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Changes of Neural Activity Correlate With the Severity of Cortical Ischemia in Patients With Unilateral Major Cerebral Artery Occlusion

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Background and Purpose—In major cerebral arterial steno-occlusive diseases, there can be remarkably decreased hemodynamic reserve without marked neurological impairments. In such settings, it is not known whether the neural activity is well maintained or disturbed according to the severity of cerebral ischemia. The present study was therefore undertaken to examine the neural activity under mild cerebral ischemia resulting from major cerebral arterial occlusion.

Methods—Seven patients with minor neurological impairment as well as either unilateral internal carotid artery or middle cerebral artery occlusion were studied. The severity of the cortical ischemia was assessed by measuring regional cerebral blood flow (rCBF) with positron emission tomography. The change in neural activity in the ischemic brain was then evaluated by means of somatosensory evoked magnetic field with magnetoencephalography.

Results—The rCBF in the primary sensory area and the strength of the initial component of somatosensory evoked magnetic field (N20 m) were significantly reduced ($P < 0.01$) and the second component (P30 m) was significantly augmented ($P < 0.05$) in the lesioned cerebral hemisphere as compared with the nonlesioned hemisphere. The asymmetry indexes for N20 m were positively correlated ($r = 0.78$) and those for P30 m were inversely correlated ($r = -0.92$) with asymmetry indexes for rCBF.

Conclusions—In patients with either unilateral internal carotid artery or middle cerebral artery occlusion and minor neural impairments, there was a reduction of afferent signal and an augmentation of the secondary response of the neurons in the primary sensory area. This showed correlation with the severity of cortical ischemia. (*Stroke*. 2002;33:61-66.)

Key Words: cerebral blood flow ■ ischemia ■ occlusion ■ somatosensory evoked potentials

In patients with major cerebral arterial steno-occlusive diseases, it is often seen that only minimal neurological symptoms develop, despite a marked decrease in hemodynamic reserve.¹⁻⁵ In such ischemic brains, it is not known whether the neural activity is actually well maintained or disturbed according to the severity of cerebral ischemia. In our previous study, using positron emission tomography (PET), we showed that there was a nearly normal blood flow response in the primary sensorimotor area after neural activation despite a marked decrease in hemodynamic reserves in patients with internal carotid artery (ICA) occlusion who did not have overt neurological impairments.⁶ However, since PET represents the change in regional cerebral blood flow (rCBF) and metabolism but does not directly measure the neural activity, our previous study could not conclude as to whether the neural activity is maintained, although such patients showed normal blood flow response in the primary

sensorimotor area after neural activation. Therefore, in the present study, we used magnetoencephalography (MEG) to take a direct quantitative measurement of electrical neural activity. We then examined whether the extent of the impairment of neural activity in the lesioned hemisphere correlated with the severity of brain ischemia in patients with major cerebral artery occlusion.

To address the issue, we determined that patient selection was critical for the following reasons. First, it is extremely difficult to evaluate the correlation between the neural damage and the severity of ischemia if the ischemic damage is extensive. This is because the neural activity is lost in the dead neuronal cells. Therefore, the sum of the electric activity in certain damaged areas does not necessarily represent the severity of ischemia. Second, if the area that transfers the electric signals into the neuronal cells in the sensory cortex is damaged by ischemic insult, it also affects the neural activity

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Profile of Patients Studied

Patient	Age, y	Occluded Vessel	Time Since Onset, mo	Neurological Symptoms (Muscle Strength)		MRI	
				At Onset	At Time of Study	Subcortical Infarctions	Regional Cortical Atrophy
S1	75	Left ICA	18	Hemiparesis (4/5) Hypesthesia	Hypesthesia	Small ones in posterior watershed	+
S2	58	Left ICA	24	Hemiparesis (4/5) Hypesthesia	Hemiparesis (4/5) Hypesthesia	Small ones in frontoparietal white matter	+
S3	72	Left MCA	3	Hemiparesis (3/5) Hypesthesia	Hemiparesis (4+/5)	Small ones in anterior watershed	—
T	54	Right MCA	10	TIA (hemiparesis (4+/5), hypesthesia)	None	Small ones in frontoparietal white matter	—
A1	18	Right ICA	22	Hemiparesis (4/5)	None	Small ones in corona radiata	—
A2	49	Right ICA	96	Visual disturbance	None	Small ones in parietal white matter	+
A3	57	Right ICA	10	Floating	None	Not detected	—

ICA indicates internal carotid artery; MCA, middle cerebral artery; and TIA, transient ischemic attack.

