plasma was measured before and 40 and 95 min after lorazepam administration with HPLC.

PET Scanning

Subjects were asked to refrain from smoking, consuming caffeinated drinks and eating at least 4 hr before the study. PET scans were performed with a tomograph (resolution 6 × 6 × 6.5 mm FWHM, 15 slices). Procedures for subject positioning, scanning protocol, arterialized blood sampling and conditions of study were as previously described (*14*). Briefly, a 20-min emission scan was obtained beginning 35 min after injection of 4–5 mCi FDG. Metabolic images were computed as previously described (*14*).

Behavioral and Cognitive Evaluation

Before placebo or lorazepam and at 20 min and 2 hr after placebo or lorazepam administration, subjects were asked to evaluate on an analog scale (rated 0–10) their desire for more of a drug and their subjective perception of intoxication, sleepiness, dizziness, highness, anxiety and tiredness. During the same time intervals subjects were also evaluated with the Stroop test, Word Association test, Symbol Digit Modality test and arithmetic calculations (*15*).

Image Analysis

Regions were selected using a previously published template (*16*) of 115 nonoverlapping regions grouped into 13 composite cortical, subcortical and cerebellar regions. Measurement of global brain metabolism was obtained by averaging the values from the pixels located in the brain tissue component of the brain images as previously described (*16*).

Statistical Analysis

Absolute and relative (ratios of regional-to-global brain metabolism) values were analyzed using three-way repeated measurement analysis of variance (ANOVA) to evaluate statistical significance of the differences between baseline and postlorazepam condition. The analysis occurred between the first and second replications (studies 1 and 2) and between the 13 brain regions. The analysis permitted examination of the main effects and the sample interactions of the factors in the three-way treatments × regions × replications within-subjects design. Post-hoc t-tests on the regional measure were then performed on the significant effects.

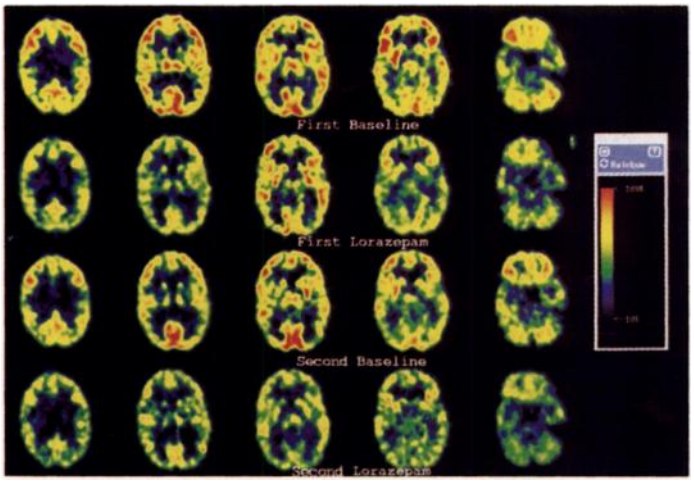

FIGURE 1. FDG-PET images of normal subject for study 1 with placebo (baseline 1), study 1 with lorazepam, study 2 with placebo (baseline 2) and study 2 with lorazepam.

