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＜研究報告＞

Cortical tissue oxygenation during static handgrip exercise and postexercise muscle ischemia

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Abstract

The present study examined the time course of cerebral oxygenation in sensorimotor (SM) and prefrontal (PF) cortices during right hand exercise and postexercise muscle ischemia by near-infrared spectroscopy (NIRS). Fourteen healthy volunteers performed a 3-min sustained handgrip exercise (SHG) followed by a 6-min recovery period (Control). Subjects also underwent the experiment of postexercise muscle ischemia (PEMI) experiment in which arterial blood flow in the right upper arm was arrested immediately after SHG. The oxygenated hemoglobin (oxyHb), deoxygenated hemoglobin (deoxyHb) and total hemoglobin (totalHb) were measured from the left PF and SM areas by NIRS. Mean arterial blood pressure (MAP) and heart rate were simultaneously measured by a Finometer and ECG recordings. During SHG, the oxyHb and totalHb increased significantly from preexercise levels in PF and SM with a reciprocal decrease in deoxyHb. The time course of oxyHb and totalHb was similar to that observed in the MAP responses during SHG. After SHG, the oxyHb and totalHb sustained the increased levels during PEMI in both PF and SM whereas those in Control returned to the preexercise level. These results suggested a significant increase in the regional cerebral blood flow resulting from neuronal activation in both PF and SM during SHG and PEMI.

Key words: near-infrared spectroscopy sensorimotor cortex, prefrontal cortex, regional blood flow

Introduction

It is widely accepted that the increase of arterial inflow couples with the increased metabolic demand due to neuronal activation in the cerebral tissues (*Fox & Raichle 1986 ; Hoshi et al. 2001 ; Huppert et al. 2006 ; Kato et al. 1993 ; Kleinschmidt et al. 1996 ; Rostrup et al. 2002*). Positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) techniques have directly demonstrated increases in regional cerebral blood flow over cortical areas such as sensorimotor (SM) and prefrontal (PF) cortices during motor tasks (*Benwell et al. 2005 ; Friedman et al 1991 ; Fox and Raichle 1996 ; Kato*

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et al. 1993 ; Liu, et al. 2003) ; however, these techniques do not allow the time courses of cortical oxygenation during sustained handgrip exercise. Near infrared spectroscopy (NIRS) can provide a non-invasive and continuous measurements of cerebral oxygenation during exercise. This technique is based on the differential absorption properties of chromospheres in the near infrared region, i.e. between 700 and 1000 nm. The validity of NIRS in evaluating changes of cerebral oxygenation and blood volume has been established under a variety of experimental conditions including : jugular bulb venous oxygen saturation which is considered an index of mixed cerebral oxygenation (*Pollard et al. 1996*), blood oxygen level dependent (BOLD) changes measured by functional MRI (*Kleinschmidt et al. 1996*).

Doppler ultrasound measurements of mean flow velocity in the middle cerebral artery (MCA) revealed a significant increase of flow velocity in MCA during static and rhythmic handgrip exercise (*Ide et al. 1998 ; Giller et al. 2000 ; Pott et al. 1997 ; Sadamoto et al. 2005*), The blood volume flow in internal carotid artery (ICA), locating in the upstream artery of MCA, also increased from the preexercise resting level during static handgrip exercise (SHG) in our previous study (*Pott et al. 1997 ; Sadamoto et al. 2005*). In addition, these increases in arterial inflow of MCA and ICA were shown to be sustained during postexercise muscle ischemia (PEMI) (*Sadamoto et al. 2005*). However, we do not know the time course of cerebral oxygenation during SHG and PEMI. In addition, it has not yet been identified where the increased arterial flow directed to the cerebral tissues. Thus, a limitation of the previous finding was no identification of the localized cerebral oxygen status in the brain. Neurophysiologic studies with transcranial magnetic stimulation (*Gandevia et al. 1996*) and fMRI (*Benwell et al. 2005 ; Fox and Raichle 1996 ; Kato et al. 1993 ; Liu, et al. 2003*) and PET (*Friedman et al. 1991*) studies indicated cortical activation in SM and PF areas during sustaining handgrip contraction.

