Original Research

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Hemodynamic response following neuronal activity in cases with severe stenosis of the cervical internal carotid artery and its serial change through carotid artery stenting

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●Abstract●

Objective: Regional cerebral blood flow (CBF) increasing focally at sites of neural activity is called "hemodynamic response (HDR)". In cases with severe cerebral ischemia, HDR may be disturbed and cause disruption of normal neuro-vascular coupling. HDR was measured during a motor task using functional near infrared spectroscopy (fNIRS) in cases with severe cervical internal carotid artery (ICA) stenosis before and after carotid artery stenting (CAS). Ischemia and the influence of therapy for it on HDR was analyzed.

Methods: Seventeen right-handed patients with severe cervical ICA stenosis admitted for CAS were examined. fNIRS during a motor task was performed and concentration changes in oxygenated hemoglobin (HbO2), deoxygenated hemoglobin (HbR), and total hemoglobin (tHb) were calculated in these patients in addition to routine evaluations. The same measurements were repeated after CAS and serial data were evaluated. In order to analyze the relevance of HDR to CBF status, Xenon-enhanced computed tomography (Xe-CT) was performed before and after CAS.

Results: Some abnormalities in the HDR curve and its recovery after CAS were detected, including a delay in peak time of tHb concentration, of more than 10 seconds during the 20 second stimulation, in 9 cases. $TTP^{0.7}$ (time to peak) value, defined as the time to reach seventy percent of maximum tHb concentration, was observed to be higher in patients with low CBF at rest before CAS. In the group with a high $TTP^{0.7}$ value, CBF at rest before CAS was lower than 35mL/100g/min., significantly lower than the group without a high $TTP^{0.7}$ value ($P<0.01$). Additionally, in the group with a high $TTP^{0.7}$ value, CBF increase after CAS was significantly higher than the group with a lower $TTP^{0.7}$ value ($P<0.01$).

Conclusions: In some cases with severe ICA stenosis, cortical hemodynamics, and oxygen metabolism during functional activation are disturbed, and CAS can modulate these changes. This result is important in that intervention for cervical IC stenosis can not only reduce ischemic events, but also influence cortical hemodynamics during functional activity.

●Key Words●

carotid artery stenting, hemodynamic response, internal carotid artery stenosis, ischemia, near-infrared spectroscopy

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Introduction

It is a widely accepted theory that cerebral blood flow increases focally at neural activity sites in the normal cortex[23]. This phenomenon is called hemodynamic response (HDR), a physiological mechanism to maintain normal cortical function. However, increase in cerebral blood flow (CBF) was reported to be several times greater than needed in positron emission computed tomography (PET) studies[8]. Although the reason for this marked increase in oxygenated blood has not been elucidated, this observation has become a firm basis from which many functional methods, such as PET, functional magnetic resonance imaging (fMRI)[20], and functional near-infrared spectroscopy (fNIRS)[14] are derived. From the viewpoint of neuro-vascular coupling during functional activity, HDR plays an important role on the vascular side in order to supply enough energy to neural cells. In cases with severe cerebral ischemia, HDR may be disturbed and can cause disruption of normal neuro-vascular coupling during functional activity.

fNIRS is a developing neuroimaging technique that can simultaneously and non-invasively measure relative concentration changes of oxygenated hemoglobin (HbO2), deoxygenated hemoglobin (HbR), and total hemoglobin (tHb)

in the human cortex[13,14]. HbR is closely related to blood oxygen level dependent (BOLD) signal in fMRI[20], and tHb parallels cerebral blood volume (CBV)[25]. This methodology has the virtue of high temporal resolution (100 milliseconds), suitable for close observation of the time course of hemoglobin concentration change in the functional cortex.

