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Altered patterns of blood flow response during visual stimulation in carotid artery occlusive disease

Hiroshi Yamauchi,[a,*] Takashi Kudoh,[a] Kanji Sugimoto,[a] Masaaki Takahashi,[a] Yoshihiko Kishibe,[a] and Hidehiko Okazawa[b]

[a]*Research Institute, PET Division, Shiga Medical Center, 5-4-30 Moriyama, Shiga 524-8524, Japan*
[b]*Biomedical Imaging Research Center, Fukui University, Fukui, Japan*

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To correctly interpret the results of functional neuroimaging studies in stroke, it is essential to understand how cerebrovascular disease influences hemodynamic response during neural activation. To investigate the effect of internal carotid artery (ICA) occlusive disease on the pattern of cerebral blood flow (CBF) response during visual stimulation, we used positron emission tomography to study 13 patients with ICA steno-occlusive lesions. We measured the changes of CBF during visual stimulation in the primary visual cortex and in the surrounding region, including the higher-order visual cortex, and examined their correlation with the baseline value of oxygen extraction fraction, a measure of hemodynamic impairment, in the ICA distribution.

With visual stimulation, CBF in the primary visual cortex significantly increased in all patients, while in the surrounding region, CBF showed variable changes, including decreases in some patients. In 9 patients with unilateral ICA lesions, the CBF change in the surrounding region ipsilateral to the ICA lesion was significantly decreased compared with the value in the contralateral hemisphere, while the CBF change in the primary visual cortex showed no hemispheric difference. The hemispheric values of oxygen extraction fraction in the ICA distribution and the amount of CBF increase in the visual cortex were independently and negatively correlated with the CBF change in the surrounding region. We conclude that the pattern of CBF response during visual stimulation may change in ICA occlusive disease. We suggest that the redistribution of CBF during visual stimulation may be a contributing mechanism.

Keywords: Blood flow response; Visual stimulation; Carotid artery occlusive disease

Introduction

Functional neuroimaging methods, particularly those using functional magnetic resonance imaging (fMRI) (Ogawa et al., 1990; Raichle, 1998), are increasingly being applied in investigations of patients with cerebrovascular disease, and the findings suggest their usefulness for monitoring functional changes after stroke (Calautti and Baron, 2003; Herholz and Heiss, 2000). The regional distribution of hemodynamic response during neural activation was different between stroke patients and healthy subjects, suggesting that functional reorganization occurs after stroke. The interpretation of these differences is based on the assumption that stroke patients preserve intact neurovascular coupling and show activation-induced hemodynamic responses similar to those of healthy subjects throughout the brain. However, this assumption may not be valid in all cases (D'Esposito et al., 2003). At present, it is not well understood how cerebrovascular disease influences patterns of hemodynamic response during neural activation. Thus, more information is needed to avoid misinterpreting the results of functional neuroimaging studies in stroke.

A few investigations in patients with cerebrovascular disease have shown changes in the nature of activation-induced hemodynamic response in the target region (D'Esposito et al., 2003). However, little is known about how increased neural activity affects the hemodynamics in the area surrounding the activated region. A study using fMRI in the normal brains of cats showed a positive blood oxygenation level-dependent (BOLD) and cerebral blood volume (CBV) change in the primary visual cortex during visual stimulation, whereas a prolonged negative BOLD and CBV change occurred in the adjacent suprasylvian gyrus containing higher-order visual areas (Harel et al., 2002). Reallocation of cortical blood resources may overcome a local demand for increased CBF induced by increased neural activity. In patients with cerebrovascular disease, the hemodynamic reserves of the brain may be reduced (Powers, 1991), and thus, it is likely that hemodynamic response in the primary activated region may occur at the sacrifice of perfusion of the surrounding region, even if the neural activity of the surrounding region is increased. This

* Corresponding author. Fax: +81 775 82 6041.
E-mail address: yamauchi@shigamed.jp (H. Yamauchi).
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redistribution of CBF during activation would affect cerebral patterns of activation-induced hemodynamic response. However, the development of the redistribution needs a marked CBF increase in the primary activated region, though the brain has less hemodynamic reserve. This is probably why few studies have demonstrated this phenomenon in patients with cerebrovascular disease.