From these considerations, the present study is designed to examine the time course of the regional oxygenation in PF and SM areas in cortices during SHG and PEMI by using NIRS technique.

Methods

Subjects.

The fourteen female volunteers whose mean age was 21 ± 0.2 yr participated in the present study. Their average weight and height and maximum voluntary contraction of handgrip were 56 ± 2 (SD) kg, 159 ± 2 cm, and 32.2 ± 1.2 kp, respectively. None had any significant medical problems, and all were considered to have normal cardiovascular functions on the basis of normal medical history and physical examinations. All subjects gave informed written consent to participate in this study before the start of experiments. Volunteers abstained from caffeine for 18 hours before the study. All subjects were familiarized with the testing apparatus of experiments. The aim and protocols in the present study were approved by the Guiding Principles for Human Studies of Ethical Committee in the Japan Women's College of Physical Education".

Study protocols.

Experimental protocol followed our previous study in which arterial flow velocity of MCA and blood flow volume of ICA was determined by ultrosonogrphy (*Sadamoto et al. 2005*). The subjects reported to our laboratory on three days for control and occlusion experiments separated by 2–7 days. All experiments were

conducted in a well-ventilated laboratory regulated at 24±1℃. On the first day, the subject performed maximum voluntary contraction (MVC) of handgrip of the right hand. The MVC was determined as the highest value of three trials of 3s. Thereafter, subjects practiced to sustain handgrip exercise used in the present study and experienced measurements of NIRS. On the second or third day, control (CON) or occlusion (OCCL) experiment was conducted. Subjects rested in a sitting position for 10–15 min while preexercise baseline levels of all parameters were measured. Then, the subject performed a sustained handgrip exercise (SHG) with a ramp load increasing from 10% to 30% of MVC for 3 min followed by a 6-min recovery period in CON experiment. After 20- to 30-min rest, OCCL experiment was conducted. The subject performed the same exercise and arterial blood flow in the right upper arm was arrested for 3 min in the recovery period. The postexercise muscle ischemia (PEMI) was initiated by inflating a previously placed arm cuff to 250 mmHg immediately before the handgrip exercise was ended. The target force, ramp load from 10 to 30% MVC, was displayed on a cathode-ray tube display placed in front of the subject. The subject could easily adjust the generating force to the target force during SHG because of the practice done on the first day.

Near-infrared spectroscopy (NIRS).

We used an NIRO-300 spectrometer (Hamamatsu Photonics, Hamamatsu) to monitor oxygenated (oxyHb), deoxygenated (deoxyHb), and total hemoglobin (totalHb) in the left prefrontal (PF) area. The method is explained elsewhere in detail (*Cope and Delpy 1988*). The multi-channel NIRS topography system (OMM 3000, Shimazu, Kyoto) was also used to monitor oxyHb, deoxyHb, and totalHb in the left sensorimotor (SM) area, of which optodes

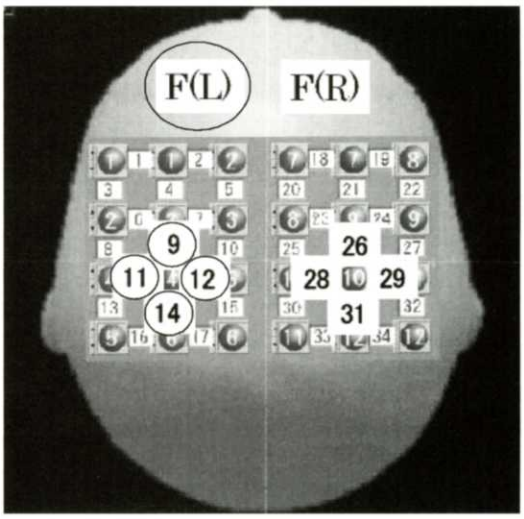

Fig. 1 Measurement sites for cerebral tissue oxygenation
Near-infrared spectroscopy (NIRS) probes were placed at left prefrontal [F (L)] and left sensorimotor areas (9-11-12-14) according to the international 10–20 system for EEG electrode placement.

placed tightly on the skull using a holder cap fabricated from custom-made thermoplastic resin (**Fig. 1**). The center of the 4 light source optodes was located in the C 3 portion which was determined according to 10–20 system for EEG. Four light sources (No 9, 11, 12, 14) around one detector optode (C 3) were placed of which interoptode distance was set to 3.0 cm.