The primary purpose of carotid artery stenting (CAS) is to reduce the risk of future stroke in patients with severe cervical internal carotid artery (ICA) stenosis[10]. However, CBF status must be considered before and after CAS in addition to future ischemic events. From a clinical standpoint, hemodynamic stroke, cerebral atrophy, and higher cortical function impairment are attributable to persistent hypoperfusion pre-operatively, while intracortical and subarachnoid hemorrhage, epilepsy, or confusion are attributable to hyperperfusion post-operatively.

HDR during a motor task was measured using fNIRS in cases with severe cervical ICA stenosis during the peri-operative period. Relationship between disturbed HDR and CBF status during CAS was analyzed. This study aimed to elucidate how ischemia influences cortical functional activity and how revascularization influences this "functional activation under ischemia" using a novel approach.

Materials and Methods

1. Subjects

Seventeen right-handed patients (16 males and 1 female, mean age: 73.7± 6.5 years) with severe cervical internal carotid artery (ICA) stenosis admitted to this hospital for CAS were examined. Inclusion criteria for this study were as follows. 1) Severe ICA stenosis of greater than 70% based on NASCET measurements[10], confirmed by digital subtraction angiography (DSA). 2) Successful performance of the full task in this study, as described later. 3) No apparent infarcts in the primary motor cortex (M1) on MRI. Infarcts were defined as hyperintense focal lesions of at least 3 mm in diameter, on T2-weighted images. All the subjects provided written informed consent after receiving a full explanation of the study.

2. Methods

fNIRS and Xenon enhanced computed tomography (Xe-CT) were performed in these patients in addition to a routine work-up, such as DSA, cervical ultrasound, non-enhanced cervical computed tomography, CT angiography, and anatomical MRI.

1) NIRS measurement

For NIRS-imaging measurement, we used a three-wavelength (780, 805, and 830nm) NIRS-Imaging system (OMM2001, Shimadzu, Japan) consisting of emitting and detecting optical fibers. Detecting optical fibers were attached to a square pad placed on the affected side of the hemisphere. The distance between each fiber was 3 cm. The midpoint of each two fibers, at a depth of 1.5 to 2 cm on the cortical surface was the detecting point[14]. In order to record specific oxygenation change in and around the M1 during motor tasks, the central detecting channel was set to the estimated hand area of M1, just anterior to the central sulcus and 6 cm lateral to the midline measured along the course of the sulcus. The sulcus was determined from the Taylor Haughton line using surface anatomical landmarks[9,21,26] (a line connecting a point 4 cm posterior to bregma, and the intersection of the condylar line and Sylvian fissure). In order to confirm that the measured area was located at the designated M1, MRI was taken in two patients with a skin marker, a vitamin E capsule. The sampling time of data acquisition was 130ms. Each patient was instructed to close his/her right hand repetitively into a fist at a pace of 1.5Hz for a period of 20 seconds, then to rest for 20 seconds in each trial. All patients practiced the motor task for more than 3 minutes before experiments, so that everyone could perform the task fluently. During the experiment, the same examiner continuously monitored their task performance. Ten consecutive trials were conducted for each subject and time-locked averaging was performed after eliminating trials that contained inappropriate signals, such as motion artifacts or incomplete task performance.

The same measurements were repeated seven to ten days after surgery and serial data were evaluated. Task performance including pace and force of hand grasping was monitored by the same examiner and confirmed to be the same between the pre-operative and post-operative sessions.

2) Xenon enhanced CT

Xe-CT was performed to measure hemispheric CBF (mL/100g/min) using xenon inhalation, with and without acetazolamide loading, before CAS in all patients, and without acetazolamide 3 to 5 days after CAS in 16 patients. Multi-slice CT was performed with an Aquilion 16 (Toshiba, Japan) and xenon inhalation equipment (XETRON-VI; Anzai Medical, Japan). Vascular reserve capacity is defined as "(CBF after acetazolamide loading-CBF at rest)/(CBF at rest) ×100 (%))" and CBF increase ratio is defined as "(CBF after CAS-CBF before CAS)/ (CBF before CAS) ×100 (%))".