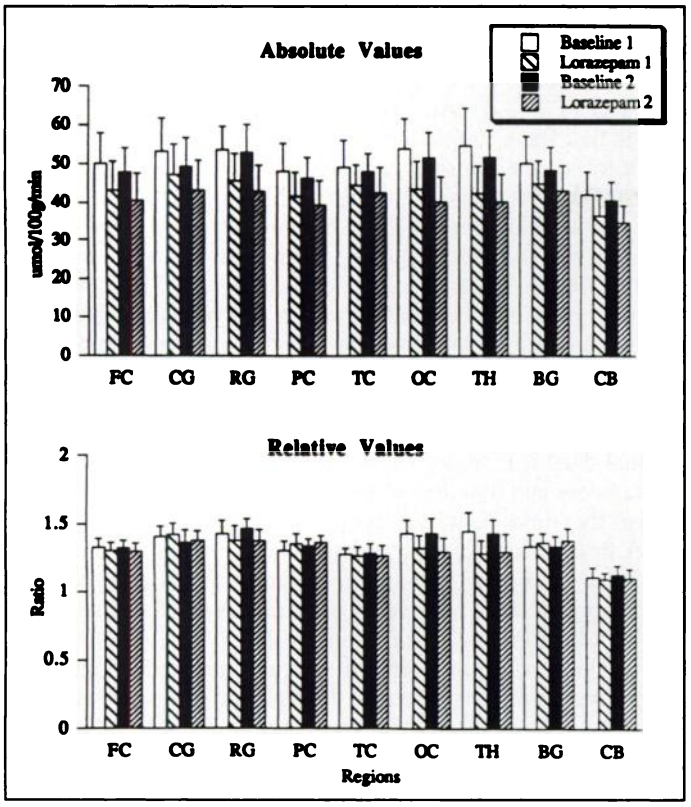

FIGURE 2. Absolute and relative glucose metabolic rate in brain regions of FDG scans of study 1 with placebo (baseline 1), study 1 with lorazepam, study 2 with placebo (baseline 2) and study 2 with lorazepam. Since there was no laterality effect for frontal, parietal, temporal and occipital cortices, the data for the right and the left was averaged in this figure. FC = frontal cortex; OF = orbitofrontal gyri; CG = cingulate gyrus; PC = parietal cortex; TC = temporal cortex; OC = occipital cortex; TH = thalamus; BG = basal ganglia; CB = cerebellum.

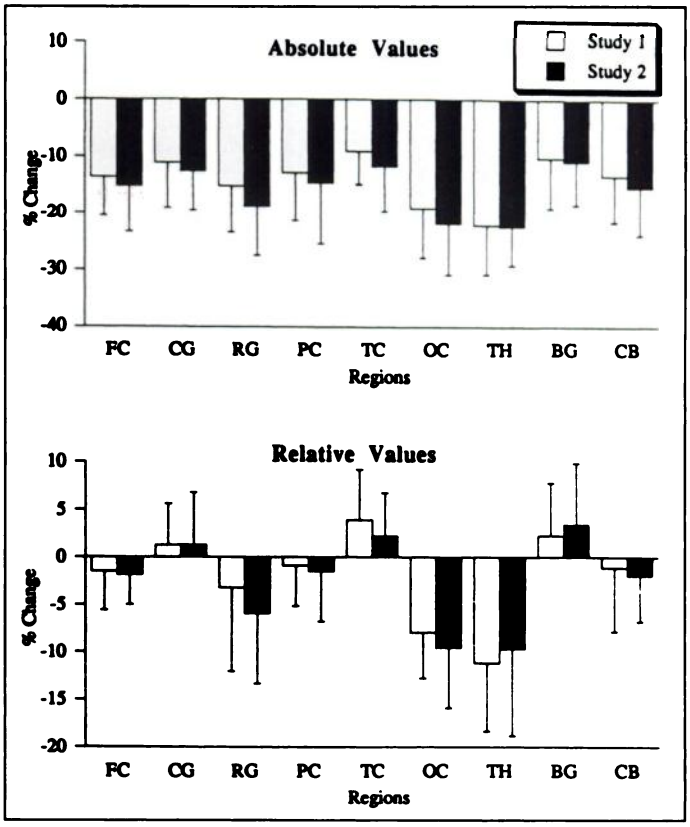

FIGURE 3. Percent absolute and relative glucose metabolic rate in brain regions after lorazepam administration in studies 1 and 2.

Intraclass correlation coefficients were calculated to estimate test-retest reliability using an ANOVA model that corrected for mean shifts between studies 1 and 2 (*17,18*). These estimates of reliability were calculated for the individual PET measurements of regional metabolism, as well as for the regional metabolic rates averaged across the two replications.

RESULTS

The concentration of lorazepam in plasma was similar for both studies and corresponded to 6.8 ± 4.4 and 6.2 ± 3.8 ng/ml at 20 min and to 10.6 ± 7.2 and 9.9 ± 5.9 ng/ml at 95 min post-lorazepam administration.

Lorazepam significantly decreased cognitive performance while increased the subjective perception of intoxication, sleepiness and dizziness. The magnitude of these effects did not differ between studies 1 and 2 (Table 1). The only significant change with repeated testing was an improvement in the baseline performance of the Stroop's color-word interference subtest (Table 1).

Lorazepam significantly decreased whole-brain metabolism in the two sets of studies (Fig. 1). The decreases in absolute (baseline-to-lorazepam) and in the percent change in global and regional metabolism did not differ for studies 1 or 2, and, for both studies, the largest changes occurred in thalamus and occipital cortex (Figs. 2 and 3). A summary of the ANOVA accomplished on the within s.d. scores is shown in Table 2. The analysis confirmed highly significant ($p \leq 0.001$) differences in metabolism between baseline and lorazepam conditions when averaged across brain regions and replications conditions, and a highly significant ($p \leq 0.001$) difference in average metabolism for study 1 and study 2. Post-hoc t-test analysis revealed that the drug effects were significant for all brain regions but for the replication effect they were only significant in the right and left frontal cortex ($p \leq 0.05$) and in the cingulate gyrus ($p \leq 0.003$).

The same regional pattern of changes induced by lorazepam for the absolute measures was also observed for the "relative" measures (Figs. 2 and 3). The ANOVA calculated for the "relative" measures produced results essentially identical to those summarized in Table 2 for the absolute values except for the replication effect which did not differ between studies 1 and 2.