Cardiovascular measurements.

Mean arterial blood pressure (MAP) was recorded continuously from the third finger on the left arm by non-invasive plethysmography with a Finometer (Finapres Medical Systems BV, Amsterdam). Electrocardiogram (ECG) was recorded continuously through lead II (68 M2, NEC-Sanei, Tokyo). A force transducer (Kyowa-Dengyo, Tokyo) was used to measure the force of muscle contractions. The analog data of the Finometer, HR, and muscle force

were continuously recorded on a computer hard disk through a 16-bit A/D board with a sampling rate of 100 Hz (Arco-10, Arcosystem, Chiba), and later fed to calculation for the beat-to-beat systolic (SAP) and diastolic arterial blood pressure (DAP) and heart rate (HR). Mean arterial blood pressure (MAP) was calculated from the equation of (SAP-DAP)/3 + DAP.

Data treatment and statistical analysis.

The average of HR, MAP, and oxyHb, deoxyhb, and totalHb obtained for 3 min before start of exercise during rest was defined as the preexercise level for each parameter. The continuous data in these variables were averaged for every 10s during SHG as well as PEMI and used for the following statistics. A two-way analysis of variance with repeated measures was used to see the effect of time and experimental condition for HR, MAP, oxyHb, deoxyHb, and totalHb. When a significant *F*-value in the main effects and/or in the interaction effect (time x experimental condition), Dunnett's *post hoc* test was applied to see whether the average at individual time was significantly different from the preexercise level. Similarly, Turkey's *post hoc* test was used to see a significant difference between CON and OCCL experiments in the average at individual time. Data are presented as means ± SD. The level of significance was set at $P<0.05$.

Results

Fig. 2 shows time courses in HR and MAP during SHG and PEMI averaged from 14 subjects in CON and OCCL experiments. During SHG, HR increased significantly from the preexercise level in CON and OCCL whereas the OCCL, performed after CON experiment, showed rather a higher increase than CON. After the end of SHG, HR in both CON and OCCL returned quickly to the resting level and the level of OCCL was also higher than that of CON. MAP began to increase approximately 30s after the onset of SHG and then progressively increased till the end of SHG in both CON and OCCL. After SHG, the MAP in CON rapidly returned to the preexercise level while MAP in OCCL sustained a higher level during PEMI. Statistical difference was observed in MAP between CON and OCCL during PEMI.

Figs. 3–5 represents, respectively, the time courses in oxyHb, deoxyHb and totalHb obtained from the left PF and SM areas. In PF area, the oxyHb (**Fig. 3**) during SHG showed a gradual and apparent increase in both CON and OCCL from 30 s after the onset of SHG to the end of SHG. The time course of increase in oxyHb in CON and OCCL followed a similar pattern of the increase in MAP (**Fig. 2**). The increase in oxyHb during SHG was accompanied by a slight decrease in deoxyHb (**Fig. 4**) in both CON and OCCL. Thus the time course of deoxyHb showed a reciprocal change of oxyHb during SHG. The totalHb (**Fig. 5**) showed a significant increase resulting from the significant increase in oxyHb and the slight decrease in deoxyHb in both CON and OCCL. Similar time courses in oxyHb, deoxyHb and totalHb in PF area was observed in SM areas (no 9, 11, 12, 14 in **Figs. 3–5**) that there was a significant increase in oxyHb and totalHb with a slight decrease in deoxyHb in response to SHG.