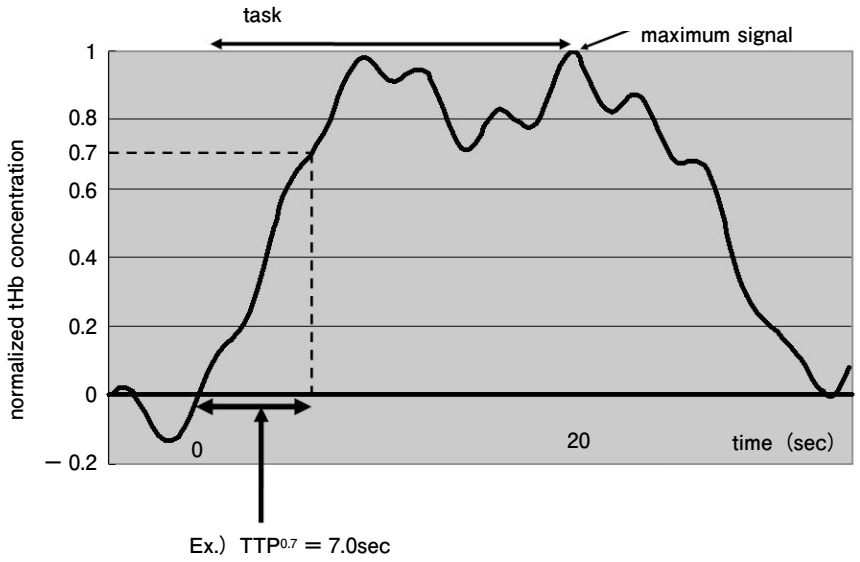

Fig. 1 Schematic illustration of $TTP^{0.7}$ as the time (seconds) to reach seventy percent of maximum tHb concentration. Since peak concentration of tHb fluctuates from 10 to 20 seconds forming a plateau, it is difficult to determine the time to maximum signal ($TTP^{1.0}$). On the other hand, $TTP^{0.7}$ in this figure is easily determined as 7 seconds.

3. Carotid artery stenting (CAS)

CAS was performed on 17 patients, including two patients with bilateral IC stenosis. Standard CAS technique for this country at the time of the study was employed using a transfemoral or transbrachial approach with distal embolic protection device (PercuSurge Guardwire ® system; Medtronic, Minneapolis, MN, USA)[11] using a Nitinol stent (Precise® or SMART stent®; Cordis, Warren, NJ, USA).

4. Data processing

Changes in HbO2, HbR and tHb, were calculated using differences in the absorption indices at three wavelengths as described below[16].

$$HbO2 = (-1.4887 \times \Delta Abs780nm) + (0.5970 \times \Delta Abs805nm) + (1.4847 \times \Delta Abs830nm)$$

$$HbR = (1.8545 \times \Delta Abs780nm) - (0.2394 \times \Delta Abs805nm) - (1.0947 \times \Delta Abs830nm)$$

$$tHb = HbO2 + HbR = (0.3658 \times \Delta Abs780nm) + (0.3576 \times \Delta Abs805nm) + (0.39 \times \Delta Abs830nm)$$

The hemodynamic response curve (HDR curve), consisting of the time course of concentration changes in HbO2, HbR, and tHb in each patient before and after CAS, was observed.

As described later, a time delay in reaching maximum tHb concentration during the motor task was the most prominent feature in this patient group. In order to analyze this feature quantitatively, a parameter which describes this condition properly needs to be defined. Time to peak concentration (TTP), commonly used in fMRI studies[15], can illustrate this condition, although it can sometimes be inaccurate in a strict sense as the peak and plateau concentrations may fluctuate, even in normal adults. Thus, time (seconds) to reach seventy percent of maximum tHb concentration was adopted to describe this parameter ($TTP^{0.7}$, **Fig. 1**), as it is not influenced by this fluctuation, and therefore is empirically stable under any conditions. These data were then analyzed, specifically focusing on the relationship between $TTP^{0.7}$ and CBF.