In this study, we quantitatively evaluated the CBF response during visual stimulation in patients with internal carotid artery (ICA) steno-occlusive lesions using positron emission tomography (PET). In healthy subjects, the visual stimulus used in this study can induce large CBF changes in the primary visual cortex, while a less marked increase of CBF occurs in the surrounding region, including the higher-order visual cortex (Vafaee et al., 1998; Zeki et al., 1991). In ICA occlusive disease, the redistribution of blood in the posterior circulation may occur to compensate for reduced flow in the anterior circulation and may, in turn, decrease the hemodynamic reserve in the posterior circulation (van Everdingen et al., 1997). In such cases, when the demand for CBF in the posterior circulation is increased with increased visual activity, blood in the posterior circulation may be mainly allocated to the primary visual cortex, which may affect the hemodynamic response to visual stimulation in the surrounding region. The purpose of this study was to determine whether the redistribution of CBF during visual stimulation occurs in patients with ICA occlusive disease.

Patients and methods

Patients

We studied 13 patients, of whom 10 were men, aged 62 ± 10 (mean ± SD) years. All had angiographically documented occlusion or stenosis (>70% diameter reduction) of the extracranial internal carotid artery (ICA). The clinical and neuroradiological data for each patient are summarized in Table 1. Three patients had no symptoms, 2 had a transient ischemic attack (TIA), and 8 had a minor hemispheric stroke with mild disability. All symptoms were related to the affected carotid artery distribution, and no patient had visual symptoms. All patients had normal visual acuity and visual field. In the asymptomatic patients, arterial disease was suspected because of the findings on echo angiograms performed as part of screening for cerebral arterial disease concomitant with coronary arterial disease. Nine patients had infarcts on MRI. No abnormality was found in the primary visual cortex or in the white matter corresponding to the optic radiation. Conventional angiography revealed bilateral ICA disease in 4 cases. In the 3 symptomatic patients with bilateral disease, only the side with more severe vascular lesions was symptomatic. Collateral pathways from the posterior circulation to the anterior circulation were present in 6 cases. No significant disease of the posterior cerebral artery was seen in any patient.

PET measurements

All the subjects underwent PET scans with a whole-body, Advance (General Electric Medical System, Milwaukee, WI) PET scanner, which permits simultaneous acquisition of 35 image slices with inter-slice spacing of 4.25 mm (DeGardo et al., 1994; Okazawa et al., 2001). Under the guidance of the Ethics Committee of the Shiga Medical Center, written informed consent was obtained from each subject. Performance tests showed the intrinsic resolution of the scanner to be 4.6 to 5.7 mm in the transaxial direction and 4.0 to 5.3 mm in the axial direction. As part of the scanning procedure but before the tracer administration, ^{68}Ge/^{68}Ga transmission scanning was performed for 10 min for attenuation correction. For the reconstruction of the PET data, images were blurred to 6.0-mm full width half-maximum in the transaxial direction using a Hanning filter. Functional images were reconstructed as 128 × 128 pixels, with each pixel representing an area of 2.0 mm × 2.0 mm.

Table 1
Patient data

Patient	Age	Sex	Type of stroke (month)[a]	Concordant conditions	Location of infarct	Degree of ICA stenosis	Occlusive diseases on other arteries	Time (day) between angiography and PET	Collateral pathways
1	69	F	Asymptomatic	None	None	L ICAO	L VAS (70%)	8	LM
2	73	F	Asymptomatic	HT, IHD	Bilateral putamen	L ICAS (70%)	R ICAS (50%)	30	P com.
3	76	M	Asymptomatic	DM	None	L ICAS (80%)	None	9	None
4	54	M	TIA (3)	HT	None	R ICAS (80%)	None	7	LM
5	76	F	TIA (2.6)	HT	None	L ICAS (75%)	R ICAS (50%)	16	None
6	48	M	Minor stroke (1.9)	None	R parietal cortex	R ICAS (80%)	None	21	A com.
7	49	M	Minor stroke (1.6)	None	L parietal cortex	L ICAS (75%)	None	27	None
8	51	M	Minor stroke (3)	DM	R frontal subcortex, R internal capsule	R ICAO	None	17	A com., Oph.
9	57	M	Minor stroke (2)	HT	R corona radiata	R ICAS (90%)	R VAS (70%)	11	A com., P com.
10	59	M	Minor stroke (35)	HT, DM	L frontal and parietal cortices	L ICAS (75%)	None	7	P com., LM
11	63	M	Minor stroke (31)	DM	L frontal cortex	L ICAS (90%)	None	29	A com.
12	68	M	Minor stroke (8)	HT	R parietal cortex	R ICAO	L ICAS (50%)	30	A com.
13	75	M	Minor stroke (1)	HT, DM, IHD	R frontal cortex	R ICAS (80%)	L ICAS (70%)	7	A com., P com.