During PEMI in CON, the oxyHb in PF area returned to the preexercise level (**Fig. 3**), whereas the oxyHb in OCCL sustained a higher level during PEMI, resulting a significant difference between CON and OCCL in the oxyHb in PF area. The deoxyHb in PF area (**Fig. 4**) showed a reciprocal change in oxyHb, showing a significantly lower deoxyHb in

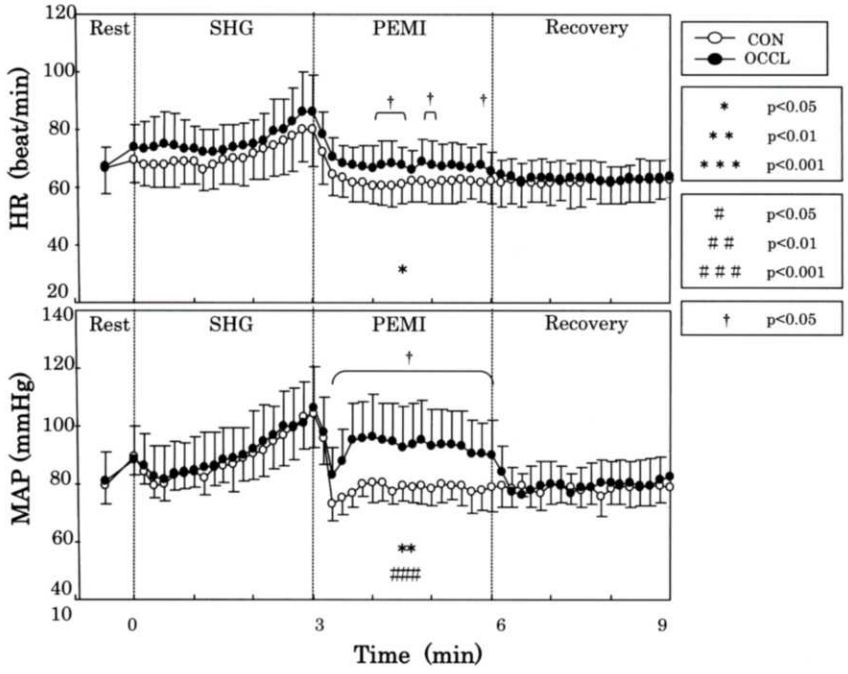

Fig. 2 Cardiovascular responses to static handgrip exercise (SHG) and postexercise muscle ischemia (PEMI) in control (CON) and occlusion (OCCL) experiments. Values are mean±SD in 14 subjects. HR, heart rate; MAP, mean arterial blood pressure; *, * *, significant main effect of experiments obtained in analysis of variance; #, # # #, significant interaction effect of experiment x time obtained in the analysis of variance; †; significant difference in mean values between CON and OCCL obtained in *post hoc* test.

OCCL than that in CON during PEMI. The totalHb in PF area (**Fig. 5**), therefore, followed a similar pattern in the change of oxyHb. In SM area (channel no 9, 11, 12, 14) during PEMI, the oxyHb and totalHb in CON returned to preexercise levels, whereas the deoxyHb in CON sustained the slightly lower level as seen during SHG (**Fig. 4**). On the contrary, the oxyHb and totalHb in OCCL sustained a higher level during PEMI with a decrease in deoxyHb as similarly seen during SHG. Thus, there was a significant difference in oxyHb and totalHb between CON and OCCL during PEMI, whereas there was no difference in deoxyHb between CON and OCCL in SM area.

Discussion

This study found a significant increase in oxyHb and totalHb during SHG with a reciprocal decrease in deoxyHb over the PF and SM areas, indicating that SHG activated PF and SM areas in the cortex. These findings agreed with the report that neuronal activation in the brain induced an increase in both oxyHb and totalHb with a slight decrease in deoxyHb, (*Bhambhani et al. 2006; Colier et al. 1999; Hoshi et al. 2001; Hoshi and Tamura 1993; Obrig et al. 1996; Quaresima et al. 2004*).