The estimates of test-retest reliability of the PET measurements of regional brain metabolic rate are presented in Table 3 for individual determinations and for the PET measurements averaged across the two replicated studies. The latter are considered particularly relevant for this type of research design, in which treatment effects in the individual brain regions are evaluated by averaging across replicated studies.

TABLE 2
Summary of Three-Way Treatments × Regions × Replications Analysis of Variance

Source	df	MS	F	Significance ($p \leq$)
Treatments	1	1191.5	804.4	0.0001
Regions	12	463.8	31.5	0.0001
Relications	1	1050.8	71.3	0.0001
Treatments × Regions	12	91.6	6.2	0.0001
Treatments × Replications	1	13.6	0.9	0.338
Regions × Replications	12	9.0	0.6	0.836
Error (ω)	780	14.7	—	—

TABLE 3
Test-Retest Reliability of Measurements of Regional Brain Metabolic Rate Assessed by Single Reading or Averaged Across 16 Subjects

	Single reading		Averaged across 16 subjects	
Region	Baseline	Lorazepam	Baseline	Lorazepam
RFC	0.868	0.781	0.991	0.983
LFC	0.781	0.726	0.983	0.977
CG	0.761	0.856	0.981	0.990
RG	0.719	0.617	0.976	0.963
RPC	0.696	0.364	0.973	0.902
LPC	0.563	0.423	0.954	0.921
RTC	0.757	0.782	0.980	0.983
LTC	0.804	0.581	0.985	0.957
ROC	0.369	0.252	0.903	0.844
LOC	0.666	0.611	0.970	0.962
TH	0.628	0.846	0.964	0.989
BG	0.805	0.809	0.985	0.985
CB	0.668	0.564	0.970	0.954

RFC = right frontal cortex; LFC = left frontal cortex; CG = cingulate gyrus; RPC = right parietal cortex; LPC = left parietal cortex; RTC = right temporal lobe; LTC = left temporal lobe; ROC = right occipital cortex; LOC = left occipital cortex; TH = thalamus; BG = basal ganglia; CB = cerebellum.

DISCUSSION

Lorazepam Effects

This study shows that the regional brain metabolic decrements induced by acute lorazepam administration are highly reproducible in a given subject when tested at a 6- to 8-wk interval. It also replicates our previous findings documenting the largest decrements in thalamus and occipital cortex (*19*). The highly significant ($p \leq 0.001$) treatments × regions interaction provides statistical support to the conclusion that the effect from lorazepam truly differs in magnitude from one region to another. Regional differences in sensitivity to lorazepam is probably not only a function of regional receptor concentration but also of regional differences in receptor subtypes and receptor reserve (*20*).

Previous studies on the effects of benzodiazepines have consistently shown decreases in brain metabolism with regional values ranging from 3% to 24% (*8,10,21*). These ranges are likely to reflect not only differences in the particular benzodiazepine drug used but also their doses and the timing of administration before FDG. For the current study where the drug and the dose were held constant, the range of values for changes in global metabolism were 0.7–11.3 μmole/100 g/min and the range of values for the brain region with the largest change were 0.8–27.1 μmole/100 g/min (thalamic region). The range of values between subjects were larger than those within the subjects and are likely to reflect biological variability. The fact that the magnitude of the changes were not related to differences in concentration of lorazepam in plasma indicates that the variability is not only due to differences in metabolism of drug but that they may also reflect differences in sensitivity of the benzodiazepine-gaba receptors and/or alternatively differences in other circuits that regulate responses to gabaergic stimulation.

Test-Retest Reproducibility

This study showed that the regional metabolic changes induced by lorazepam are reproducible. In contrast, we found a highly significant replication effect on the absolute metabolic measures, with both baseline and lorazepam means being lower in study 2 than in study 1. These results differ from those previously published on the test-retest reproducibility of baseline FDG-PET (*5,6*). An important contributor to this discrepancy is that the current study employed an ANOVA were the values for all the brain regions were entered in the replication analysis whereas previous studies had been limited to comparisons of individual regions. For the current study the post-hoc t-tests for the individual regions were significant in cingulate gyrus ($p \leq 0.003$) and frontal cortex ($p \leq 0.5$). If we had originally performed individual region analysis we would have concluded that the FDG baseline values were reproducible and that the only brain region that differed, after correction for multiple comparisons, was the cingulate gyrus. Although one can argue about optimal statistical strategies for analyzing regional data, it is important to realize that these vary between investigators and that they affect the results. Another difference is that the time between metabolic scans was significantly longer in this study than in previous ones, which were usually performed within a 1-wk period. One cannot rule out the possibility that there may be significant variations in metabolic activity over periods of time longer than 6 wk. Also, for the current study, subjects received a lorazepam scan in between the two baseline scans, whereas the baseline scan was followed by another baseline scan in previous studies. This is particularly relevant in that the second scan was experienced while under the effects of lorazepam which consistently decreased anxiety in the subjects thus providing them with the memory of an experience that would have been perceived as less anxiety provoking than the initial baseline scan. Decreased anxiety on the second baseline could explain the lower metabolism for study 2 since decreased anxiety during scanning conditions has been associated with lower cerebral blood flow and metabolism (*22*). Finally, though unlikely, one has to consider a carry-over effect in which there was incomplete recovery of the baseline values after the first lorazepam administration. Long-lasting (>1 mo) effects of acute benzodiazepines administration have been reported tolerance to further drug administration (*23*). Studies evaluating reproducibility of two baseline scans at 6–8-wk intervals without any pharmacological intervention between them are required to determine whether the changes reflect a drug or a test-retest variability effect.