[a] The times in bracket indicate the interval between the onset of each symptom and the PET evaluation.

M, male; F, female; TIA, transient ischemic attack; HT, hypertension; IHD, ischemic heart disease; DM, diabetes mellitus; R, right; L, left; ICA, internal carotid artery; O, occlusion; S, stenosis; VA, vertebral artery; A com., anterior communicating artery; P com., posterior communicating artery; LM, leptomeningeal anastomosis; Oph., ophthalmic artery.

The subjects were positioned in the scanner with their heads immobilized with a head-holder and positioned with light beams to obtain transaxial slices parallel to the orbitomeatal line. A small cannula was placed in the left brachial artery for blood sampling. First, a baseline $H_2{}^{15}O$ study was performed (Okazawa et al., 2001). The patients were asked to fixate on a cross-hair in the center of the screen 30 s before the scan, and throughout the subsequent 3-min scan. After an intravenous bolus injection of 555 MBq of $H_2{}^{15}O$ into the right antecubital vein, a 3-min dynamic PET scan was started at the time of tracer administration. Frame durations were 5 s × 12, 10 s × 6, and 20 s × 3. Arterial blood was continuously drawn from a catheter in the radial artery by using a mini-pump (AC-2120, Atto Co., Tokyo, Japan), and the concentration of radioactivity was monitored with a coincidental flow-through radioactivity detector, Pico-Count (Bioscan Inc., Washington, DC, USA) (Votaw and Shulman, 1998), and used as an input function for data analysis.

After the baseline $H_2{}^{15}O$ study, a series of ^{15}O-gas studies was performed (Okazawa et al., 2001). $C^{15}O_2$ and $^{15}O_2$ were inhaled continuously through a mask. The scan time was 5 min, and arterial blood was sampled manually from the brachial artery 3 times during each scan. Each sample was collected for 10–20 s to average the fluctuation due to the respiratory cycle, and the radiotracer concentrations of whole blood and plasma were measured with a well counter. Bolus inhalation of $C^{15}O$ with 3-min scanning was used to measure CBV. Arterial samples were obtained manually twice during the scanning, and the radiotracer concentration of whole blood was measured.

After the ^{15}O-gas study, a second $H_2{}^{15}O$ study was performed during visual stimulation: an intravenous bolus injection of 555 MBq of $H_2{}^{15}O$ and a 3-min dynamic PET scan were performed in the same way as in the baseline study. In the activation condition, the patients were shown a yellow-blue annular checkerboard whose contrast was reversed at a frequency of 4 Hz (Vafaee et al., 1999). Stimulation began 4 min before the start of the dynamic PET scan and continued for a total of 7 min.

In the ^{15}O-gas study, we calculated CBF, cerebral metabolic rate of oxygen ($CMRO_2$), and oxygen extraction fraction (OEF) based on the steady-state method (Frackowiak et al., 1980). $CMRO_2$ and OEF were corrected by the CBV (Lammertsma and Jones, 1983). In the $H_2{}^{15}O$ study, CBF was calculated using the autoradiographic method with a partition coefficient of 0.9 (ml/g) (Herscovitch et al., 1983; Raichle et al., 1983).