One may explain that the increase in oxyHb

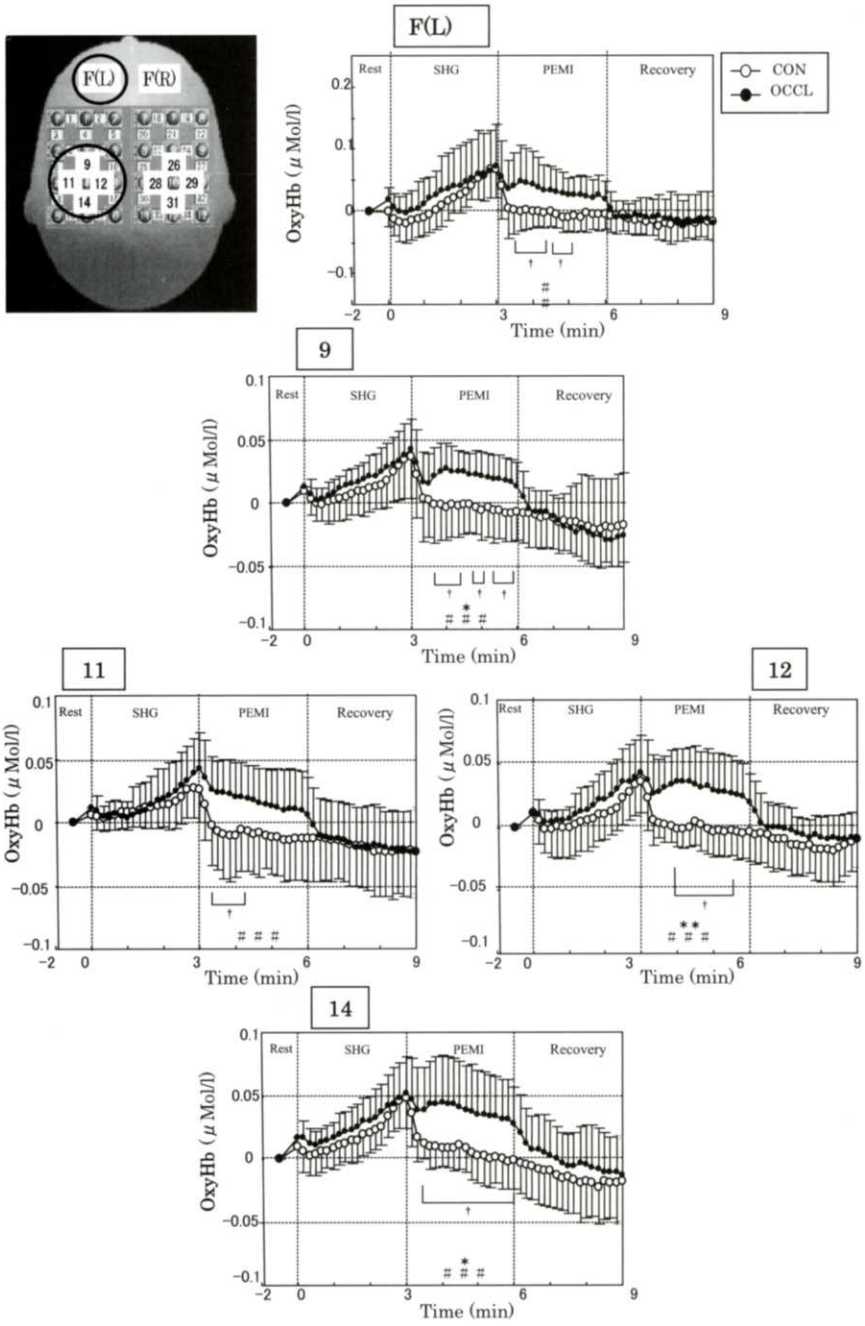

Fig. 3 Changes in oxygenated hemoglobin (OxyHb) in the left prefrontal and sensorimotor cortices during static handgrip (SHG) and postexercise muscle ischemia in control (CON) and occlusion (OCCL) experiments.
Values are mean±SD in 14 subjects. F (L) ; the left prefrontal area, 9, 11, 12, 14 ; the left sensorimotor areas, ∗ ; significant main effect of experiments obtained in the analysis of variance, ##, # # # ; significant interaction effect of experiment x time obtained in the analysis of variance, † ; significant difference in mean values between CON and OCCL obtained in *post hoc* test.