Patient T had TIAs before and after entry into the study. Muscle strength was described according to scale of Daniel manual muscle testing.

of neuronal cells in the cortex. Therefore, the patients with severe neurological impairment and/or ischemic lesions including basal ganglia, brain stem, or cervical cord should be excluded from this type of study.

In unilateral occlusion of the ICA or middle cerebral artery (MCA), the area around or posterior to the central sulcus is most susceptible to ischemia because such areas receive their blood supply from the peripheral branches of the MCA. Even mild cortical ischemia caused by ICA or MCA occlusion could result in a significant change of neural activity in the primary sensory area. MEG can measure the neural activity in the primary sensory area by means of somatosensory evoked magnetic field (SEF). Therefore, to determine whether there would be a correlation between the changes in the neural activity and underlying cerebral ischemia, we examined the SEFs and rCBF around the primary sensory area by using MEG and PET in the patients with an occluded ICA or MCA but without severe neurological impairment or extensive ischemic lesions.

Subjects and Methods

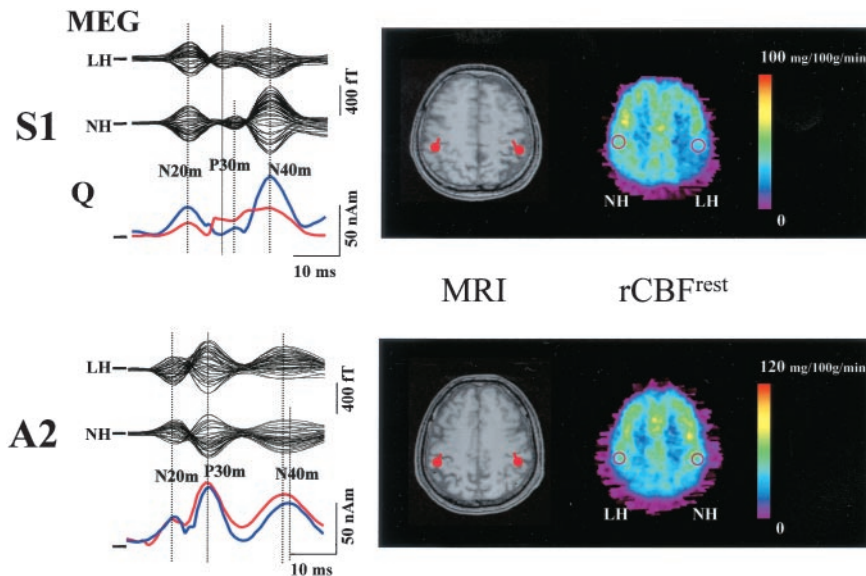
Seven patients (5 men and 2 women) with unilateral complete occlusion of either the ICA or MCA were included in the study (Table). The age of the patients at the time of the study ranged from 18 to 75 years (mean, 52 years). All of the patients were right-handed. The cerebral artery occlusion was diagnosed with the use of cerebral arteriography. Five patients had ICA occlusion and 2 had MCA occlusion. The lesioned side was right hemisphere in 4 patients and left in 3 patients. All of the patients with ICA occlusion had collateral blood flow through the anterior communicating artery. Two patients with MCA occlusion had well-developed collateral blood flow through the leptomeningeal anastomoses from the anterior and posterior cerebral arteries. Patients with dysesthesia, hyperpathia, or cervical spondylosis were excluded from the study.