Data analysis

We analyzed 10 tomographic planes from 46.25 to 84.5 mm above and parallel to the orbitomeatal line, which corresponded to the levels from the basal ganglia and thalamus to the centrum semiovale. The hemisphere supplied by the diseased carotid artery in patients with unilateral vascular disease or the hemisphere supplied by the more severely diseased carotid artery in patients with bilateral vascular disease is referred to as the “ipsilateral” hemisphere.

First, we evaluated the changes in CBF during visual activation in the visual cortex and the surrounding region by using the CBF images obtained from the $H_2{}^{15}O$ study. The region of interest (ROI) was placed on the CBF images during visual activation. Based on the atlas prepared by Kretschmann and Weinrich (1986), the lower 3 planes from 46.25 to 54.75 mm above the orbitomeatal line were examined by placing a total of 2 circular regions of interest (ROIs) 16 mm in diameter compactly over the gray matter of the medial occipital cortex in each hemisphere along the postero-anterior direction from the posterior end (for the primary visual cortex) and by placing a total of 3 circular ROIs of the same size compactly over the gray matter of the lateral cortex in each hemisphere along the medio–lateral direction from the posterior primary visual cortex ROI (for the surrounding region) (Fig. 1). The same ROIs were transferred to the CBF image at baseline. The regional values in the primary visual or surrounding cortex of the ipsilateral or contralateral hemisphere were calculated as the average for all ROIs in each hemisphere. In addition, all 10 planes from 46.25 to 84.5 mm above the orbitomeatal line were examined by placing a total of 10 to 12 circular ROIs 16 mm in diameter compactly over the gray matter of the lateral cortex in each hemisphere (Yamauchi et al., 2003). The averaged values in all ROIs in the bilateral hemispheres, excluding the primary visual cortex and surrounding region ROIs, are referred to as the global values. These global values were used for the normalization of the values during visual stimulation to negate the effect of the fluctuations in whole-brain values that were not specifically related to the visual stimulation. In each patient, we corrected the CBF values in the primary visual or surrounding cortex during activation by dividing by the correction factor [global value

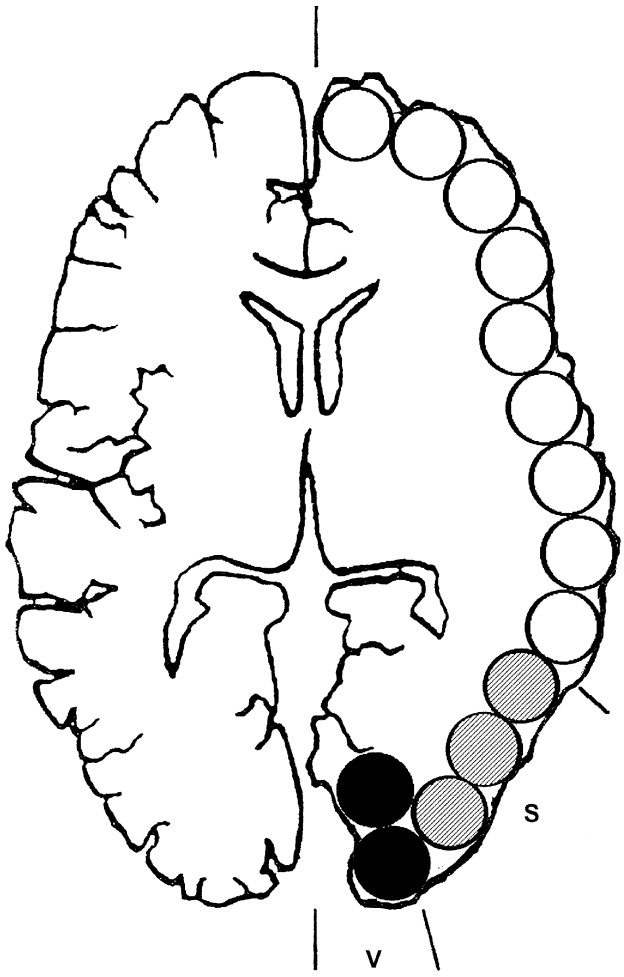

Fig. 1. A diagram illustrating the circular regions of interest placed over the cerebral cortex divided into the primary visual cortex (V, closed circles), the surrounding cortex (S, hatched circles), and the gray matter of the lateral cortex (open circles).