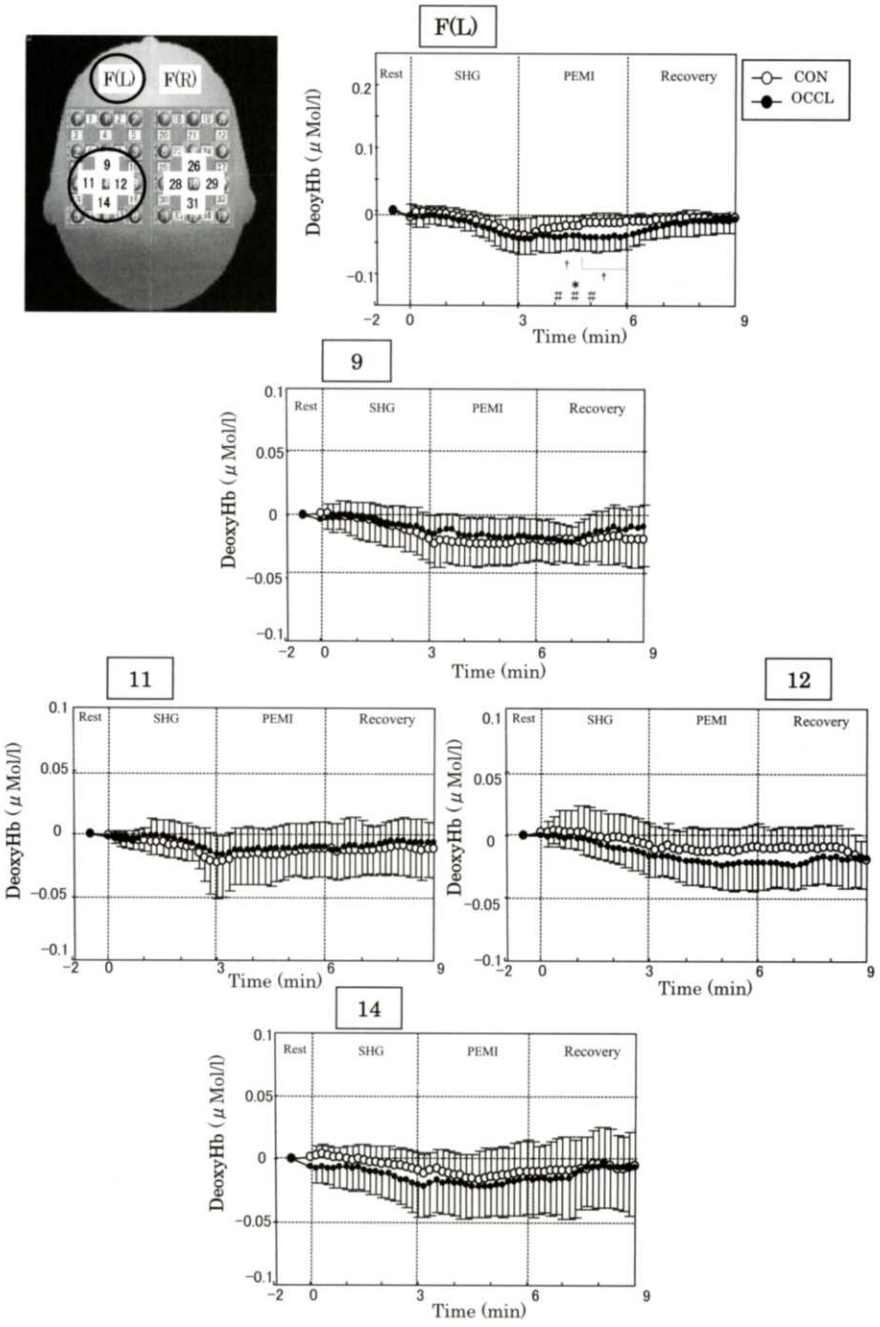

Fig. 4 Changes in deoxygenated hemoglobin (DeoxyHb) in the left prefrontal and sensorimotor cortices during static handgrip (SHG) and postexercise muscle ischemia in control (CON) and occlusion (OCCL) experiments.
Values are mean±SD in 14 subjects. F (L) ; the left prefrontal area, 9, 11, 12, 14 ; the left sensorimotor areas, ＊, significant main effect of experiments obtained in the analysis of variance, # # # ; significant interaction effect of experiment x time obtained in the analysis of variance, † ; significant difference in mean values between CON and OCCL obtained in *post hoc* test.