At the time of the study, 3 patients (S1, S2, S3) had neurological impairment; 1 patient (T) had transient ischemic attacks. The other 3 patients (A1, A2, A3) did not have any kind of neurological impairment. Two patients (S1 and S2) had a permanent and mild reduction of tactile and pain sensation to brush-touch and pin-prick tests in the impaired limbs that was 80% to 90% of the intact limbs, but their joint and vibration sensation was preserved (the patients reported the percentage of subjective sensory reduction in the impaired limb as compared with the intact limb). Patient S3 had both motor and sensory impairment at the onset of the disease, but only

mild motor weakness was observed at the time of the study. Patient T had multiple episodes of transient ischemic attacks with mild sensorimotor impairment in the arm. It was probably because of the well-developed collateral blood flow that the 2 patients with MCA occlusion (S3 and T) had only mild infarct manifestation. Patient A1 had sensorimotor impairment and the other 2 patients (A2 and A3) had visual disturbance and floating sensation at the onset of the disease but were free of such symptoms at the time of the study. The intervals between the initial episode of ischemia and the time of the study ranged from 3 to 96 months (mean, 26.1 months). The muscle strength at the onset and the time of the study are described in the Table, according to manual muscle testing.⁷ T1- and T2-weighted MRIs, 5-mm-thick parallel to the orbitomeatal line, were obtained within 2 weeks before entry into this study. The study was approved by the Institutional Human Use Committees, and written informed consent was obtained from all patients.

Somatosensory Magnetic Field

The magnetic responses of the patients' primary sensory area obtained by electrical stimulation to the contralateral median nerve were recorded with a BTi 37-channel neuromagnetometer (Biomagnetic Technology Inc). The median nerves were stimulated at the wrist by a square pulse with 0.2-ms duration and a strength of 140% above the motor threshold for each subject, ranging from 3.4 to 8.4 mA, at randomized intervals between 600 and 1000 ms with steps of 200 ms. Recording of the magnetic fields started 50 ms before the stimulation and continued for 400 ms. The digital sampling rate was 1041.7 Hz. More than 200 magnetic responses were collected and averaged for each session. The response including deflections extending ± 3000 fT were discarded before averaging. The waveforms were then filtered in the range of 1 to 80 Hz by the fast Fourier transform. At least 2 sessions were performed for each cerebral hemisphere. The single equivalent current dipole (ECD) model was used for the estimation of the strength and the location of the neural activity corresponding to each MEG component.⁸ The criteria for the application of the single ECD model were defined as (1) the correlation between the expected and measured magnetic field must continue to be >0.96 and (2) the dipole must stay at the same location for >10 ms. Only activities satisfying these criteria were included. The magnitude of the estimated ECD moment (Q value) at the peak of each deflection was regarded as the strength of the MEG responses and averaged.⁹ The dipoles were superimposed onto the MRIs with the use of the sensor position indicator of the BTi MEG system. The MEG responses were discarded if their origin was estimated in any cortical area other than the hand area of the postcentral gyrus. The MEG responses evaluated in the present study were the 3 deflections within 50 ms after the median nerve stimulation, designated as N20 m, P30 m, and N40 m, respectively.



rCBF images (red circles), encircling the area corresponding to the ECD location in MRI. Q indicates strength of SEF component; $rCBF^{rest}$, rCBF in the primary sensory area at resting state.

Regional Cerebral Blood Flow

Quantitative measurement of rCBF was performed with the use of the oxygen-15-labeled water ($H_2^{15}O$) autoradiographic method and PET.¹⁰ A HEADTOME IV PET scanner (Shimadzu Co) was used for measurements of CBF.¹¹ The CBF images at resting state were obtained to evaluate the rCBF in the primary sensory area of the lesioned and nonlesioned hemisphere. The CBF images were coregistered to T1-weighted MRIs by the statistical parametric mapping version 99 (SPM99).¹² The anatomic localization of the primary sensory area was identified by overlaying the estimated ECDs for SEF on the MRIs, to which the PET images were coregistered (Figure 1). A circular region of interest containing 100 pixels was drawn on the CBF image, encircling the area corresponding to the estimated ECD location of each cerebral hemisphere. The CBF was calculated by an autoradiographic method, with a lookup table procedure used over a 2-minute accumulation period after the intravenous injection of 1480 MBq of $H_2^{15}O$. The details of the CBF measurement are described in our previous report.⁶

Data Analysis

To evaluate the change of neural activity in cortical ischemia, the peak latency and Q value for these deflections (Q^{N20m} , Q^{P30m} , and Q^{N40m}), and the rCBF around the primary sensory area at rest state ($rCBF^{rest}$) were compared between the lesioned hemisphere (LH) and nonlesioned hemisphere (NH). The statistical significance of the difference between the lesioned and nonlesioned hemispheres (LH/NH difference) was determined by paired *t* test. The asymmetry index for the values was calculated by dividing the values of the LH by that of the NH. The asymmetry index was used to compare the changes of neural activity in the LH among the patients because both the strength of the SEF dipole and the rCBF in the NH varied with the patients, although MRI and PET of all the patients demonstrated no abnormalities in the NH, as described below. A value of $P < 0.05$ was considered significant.