(activation)/global value (baseline)], which were determined individually. We assumed that the difference between the corrected CBF values during activation and the values at baseline reflected the changes specific to visual stimulation.

Second, we evaluated the degree of hemodynamic impairment in the ICA distribution by using the images obtained from the ^{15}O-gas study. All the 10 planes from 46.25 to 84.5 mm above the orbitomeatal line were analyzed. The ROI was placed on the CBF images. Each image was examined by placing a total of 10 to 12 circular ROIs 16 mm in diameter compactly over the gray matter of the lateral cortex in each hemisphere (Yamauchi et al., 1990). The ROIs in all 10 images covered the distribution of the MCA as well as the watershed areas between the anterior cerebral artery and MCA and between the MCA and posterior cerebral artery. The same ROIs were transferred to the other images. The mean hemispheric value of OEF, a measure of hemodynamic impairment (Powers, 1991), in each hemisphere was calculated as the average of the values of all circular ROIs. In 6 patients with infarction in the cerebral cortex, the regions of interest that overlapped a well-demarcated area of decreased $CMRO_2$ corresponding to low-intensity areas on T1-weighted MR images were excluded from the analysis for this purpose.

Statistical analysis

We compared the values of the CBF obtained at baseline and during activation using the paired *t* test; statistical significance was accepted at $P < 0.0125$ (0.05/4) by using a Bonferroni correction to reduce type I error due to the multiplicity of the correlations tested. The changes of the CBF in the ipsilateral and contralateral hemispheres were compared using the paired *t* test; statistical significance was accepted at $P < 0.025$ (0.05/2). Simple or stepwise multiple linear regression analysis was used to analyze the relationship between the change of CBF in the region surrounding the primary visual cortex during activation and other variables. Significance was established at $P < 0.05$. We applied this analysis to the CBF changes in the region surrounding the primary visual cortex as the dependent variable and the hemispheric value of the baseline OEF in the ICA distribution, the CBF changes in the primary visual cortex, and age as the independent variables. We adopted data pairs from the 2 hemispheres for each patient because of the suspected hemispheric difference of baseline hemodynamics depending on the severity of arterial disease in each patient, although the data were not independent from each other.

Results

In each patient, we determined the CBF values in the primary visual or surrounding cortex during visual activation. We corrected these values to negate the effect of irrelevant fluctuations by dividing by an individually determined correction factor, whose average value was 1.02 ± 0.11. Compared with the baseline values, the corrected CBF values during visual stimulation in the primary visual cortex were significantly increased, while those in the surrounding region were not (Table 2). When only patients with unilateral ICA lesions ($N = 9$) were analyzed, the change of CBF in the surrounding cortex ipsilateral to the ICA lesions was significantly decreased compared with the value in the contralateral hemisphere (−0.05 ± 2.50 versus 1.14 ± 2.21 ml/100 g/min, $P = 0.01$), while the CBF changes in the primary visual cortex showed no significant difference between hemispheres (6.80 ± 4.81 versus 7.94 ± 6.48 ml/100 g/min).

Table 2
Baseline and activation values of CBF in the primary visual cortices and the surrounding regions ipsilateral and contralateral to the more severe carotid artery disease

Region	Condition		
	Baseline	Activation	Change
Primary visual cortex			
Ipsilateral	44.87 ± 7.47	51.25 ± 9.64*	6.37 ± 4.12
Contralateral	45.28 ± 7.87	52.26 ± 9.51*	6.98 ± 5.65
Surrounding region			
Ipsilateral	36.96 ± 6.19	37.43 ± 6.51	0.46 ± 2.30
Contralateral	37.76 ± 6.39	38.68 ± 6.31	0.91 ± 1.99

Values are the mean ± SD (ml/100 g/min).
The values of CBF during activation were corrected by dividing by the correction factor (global value (activation)/global value (baseline)).
* $P < 0.001$, compared to the baseline (paired *t* test).