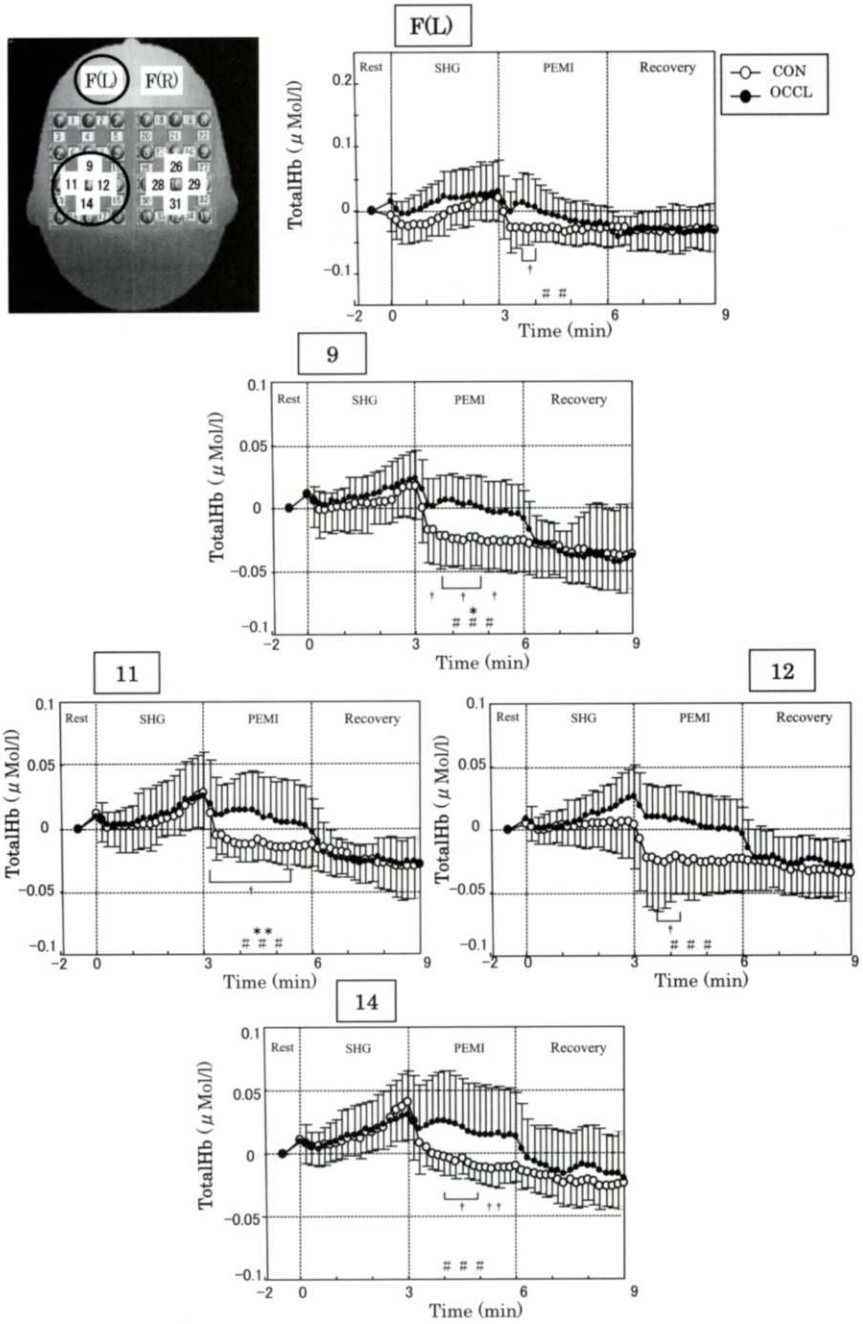

Fig. 5 Changes in total hemoglobin (Total Hb) in the left prefrontal and sensorimotor cortices during static handgrip (SHG) and postexercise muscle ischemia in control (CON) and occlusion (OCCL) experiments.
Values are mean±SD in 14 subjects. F (L) ; the left prefrontal area, 9, 11, 12, 14 ; the left sensorimotor areas, ＊, ＊＊ ; significant main effect of experiments obtained in the analysis of variance, ＃＃, ＃＃＃ ; significant interaction effect of experiment x time obtained in the analysis of variance, † ; significant difference in mean values between CON and OCCL obtained in *post hoc* test.