Results

MRIs showed focal cortical atrophy at the primary sensory area and the adjacent parietal cortex in 3 patients (S1, S2, and A2) but no cortical atrophy in 4 patients (S3, T, A1, and A3) (Table and Figure 1). Two or 3 small subcortical infarctions were recognized around the primary sensory area in 5 patients (S1, S2, S3, T, and A2), and 1 patient (A1) had 2 small infarctions in the corona radiata. There was no correlation

between the number/size of the subcortical infarctions and the values for rCBF/SEF. None of the patients had evident lesions in the internal capsule or thalamus of the LH. There were no abnormalities in the nonlesioned cerebral hemisphere or brain stem of any of the patients.

Figure 1 demonstrates the waveforms of SEF in the LH and NH and sequential changes of strength of the SEF response (Q values) for two patients: one with permanent sensorimotor impairment at the time of the study (S1) and one without any neurological impairment at the time of the study (A2). Within 50 ms after the stimulation, there were 3 SEF components at the latencies of 20 ms, 30 ms, and 40 ms, which were named N20 m, P30 m, and N40 m, respectively. In all of the patients, as illustrated in Figure 1, the initial response, N20 m (representing the first cortical response in the primary sensory area), was weaker. The following response, P30 m, was stronger in the LH as compared with the NH. In patient S1, the difference of the Q value at the peak of N20 m and P30 m between the two hemispheres was larger and the reduction of CBF was more remarkable than those in patient A2.

The latency and the Q value of the SEF components and rCBF at resting state ($rCBF^{rest}$) were measured to determine the correlation between SEF and rCBF. The results are given in Figure 2. In all of the patients, the $rCBF^{rest}$ was significantly reduced in the LH as compared with the NH ($P < 0.01$). The SEF components, N20 m and P30 m, could be recorded in all patients, whereas N40 m could not be detected in 1 of the patients. There was no significant LH/NH difference in the peak latencies of the SEF components. The Q^{N20m} in the LH was significantly small compared with the NH ($P < 0.01$). Conversely, the Q^{P30m} in the LH was significantly strong compared with the NH ($P < 0.05$). Q^{N40m} tended to be larger in the LH than in the NH in 5 of the 6 patients whose N40 m could be recorded; however, this did not reach statistical significance. These data suggest that the rCBF at resting state and the first somatosensory response in the primary sensory area are reduced and that the secondary cortical activity is

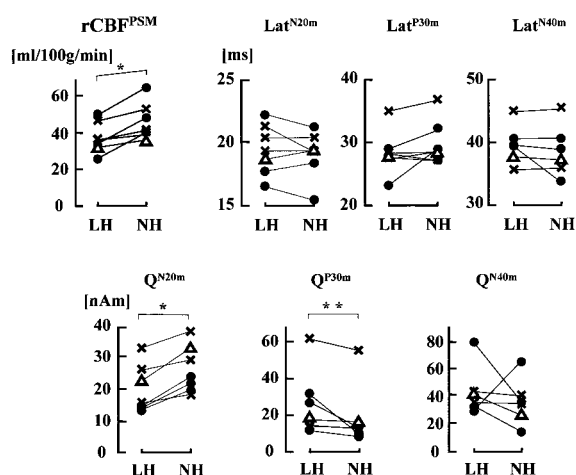


Figure 2. Comparison of rCBF at rest ($rCBF^{rest}$) around the primary sensory area and the latency (Lat^{N20m} , Lat^{P30m} , and Lat^{N40m}) and Q value (Q^{N20m} , Q^{P30m} , and Q^{N40m}) for SEF components between LH and NH. Results obtained from patients with sensorimotor impairment (closed circles) and transient ischemic attacks (open triangles) and those without sensorimotor impairment (crosses) are shown. rCBF and Q for N20 m were significantly smaller and Q for P30 m significantly larger in LH compared with NH. * $P<0.01$, ** $P<0.05$.

augmented in the LH of patients with unilateral ICA or MCA occlusion.