Analysis of data for individual patients revealed that the changes of CBF during activation varied among patients or between hemispheres in the same patient but were correlated with the baseline hemodynamic parameters (Fig. 2). In simple linear regression analysis of the data of the 26 hemispheres, the CBF change in the surrounding region was significantly and negatively correlated with the OEF value in the ICA distribution ($r = -0.39$, $P < 0.05$) (Fig. 3), and it had a tendency to be correlated negatively with the CBF change in the visual cortex, though the tendency was without statistical significance ($r = -0.26$, $P = 0.19$). The CBF change in the visual cortex was not significantly correlated with the OEF value in the ICA distribution. When the hemispheres were divided into those with relatively high and low OEF values (13 hemispheres in each category when a cutoff of OEF of 49% was applied, Fig. 3), the variability of the CBF changes in the primary visual cortex was larger in the hemispheres with lower OEF than in the hemispheres with higher OEF (7.72 ± 5.55 versus 5.62 ± 3.99 ml/100 g/min).

When the baseline values of OEF from the 2 hemispheres for each patient, the CBF changes in the primary visual cortex, and age were entered into a stepwise multiple linear regression analysis, it produced a model for the change of CBF in the surrounding cortex that included the baseline values of OEF and the CBF change in the primary visual cortex: S-CBF change = −0.31OEF − 0.19(V-CBF change) + 17.02, $R = 0.565$, $P = 0.012$. In this model, the baseline values of OEF accounted for 15.3% of the variance for the CBF change in the surrounding region, while the CBF change in the primary visual cortex accounted for 16.7%. The values of OEF in the ICA distribution and the amount of CBF increase in the primary visual cortex were independently and negatively correlated with the change of CBF in the surrounding region (Table 3); the patient age was not a significant independent predictor.

Discussion

This study showed that in some patients with ICA occlusive disease, during visual stimulation, an increase of CBF in the primary visual cortex is accompanied by a decrease of CBF in the surrounding region. This pattern of CBF response during visual stimulation was associated independently with an increased OEF

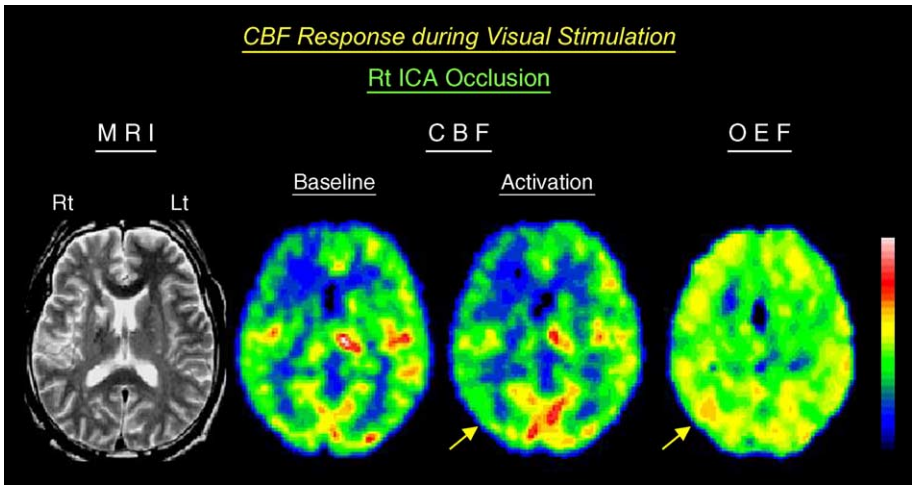

Fig. 2. Examples of PET images of the cerebral blood flow (CBF) obtained at baseline (the second column) and during visual stimulation (the third column), and the oxygen extraction fraction (OEF) in a patient with right (Rt) internal carotid artery (ICA) occlusion and subcortical infarction (the first column). The image of CBF during activation was corrected by dividing by the correction factor: global values (activation)/global values (baseline). CBF decreased during activation in the region surrounding the primary visual cortex (arrow). Increased OEF was found in the hemisphere with ICA occlusion, including the surrounding region (arrow).

(less hemodynamic reserve) in the ICA distribution and a marked increase of CBF in the primary visual cortex.