Results

CAS was performed successfully on 18 sides of ICA stenosis in 17 patients, including 2 cases of staged-bilateral stenting. One case ended in a trial only due to difficulty in accessing the lesion. No patient developed symptomatic hyperperfusion syndrome, however one had a minor post-operative stroke. Mean CBF before and after CAS were 34.8 ±7.9 and 35.9±7.5mL/100g/min. (±SD), respectively. Mean vascular reserve capacity before CAS was 37.1% and mean CBF increase ratio was 5.2%.

1. fNIRS measurement

In half of these cases, typical activation patterns in M1 similar to those reported previously[2] in normal adults were observed. They consisted of a rapid increase followed by a plateau in HbO2 and tHb concentration, plus a decrease in

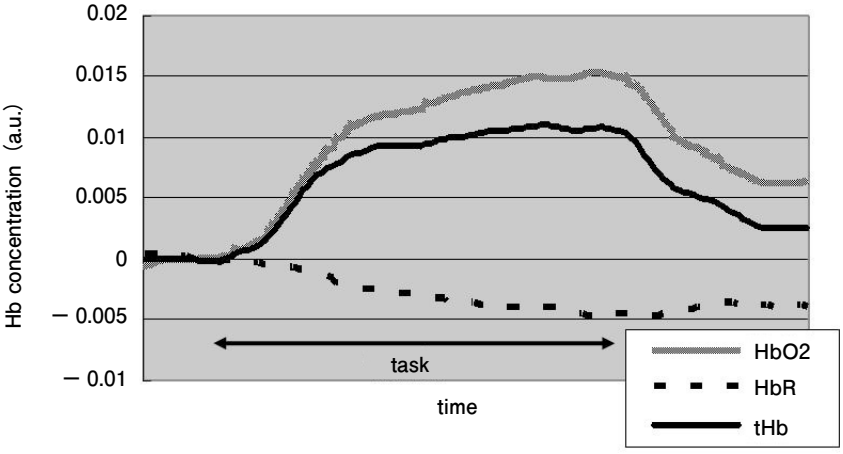

Fig. 2 Typical time course of relative hemoglobin concentration change in M1 observed in half of the patients, which consists of a rapid increase followed by a plateau in HbO2 and tHb concentration, and a decrease in HbR concentration. This pattern is identical to those reported previously in normal adults[28].
a.u.: arbitrary unit

HbR concentration, as shown in **Fig. 2**. This pattern did not show any change after CAS. In some cases, abnormal activation patterns in M1 were observed, such as persistent HbR increase or lack of HbR decrease. These changes will not be discussed further in this study as they have been described previously[18].

A distinctive feature observed for 9 cases was a time delay to peak tHb concentration of more than 10 seconds. Mean $TTP^{0.7}$ was 9.2±3.5sec. Measurements after CAS showed recovery of these abnormal responses in some cases.

Here, a representative case that showed a marked time delay in peak tHb concentration before CAS, and its recovery after treatment is presented.

2. Case illustration

The patient is a 72-year old male with a history of transient ischemic attack of his right hand, referred to this hospital for CAS. Pre-operative examination indicated some abnormalities as follows. DSA showed severe bilateral cervical ICA stenosis with 85% stenosis on the right and 99% on the left using the NASCET method (**Fig. 3A**). Right vertebral angiography showed a collateral blood supply from the left posterior cerebral artery and the left posterior choroidal artery into the left ICA territory (**Fig. 3C**). Xe-CT studies showed bilaterally reduced CBF at rest (28.8 and 28.5mL/100g/min. in the right and left hemispheres, respectively) and reduced vascular reserve capacity (67 and 12% in the right and left hemispheres, respectively). The HDR curve for tHb in this patient before CAS indicated a marked time delay in peak tHb concentration (**Fig. 4**, black line) and a $TTP^{0.7}$ value of 14 seconds. CAS on the left ICA stenosis was successfully performed (**Fig. 3D**) using a transbrachial approach with a distal embolic protection device (PercuSurge Guardwire®) and self-expandable Nitinol stent (Precise®: 9mm ×40mm). Post-operatively, major and minor adverse events did not occur, including symptomatic hyperperfusion syndrome. CBF studies 5 days after CAS showed a marked increase in CBF at rest in the left hemisphere (CBF increase ratio: 36% and 40% in the right and left, respectively). tHb concentration changes during a motor task after CAS showed a recovery from abnormal HDR curve (**Fig. 4**, broken line) and $TTP^{0.7}$ value was reduced to 5 seconds.