Reliability Measurements

The intraclass reliability coefficients were used as measurements of consistency between studies 1 and 2 for baseline and lorazepam conditions separately. Although tests of significance for differences in intraclass coefficients (reliability estimates) were not included in the model, some observed differences appear associated with brain regions across baseline and lorazepam conditions, whereas other observed differences appear to reflect the impact of lorazepam. For example, left parietal and right occipital cortices provided less reliable measurements than did other regions across both baseline and lorazepam condition. In contrast, right parietal and left temporal cortices evidenced decline in measurement reliability between baseline and the following lorazepam conditions. Nevertheless, with exception of the measurements obtained from the right occipital cortex, most of the regional measurements, when averaged across two replicated studies, evidenced reliability commensurate with that generally expected for biometric and psychometric assessments (*17,18*).

Absolute Compared with Relative Measures

The "relative" metabolic measures were more stable than the "absolute" measures. The higher reproducibility of the relative than the absolute measures had been previously documented for

FDG-PET studies performed under baseline conditions (*6*). The question remaining is which is the best indicator of regional brain function. In our subject, for example, the significant difference observed in the absolute measures between studies 1 and 2 was lost for the relative measures. One could question whether the differences observed with the absolute measures represent noise or whether the relative measures are less sensitive to physiological signals. This issue is important since increasing numbers of imaging studies that evaluate functional activation use relative rather than absolute measures. Relative measures assume that regional measures change linearly with respect to changes in global metabolism and/or global cerebral blood flow. Studies are required to establish the relationship between the changes in metabolic activity in the various brain regions as a function of changes in whole brain metabolism.

CONCLUSION

Regional brain metabolic changes induced by the benzodiazepine agonist are highly reproducible in magnitude and pattern. We found that also shows that the metabolic rate was consistently lower in the second study than in the first. The mechanism accounting for the decreases in the replication study requires further evaluation.

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SPECT and MRI Evaluations of the Posterior Circulation in Moyamoya Disease

Ichiro Yamada, Yuji Murata, Isao Umehara, Soji Suzuki and Yoshiharu Matsushima

Departments of Radiology and Neurosurgery, Faculty of Medicine, Tokyo Medical and Dental University, Tokyo, Japan

We evaluated the posterior circulation in patients with moyamoya disease by SPECT and MRI. **Methods:** Six patients with idiopathic moyamoya disease were studied by SPECT, MRI and angiography. Patients received an injection of 555–740 MBq of ^{99m}Tc-HMPAO, after which SPECT images were taken. The cerebral-to-cerebellar activity ratio in five cerebral regions was calculated to assess the regional cerebral blood flow (rCBF). The SPECT and MRI findings were then compared with angiographic. **Results:** Of the 12 posterior cerebral arteries (PCAs) in the six patients studied, seven PCAs (58%) in five patients had a stenotic or occluded lesion. Furthermore, rCBF in all five regions significantly decreased as the degree of steno-occlusive lesions of the PCA progressed. No significant correlation, however, was found between the steno-occlusive lesions of the internal carotid artery bifurcation and the rCBF. The rCBF significantly decreased in the absence of leptomeningeal collateral vessels from the PCA to the anterior circulation. On the basis of the MR images, the frequency of cerebral infarctions significantly increased in patients with steno-occlusive PCA lesions. **Conclusion:** The rCBF in moyamoya disease decreases proportionally with the degree of steno-occlusive lesions of the PCA. The steno-occlusive PCA lesions decrease the number of leptomeningeal collateral vessels to the anterior circulation, thereby causing severe cerebral ischemia that is likely to result in infarctions.

Key Words: moyamoya disease; technetium-99m-HMPAO; regional cerebral blood flow; posterior circulation; SPECT

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For correspondence or reprints contact: Ichiro Yamada, MD, Department of Radiology, Faculty of Medicine, Tokyo Medical and Dental University, 1-5-45 Yushima, Bunkyo-ku, Tokyo 113, Japan.