Figure 3A demonstrates the asymmetry index of all patients studied for $rCBF^{rest}$, Q^{N20m} , Q^{P30m} , and Q^{N40m} . The asymmetry indexes for $rCBF^{rest}$ and Q^{N20m} were small and those for Q^{P30m} were large in patients S1, S2, and S3; however, they were close to 1 in patients A1, A2, and A3. In patient T, the asymmetry indexes showed the intermediate value. There was a significant positive correlation ($r=0.78$) between the asymmetry indexes for $rCBF^{rest}$ and Q^{N20m} . In contrast, there was a significant inverse correlation ($r=-0.91$) between the asymmetry indexes for $rCBF^{rest}$ and Q^{P30m} (Figure 3B). These results indicate that the magnitude

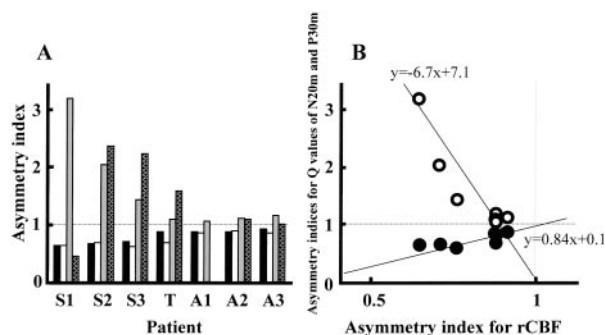


Figure 3. A, Asymmetry index for measured values. Asymmetry index for rCBF at rest (closed columns), the strength of N20 m (open columns), P30 m (gray columns), and N40 m (hatched columns) are shown. Asymmetry index for the strength (Q value) of N20 m was smaller and that of P30 m prominently larger in patients with neurological impairment than in those without. B, Correlation between asymmetry indexes for rCBF and the strength of N20 m (closed circles) and P30 m (open circles). Asymmetry index for rCBF was positively correlated with that of N20 m ($r=0.78$) and inversely correlated with that of P30 m ($r=-0.92$).

of N20 m and P30 m correlates well with the change of rCBF around the primary sensory area of ischemic hemisphere.

Discussion

Evidence indicates that there are 3 identifiable deflections during the first 50 ms of SEF recordings, namely, N20 m, P30 m, and N40 m.^{13–21} N20 m represents the summation of excitatory postsynaptic potentials (EPSPs) of the pyramidal neurons in area 3b located in the posterior wall of central sulcus, as these neurons are excited at their basal dendrites through specific thalamocortical afferent. Although the source of P30 m is controversial, it has been proposed that the source of P30 m is either an EPSP of pyramidal cells in the precentral gyrus and/or the postcentral gyrus^{15,16} or an inhibitory postsynaptic potential of neurons in the postcentral gyrus.²¹ The source of N40 m is considered to be localized around the bottom of the central sulcus (area 3a).²⁰

In the present study, we have shown that there is a marked reduction of the strength of N20 m and a marked increase of P30 m in the LH compared with the NH in patients with unilateral ICA or MCA occlusion. Based on the studies in which the interhemispheric asymmetry in healthy persons was studied,^{22,23} no significant interhemispheric difference in the strength of N20 m and P30 m has been noted at the population level,²³ although in some individuals, the N20 m in the left hemisphere has been shown to be stronger than the right hemisphere. Therefore, the reduction of N20 m and the increment of P30 m in the LH are likely to result from the change in neural activity caused by cerebral ischemia, not from normal variation.

We found a marked decrease of N20 m strength in the LH of the patients with neurological impairment (S1, S2, and S3), whereas there were only minor interhemispheric differences in those without (A1, A2, and A3). Furthermore, there was a significant correlation between $rCBF^{rest}$ and the strength of N20 m, indicating that the extent of the reduction of N20 m correlates with the severity of cortical ischemia. Because N20 m represents the EPSPs of the pyramidal cells in area 3b after median nerve stimulation, decrease of pyramidal cells and interruption of thalamocortical fibers caused by ischemia are likely to result in a reduction of the strength of N20 m. On the other hand, it is known that there is a metabolic depression in thalamus and basal ganglia in the presence of cortical ischemia, and similarly subcortical ischemic lesion induces cortical metabolic depression, which is known as cerebral diaschisis.²⁴ In addition, it has been reported that only severely reduced blood flow impairs neural activity.²⁵ Therefore, the reduction of N20 m might reflect not only the severity of cortical damage but the cerebral diaschisis caused by cortical ischemia.