Several studies in patients with cerebrovascular disease have shown a decrease of the hemodynamic response during neural activation (Carusone et al., 2002; Hamzei et al., 2003; Lee et al., 2001; Pineiro et al., 2002; Powers et al., 1988; Rossini et al., 2004; Röther et al., 2002). Although the reason for the decreased response probably varies (Inao et al., 1998; Yamauchi et al., 2002), one important mechanism may be altered neurovascular coupling due to reduced vasoreactivity (D'Esposito et al., 2003; Rossini et al., 2004). The CBF response during neural activation may be reduced when the vascular tree in the activated region is already dilated due to reduced perfusion pressure (Hamzei et al., 2003; Powers et al., 1988; Rossini et al., 2004; Röther et al., 2002) or has diffuse vascular pathology (Pineiro et al., 2002). However, this mechanism cannot explain the decrease of CBF during visual stimulation in the region surrounding the primary visual cortex in some patients studied here. Another contributing mechanism accounting for the decreased CBF is the redistribution of CBF during activation (Harel et al., 2002). In the hemisphere with less hemodynamic reserve, an increase of CBF in the primary visual cortex may occur at the expense of perfusion of the surrounding region, although the neural activity of the surrounding region is increased. The finding that the decrease in CBF in the surrounding region was associated with a marked increase of CBF in the primary visual cortex supports this mechanism.

The relationship between the CBF changes in the surrounding region and the OEF in the ICA distribution is not simple, because the CBF changes in the primary visual cortex confound this relationship. Therefore, the severity of hemodynamic impairment evaluated by the OEF values does not distinguish the patients who show an increase of CBF and those who show a decrease. Our previous study in patients with cerebrovascular disease showed that the amount of CBF increase during visual stimulation in the primary visual cortex is dependent on the baseline oxygen metabolism in the primary visual cortex (Yamauchi et al., 2002). Thus, we hypothesize that a CBF decrease in regions surrounding the primary visual cortex occurs in patients with normal metabolism in the primary visual cortex and hemodynamic

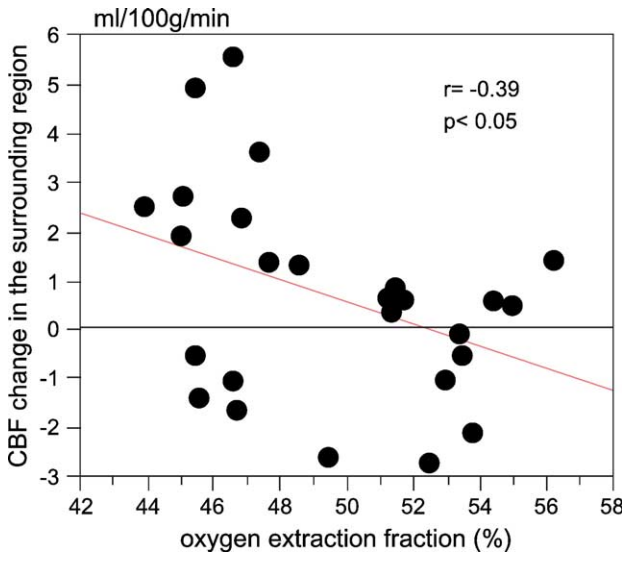

Fig. 3. The relationship of the change of CBF in the region surrounding the primary visual cortex during visual stimulation to the value of oxygen extraction fraction (OEF) in the carotid distribution in patients.

Table 3
Multiple linear regression analysis with the change of CBF in the region surrounding the primary visual cortex as the dependent variable

Variable	Coefficient	Standard error	t	P value
The value of OEF in the carotid artery distribution (%)	−0.302	0.114	−2.91	0.014
The change of CBF in the primary visual cortex (ml/100g/min)	−0.189	0.081	−2.37	0.030
Age (years)	−0.002	0.037	−0.05	0.958

OEF, oxygen extraction fraction.

impairment in the ICA distribution. The increased OEF indicates severe hemodynamic impairment due to ICA occlusive disease, while in patients with normal OEF, the degree of hemodynamic impairment is variable depending on the degree of autoregulatory vasodilation (Powers, 1991). This may be why patients with lower OEF levels show more variability in CBF changes.