3. Group analysis

Relationship between pre-operative $TTP^{0.7}$ and pre-operative CBF at rest was examined. As plotted in **Fig. 5**, a group with a high $TTP^{0.7}$ value (circled) had pre-operative CBF at rest of less than 35mL/100g/min. Detailed analysis indicated that mean pre-operative CBF at rest in the group with a high $TTP^{0.7}$ value (> 10 seconds) was 30.8±3.9mL/100g/min., significantly lower than the group with a lower $TTP^{0.7}$ value (< 10 seconds), 37.9±8.9mL/100g/min. ($P<0.01$; unpaired t test).

Relationship between $TTP^{0.7}$ and CBF increase ratio (defined in the "Methods" section) was then analyzed. Higher $TTP^{0.7}$ values (> 10 seconds) before CAS were observed in most cases with a higher CBF increase ratio (> 15%), as shown in **Fig. 6**. In the high $TTP^{0.7}$ group, CBF increase ratio was 16.7%, significantly higher than -3.5% in the low $TTP^{0.7}$ group ($P < 0.01$; unpaired t test).

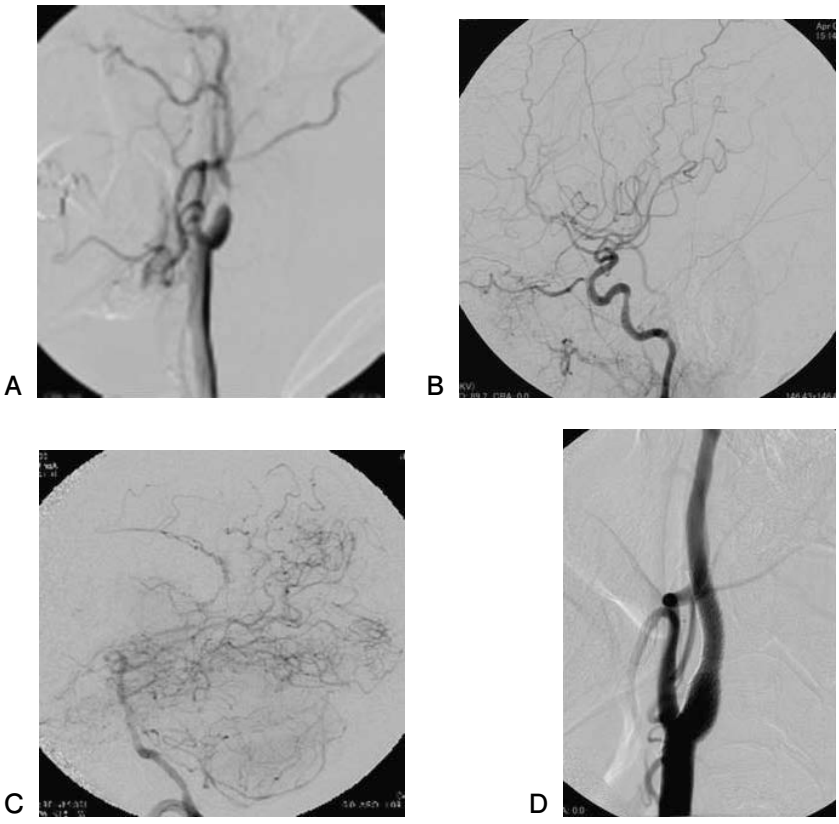

Fig. 3 Digital subtraction angiography of the presented case

A：Left cervical common carotid angiography (lateral view) before CAS, showing 99% stenosis of the ICA.