Our study also showed that the strength of P30 m increased in the patients with neurological impairment and that the increment of P30 m was inversely correlated with the severity of the cortical ischemia. There are two possible interpretations of the augmentation of P30 m: (1) a compensatory amplification of neural activity resulted from new axonal sprouting or the generation of new synaptic connections or (2) an augmentation of neural activity caused by impairment of inhibitory pathways.²⁶ Although in the present study we

could not conclude whether the neural activity generating P30 m is excitatory or inhibitory, the inverse correlation between rCBF at rest and the strength of P30 m has suggested that the neural activity generating P30 m is composed of neural processes that change in a linear association with the ongoing reduction of rCBF. Since there was no relation between the strength of N40 m and the extent of ischemia, the constitution of N40 m might be more complicated in patients with ICA or MCA occlusion.

No information is yet available as to whether there is a relation between neural activity and CBF in human ischemic brains. This is the first study showing that the change of SEF as a measure of neural activity correlates with the reduction of CBF in the patients with regional cortical ischemia. We found documentation of only one study, by Maclin et al,²⁷ which evaluated the changes of the short latency SEFs in patients with unilateral cerebral ischemia. The reduction of N20 m observed in the present study is similar to their study in which the N20 m in the patients with cerebral infarction was reduced and the extent of its reduction was correlated with the patient's ability of graphesthesia. However, their study included patients with severe sensory impairment and/or extensive ischemic lesions involving basal ganglia. It is difficult to evaluate the SEFs in patients with severe sensory impairments by using MEG because their amplitudes are small and can hardly be differentiated from environmental magnetic noise. In addition, the change of SEF could be affected by the disturbance of the signal transfer in the thalamocortical pathway when ischemic lesions are extensive, and thus the change of SEF does not necessarily represent the actual change of the activity of the neurons in the ischemic cerebral cortex. We thus believe that the criteria for patient selection should be confined to patients with minor neurological impairment who do not have any lesion in basal ganglia when evaluating the relation between the neural activity and the extent of cerebral ischemia. We found another report that had evaluated rCBF change by sensorimotor activation task in the patients who recovered from sensorimotor impairment caused by cortical infarction in MCA territory.²⁸ They observed, in their patients, rCBF increases in bilateral premotor areas but not in the sensorimotor cortices. However, 6 of their 7 patients had lesions of 202 to 367 mL, involving the post-central gyrus. We think the lesions of their patients were too extensive to examine neural activity in the primary sensorimotor area.

A number of studies using somatosensory evoked potential have been made in unilateral cerebrovascular lesions.^{28–32} Based on these studies in patients with varying severity of sensorimotor impairment, it has been shown that the amplitude of the primary complex (N20-P30) and the following deflections were attenuated when the ischemic lesions involved parietal cortex. However, no information is available as to the somatosensory evoked potential in patients with minor sensorimotor impairment. In the present study, we have shown that (1) the N20 m is attenuated, whereas the P30 m is augmented in all our subjects and (2) that the N40 m is not attenuated in 5 of 6 patients in the LH compared with the NH (Figures 2 and 3). These data suggest that the generation of all of N20 m, P30 m, and N40 m are impaired when

ischemia is extensive, whereas the generation of N20 m is impaired but P30 m is augmented when ischemia is mild. The augmentation of P30 m may be due to either an amplification to compensate for the reduction of the afferent signal or a disinhibition of neural activity after mild ischemia. This is suggested by our data that the reduction of N20 m and the increment of P30 m correlated with the severity of ischemia.

We examined the neural activity under mild regional cortical ischemia around the primary sensory area in patients with minor neurological impairment and observed a significant correlation between the rCBF and the neural activity. We believe that such results can be obtained when patient selection is confined to such conditions.

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