The possible development of the redistribution of CBF during neural activation shown in this study has some implications for functional neuroimaging studies. The redistribution of CBF as well as reduced vasoreactivity makes the correlation of neuronal activity and hemodynamic response complex in patients with cerebrovascular disease. A decrease of CBF or BOLD signal (Harel et al., 2002; Röther et al., 2002) during activation does not necessarily imply a decrease of neuronal activity. Furthermore, it changes the regional distribution of the hemodynamic response during activation when multiple brain regions with increased neural activity are located close to each other; for example, when the activation of the primary motor, premotor, and supplementary motor cortices occurs during a complex motor task (Shibasaki et al., 1993). In contrast, the redistribution of CBF supports the notion that there is a significant increase of CBF in the primary activated region even if the hemodynamic reserve of the brain is reduced due to cerebrovascular disease. A PET study showed that in unilateral major cerebral arterial occlusive diseases, CBF increased in both hemispheres with bimanual activation, but CBF increased only in the hemisphere contralateral to arterial disease when acetazolamide was administered (Inao et al., 1998). This suggests that neural activation can induce a nearly normal CBF response in brains with pre-existing vasodilation. The mechanism of vasodilation responsible for activation-induced CBF change may be different in part from the mechanism of autoregulatory vasodilation (Iadecola, 2004; Meyer and Gotoh, 1961). In addition, the present study suggests that the hemodynamic response of the target region may occur at the sacrifice of perfusion of the surrounding region. Thus, an increase of CBF in the primary activated region during a simple stimulation can be used as a qualitative index of local neuronal activity in cerebrovascular disease.

Several factors other than the reduced hemodynamic reserve due to ICA occlusive disease may contribute to the decreased CBF responses to activation in the region surrounding the primary visual cortex. Aging and stroke risk factors, including hypertension and diabetes mellitus, may be associated with reduced hemodynamic response during activation due to a decrease of vascular reactivity (D'Esposito et al., 2003). However, these factors may bilaterally affect the hemodynamic response to visual stimulation in both the primary visual cortex and the surrounding regions. Based on the findings in unilateral ICA occlusive disease in the present study, we believe that the reduction of hemodynamic reserve due to ICA occlusive disease is an important factor causing the decrease of CBF responses to activation in the surrounding region. However, we could not study controls that were matched for age and vascular risk factors. Therefore, it should be determined in future studies whether the redistribution of CBF during neural activation occurs in aged subjects with risk factors for stroke but without ICA occlusive lesions.

The implications of the present findings regarding the pathophysiology of cerebral ischemia are unclear. In the region surrounding the primary visual cortex, the reduced CBF during activation may not be sufficient to meet the increased metabolic demand due to increased neural activity. It is unlikely that the redistribution of CBF causes acute hemispheric ischemic symptoms, because the CBF decreases of at most 3 ml/100 g/min and the resultant CBF values of at most 30 ml/100 g/min during visual activation in our patients do not reach the threshold of acute neuronal dysfunction. However, there is a possibility that the hemodynamic fluctuation associated with neuronal activity may affect the long-term changes of cerebral metabolism in carotid artery disease. Some patients show progression of brain atrophy with the deterioration of cerebral cortical metabolism, without any overt symptoms (Yamauchi et al., 1995, 2000). The CBF threshold for the suppression of protein synthesis may be near the normal flow rate, and the thresholds for disturbances of energy metabolism, unit activity, neurotransmitter release, and histological injury may all increase with time during permanent vascular occlusion (Hossmann, 1994). The fluctuation of the CBF in patients with misery perfusion may cause the inhibition of protein synthesis, which might result in delayed neuronal death with time.

In conclusion, the regional distribution of the CBF response during visual stimulation changes in some patients with ICA occlusive disease. In the hemisphere with less hemodynamic reserve, a marked increase of CBF in the primary visual cortex is associated with a decrease of CBF in the surrounding region. This suggests that the redistribution of CBF during visual stimulation is a contributing mechanism. The possible development of the redistribution of CBF during neural activation should be kept in mind when patients with cerebrovascular disease are studied using functional neuroimaging techniques.

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