B：Left intracranial common carotid angiography before CAS (lateral view).

C：Right vertebral angiography before CAS (lateral view), showing collateral blood supply from the posterior cerebral artery into the ICA territory.

D：Left cervical common carotid angiography (lateral view) after CAS, showing remission of ICA stenosis.

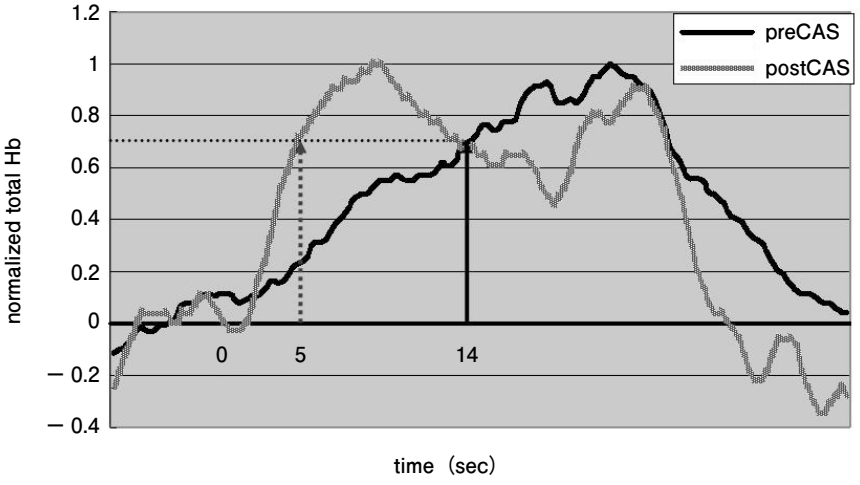

Fig. 4

Comparison of the time course of normalized tHb concentration change in M1 during motor task before (black line) and after (broken line) CAS of the presented case. HDR curve of tHb before CAS reveals a marked delay of time to peak tHb concentration and $TTP^{0.7}$ value is 14 seconds (black arrow). tHb concentration change during motor task after CAS shows recovery of HDR curve and $TTP^{0.7}$ value is reduced to 5 seconds (dotted arrow).

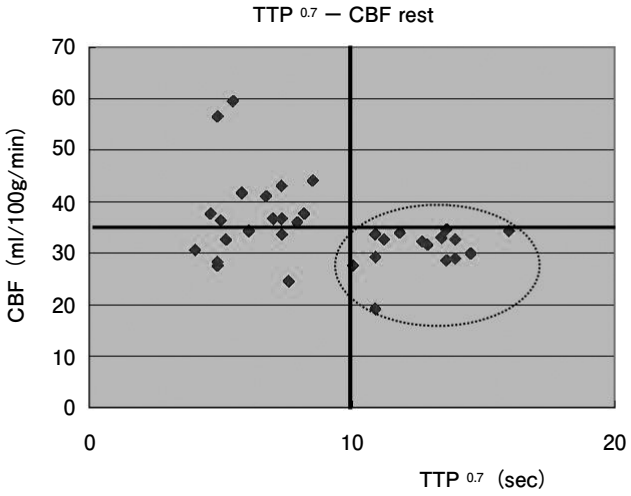

Fig. 5
Scattergram indicating the relationship between $TTP^{0.7}$ value (X-axis) and CBF at rest before CAS (Y-axis). In the group with high $TTP^{0.7}$ value of more than 10 seconds (circled), CBF at rest before CAS is lower than 35ml/100g/min.