and totalHb during SHG was caused by an increased perfusion pressure during SHG since the time courses in oxyHb and totalHb were similar to those in MAP responses and further there was a report that diastolic blood pressure during posture change affect the frontal cortical oxygenation (*Mehagnoul-Schipper et al. 2003*). However, the cerebral autoregulation was effective during exercise to counteract pressure changes over the wide range of MAP from 50–60 to 150–175 mmHg (*Lassen 1959 ; Scheinberg 1949*), it was, therefore, unlikely that the increased oxyHb and totalHb was byproduct of the increased MAP.

Alternatively, a likely explanation is that the increase in oxyHb and totalHb during SHG was due to the increase in regional cerebral blood flow resulting from neuronal activation in PF and SM areas during SHG. The reciprocal responses observed between oxyHb and deoxyHb in our data indicated an overcompensated increase in blood flow in relative to the oxygen demand for the neuronal activation (*Fox & Raichle 1986 ;*). The increases in oxyHb and totalHb accompanying with a decrease in deoxyHb were widely accepted to be observed in the activated areas in the brain (*Fox & Raichle 1986 ; Hoshi et al. 2001 ; Huppert et al. 2006 ; Kato et al. 1993 ; Kleinschmidt et al. 1996 ; Rostrup et al. 2002*). Neurophysiologic studies with transcranial magnetic stimulation (*Gandevia et al. 1996*) and fMRI (*Benwell et al. 2005 ; Liu, et al. 2003*) and PET (*Friedman et al. 1991*) studies also supported the significant activation in SM and PF areas during sustaining handgrip contraction. In addition, the blood flow data obtained in MCA (*Ide et al. 1998 ; Giller et al. 2000 ; Pott et al. 1997 ; Sadamoto et al. 2005*) and/or flow volume in ICA (*Pott et al. 1997 ; Sadamoto et al. 2005*) supported to the aforementioned explanation. Taken together, we considered that SHG produced the increase in cerebral tissue flow in PF and SM areas resulting from neuronal activation.

During PEMI, there were significant increases in oxyHb and totalHb in both PM and SM areas whereas those in CON returned to the preexercise level, suggesting that PEMI produced neuronal activation due to the upper arm occlusion and thereby the increase of regional blood flow in PM and SM areas during PEMI. It has been well known that PEMI activates muscle unmyelinated afferent nerves in the skeletal muscle, group III (Aδ fiber) and IV (C-fiber) fivers, and these afferent nerves are known to play a major role in regulating the cardiovascular response during exercise as muscle metaboreflex (*cf. Mitchell, 1990*). The stimulation in the III and IV afferents were found to produce a significant activation in bilateral SM cortex, pre-supplementary motor area (*Qiu et al. 2004 ; 2006 ; Tran et al. 2002*) and premotor cortex (*Casey, 1999*) and PF cortex (*Casey, 1999 ; Svensson P et al. 1997*). From these results, we considered that the increase in oxyHb and totalHb was produced by neuronal activation originating from the stimulation of the group III and IV afferents in the occluded upper arm muscles.

The meaning of data obtained from NIRS is in still under discussion. In particular, whether the NIRS signals reflect the intracerebral blood volume of pial and/or, probably, also blood volume of more superficial circulation. The spatial resolution and cerebral penetration depth are also limited in NIRS measurements. Therefore, further studies are needed to examine the reasonability of the present study.

In conclusion, the present study provided the time course of cerebral oxygenation in sensorimotor (SM) and prefrontal (PF) cortices during static handgrip exercise (SHG) and postexercise

muscle ischemia (PEMI), using by near-infrared spectroscopy. A significant increase in the regional cerebral blood flow indicated the neuronal activation in both PF and SM during SHG and during PEMI.

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