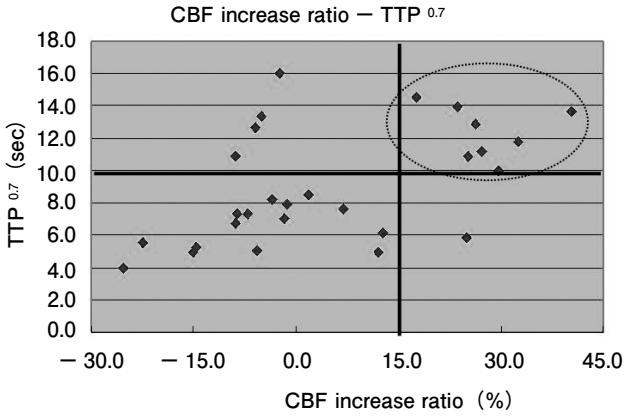

Fig. 6
Scattergram indicating the relationship between CBF increase ratio (X-axis) and $TTP^{0.7}$ value (Y-axis). In most cases with high CBF increase ratio of more than 15% (circled), $TTP^{0.7}$ values are higher than 10 seconds.

No distinct relationship was observed between vascular reserve capacity before CAS and $TTP^{0.7}$.

Discussion

1. Hemodynamic response and ischemia

Cortical oxygenation status during functional activation is made up of roughly two factors, oxygen consumption (oxygen exchange between neural cells and cortical capillaries) and blood flow change (oxygenated blood influx) in and around the activated cortex. Several methodologies, such as optical studies[19], direct oxygen measurement[27], near-infrared spectroscopy[2], and functional MRI[17], indicated that the time course of HDR is divided into two phases at the center of the activated cortex, and is undivided in its periphery. At the center of the activated cortex, the early phase shows deoxygenation due to oxygen exchange between activated cells and capillaries without enough oxygenated arterial blood influx into the activated cortex[2]. The late phase shows cortical oxygenation due to abundant oxygenated blood inflow into the activated cortex, that contains several times the needed oxygen. In the periphery of the activated cortex, a monophasic pattern of increased blood flow is observed, as oxygen consumption does not exist. Substantially, the late phase response at the center of the activated cortex and the monophasic response in the periphery of the activated cortex are equivalent, in the sense that both are representations of excessive arterial blood influx. In this study, how the blood inflow changes during the late phase of functional activation in the ischemic cortex was focused on.

Increased inflow of oxygenated blood is triggered by metabolic demands of increased neural activity, which shows an immediate rise and grows to a maximum value at about 5 sec. for a short-duration stimulus[12,19]. If the neural activity is sustained for longer periods, the amplitude of the peak is not summed, but is maintained at the same level forming a plateau, as saturation of cortical oxygenation would occur. Thus, twenty seconds of motor stimulation would form a typical HDR pattern peaking at around 5 to 10 seconds, followed by a plateau until 20 seconds in the normal cortex, also observed in half of the cases in this study (**Fig. 2**).

Almost half of the patients in this study showed this typical response before CAS, indicating that a normal functional activation pattern is preserved in some cases despite severe ICA stenosis. However, in other cases, an immediate rise in tHb, peaking within 10 seconds after motor stimulation, was not observed. Instead, gradual increases were seen throughout the 20 seconds of stimulation time in these cases. All but one of the patients that showed a delay in the increase of tHb during functional activity, defined as a high $TTP^{0.7}$ value, had decreased CBF at rest before CAS. This result implies that a high $TTP^{0.7}$ value during functional activity can be an indicator of cerebral ischemia. The reasons these patients do not form a "peak and plateau" pattern, but show a "gradual increase" might be the following. As reactivity for increasing blood flow in response to motor stimulation might be reduced in the ischemic cortex, a few stimulations are not sufficient to raise CBF and cause saturation of oxygenation status in the activated cortex. Thus, the amplitude of the peak is

sequentially summed until saturated, sometimes throughout the entire stimulation period, forming a "gradual increase" pattern that cannot be observed in the normal cortex. This hypothesis strongly relies on the viewpoint that disturbance of HDR is caused by insufficient neurovascular-coupling, not by abnormal neuronal function itself, although evidence to fully support this theory is not sufficient in this report.

2. Relevance of disturbed HDR to conventional CBF studies and their clinical application

In addition to the HbR increase at the center of the motor cortex and intracortical steal phenomenon previously reported[1,18], in cases with severe cervical ICA stenosis, a time delay to the peak activation signal was observed during motor stimulation in this study. This result suggests that a small group of patients with cervical ICA stenosis are not only at potential risk of developing ischemic events in the near future, but are also currently disturbed in cortical microcirculation during functional activity. Most of these abnormal findings were partially relieved after CAS, also supporting the implication that abnormal signals during functional activity are closely related to cortical ischemia. The fact that HDR is disturbed during functional activity in patients with cervical ICA stenosis is very important when considering their higher cortical function.

Hyperperfusion syndrome is a devastating condition, leading to cerebral hemorrhage, epilepsy and other severe clinical consequences[5]. This is one fatal complication after CAS that must be carefully avoided[3]. This phenomenon is related to disturbed autoregulation of cerebral vessels or a loss of vascular reserve in a certain group of patients with ischemic cerebral vascular disease. Changes in several parameters, such as CBV, oxygen extract fraction, and cerebral metabolic rate of oxygen in PET studies[4,22,24], a decrease in the CBF resting state and impaired increase in CBF under acetazolamide administration in single photon emission computed tomography (SPECT) studies[6,7] are reported to be indicators of ischemic CBF status. Once the hyperperfusion syndrome occurs, it demonstrates high morbidity and mortality, despite various countermeasures. Thus due caution to prevent hyperperfusion is definitely required. In this study, marked CBF increase after CAS was related to high $TTP^{0.7}$ values before CAS. As we did not have any cases with symptomatic hyperperfusion syndrome in this study, we cannot conclude that abnormal HDR is a definite predictor of hyperperfusion syndrome. However, a high $TTP^{0.7}$ value before CAS might prove to be useful in assessing its risk during the perioperative time after accumulation of substantial data. fNIRS cannot become a substitute for PET or SPECT with acetazolamide infusion at present due to the scarceness of data and lack of ability to measure CBF quantitatively. However, in the future, it has the potential to be an important tool to evaluate pre-operative CBF status, as the result of fNIRS derived from functional activation is more close to physiological phenomenon than data from the other CBF studies that depend on chemically induced CBF changes. fNIRS is a totally noninvasive technique using only infra-red light, compared to PET and SPECT that use chemical agents, including acetazolamide, and require exposure to radiation.

In this study, only one case showed both a decrease in the resting state CBF and impaired increase under acetazolamide administration, defined as stage Ⅱ ischemia by Powers classification[22]. Decrease in CBF at rest was observed in many cases, however disturbance of the cerebral vascular reserve (CVR) was not. The reason that there was no significant relationship between CVR and TTP might be attributed to the paucity of cases with CVR disturbance.

Important changes of HDR and their relevance to cortical ischemia were detected in this study. However, they are not sufficient in elucidating the complex mechanism of functional activity and cerebral blood circulation. For example, no cognitive tests were performed in this study, therefore no data concerning the relationship between real-life cortical function and HDR during functional activity was obtained. fNIRS was measured 7-10 days after CAS. However, we are not confident that HDR can be fully restored until 10 days after CAS. Furthermore, we do not have enough data on detection of hyperperfusion syndrome after CAS in this study, although we have shown that the fNIRS study before CAS has potency to forecast post-operative CBF increase. This report is a preliminary one that includes only CAS cases. Comparison of CAS and CEA cases and further exploration are still required to address these questions.

Conclusion

In some cases with severe ICA stenosis, there is not only the risk of developing stroke in the future, but also current disturbance of neuro-vascular coupling during functional activation. Vascular reconstruction including CAS can modulate these changes. This result is important in that intervention in cervical ICA stenosis can influence cortical hemodynamics during functional activity, as well as reduce future ischemic events.

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