Increased oxygenation of the cerebral prefrontal cortex prior to the onset of voluntary exercise in humans

Kanji Matsukawa,1 Kei Ishii,1 Nan Liang,1 Kana Endo,1 Ryo Ohtani,1 Tomoko Nakamoto,1 Rie Wakasugi,1 Akito Kadowaki,1 and Hidehiko Komine2

1Department of Integrative Physiology, Graduate School of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan; and 2Human Technology Research Institute, National Institute of Advanced Industrial Science and Technology, Tsukuba, Japan

Submitted 19 May 2015; accepted in final form 10 July 2015

Matsukawa K, Ishii K, Liang N, Endo K, Ohtani R, Nakamoto T, Wakasugi R, Kadowaki A, Komine H. Increased oxygenation of the cerebral prefrontal cortex prior to the onset of voluntary exercise in humans. J Appl Physiol 119: 452–462, 2015. First published July 16, 2015; doi:10.1152/japplphysiol.00406.2015.—To determine whether output from the forebrain (termed central command) may descend early enough to increase cardiac and renal sympathetic outflows at the onset of voluntary exercise, we examined the changes in regional tissue blood flows of bilateral prefrontal cortices with near-infrared spectroscopy, precisely identifying the onset of voluntary ergometer 30-s exercise at 41 ± 2% of the maximal exercise intensity in humans. Prefrontal oxygenated-hemoglobin (Oxy-Hb) concentration was measured as index of regional blood flow unless deoxygenated-hemoglobin concentration remained unchanged. Prefrontal Oxy-Hb concentration increased significantly (P < 0.05) 5 s prior to the onset of exercise with arbitrary start, whereas such increase in prefrontal Oxy-Hb was absent before exercise abruptly started by a verbal cue. Furthermore, the increase in prefrontal Oxy-Hb observed at the initial 15-s period of exercise was greater with arbitrary start than cued start. The prefrontal Oxy-Hb, thereafter, decreased during the later period of exercise, irrespective of either arbitrary or cued start. The reduction in prefrontal Oxy-Hb had the same time course and response magnitude as that during motor-driven passive exercise. Cardiac output increased at the initial period of exercise, whereas arterial blood pressure and total peripheral resistance decreased. The depressor response was more pronounced (P < 0.05) with arbitrary start than cued start. Taken together, it is suggested that the forebrain structures are not important to evoke central command, but they may trigger caudal neural circuits responsible for generating central command. This notion is supported by the finding that electrical stimulation of the human mesencephalic nucleus produced the cardiovascular responses (41). If so, activity of the forebrain structures must increase earlier than the onset of voluntary exercise, preceding the increases in the sympathetic outflows and HR.

Gross cerebral blood flows have been studied to identify cerebral neural candidates related with central command during exercise. Sato et al. (38) and Vianna et al. (43) found that blood flow velocity of the common carotid artery, middle cerebral artery, and anterior cerebral artery transiently increased during voluntary upper arm or calf exercise, whereas the cerebral artery blood flow velocity was not altered by activation of muscle afferents by using mechanically evoked passive exercise, electrically stimulated exercise, and postexercise ischemia. The characteristics of the cerebral blood flow responses suggested a central command-related increase during voluntary exercise. Regarding the responses in regional cerebral blood flow (rCBF), it has been reported by using single-photon or positron emission tomography (SPECT or PET) or functional magnetic resonance imaging (fMRI) that rCBF in the anterior cingulate and bilateral anterior and posterior insular cortices increased during voluntary static handgrip exercise, while rCBF in the prefrontal region decreased (2, 37, 39, 46, 47, 48). The rCBF responses during postexercise ischemia are controversial between studies (37, 46) and are not always coincident with the gross cerebral artery responses. The reason responsible for the dissociation between gross and regional CBF may partly depend on a difference in methods of investigation and/or relatively low temporal resolution of the CBF imaging data, which may mask the rapid changes in rCBF. Furthermore, the changes in rCBF prior to the onset of exercise have not been investigated.

We examined the dynamic changes in rCBF of the prefrontal cortex before and during voluntary ergometer exercise with near-infrared spectroscopy (NIRS), precisely determining the onset of exercise in humans. Since the prefrontal cortex projects subcortical autonomic and limbic nuclei (9, 12, 42, 45), it is hypothesized that the prefrontal cortex may play a role in triggering caudal autonomic centers responsible for central command. Suzuki et al. (40) found the predominant increases of oxygenated-hemoglobin (Oxy-Hb) levels in the prefrontal and premotor cortices prior to the onset of treadmill exercise. However, the preexercise Oxy-Hb response might be influenced by factors with no relation to exercise because the treadmill exercise was slowly started by a cued signal. It is

Address for reprint requests and other correspondence: K. Matsukawa, Dept. of Integrative Physiology, Graduate School of Biomedical and Health Sciences, Hiroshima Univ., Kasumi 1-2-3, Minami-ku, Hiroshima 734-8551, Japan (e-mail: matsuk@hiroshima-u.ac.jp).
expected that if exercise is started voluntarily, central command should be activated prior to the onset of exercise. On the other hand, if exercise is suddenly started as soon as a cued signal is given, central command is unlikely to be activated prior to the onset of voluntary exercise. Accordingly, by comparing the responses in prefrontal cerebral oxygenation and cardiovascular variables between the arbitrary and cued starts, the central command-related components of the responses will be more clearly distinguished. Furthermore, to identify whether any feedback signal from mechanical limb motion during ergometer exercise may influence rCBF, the effect of motor-driven passive cycling on the regional cerebral blood flow were examined by using the same subjects.

METHODS

Subjects. Twenty-two healthy subjects (12 males and 10 females; age, 28 ± 2 yr; height, 165 ± 2 cm; body wt, 58 ± 2 kg) participated in this study. None of the subjects suffered from any known cardiovascular and neuromuscular disease and they did not take any medications. The experimental procedures and protocols were performed in accordance with the Declaration of Helsinki and approved by the Institutional Ethical Committee. The subjects gave their informed written consent prior to the experiments. All experiments were performed in a soundproof room, in which temperature was maintained between 24 and 26°C.

Voluntary cycling exercise. Voluntary cycling exercise was performed for 30 s at 50 rpm in the supine position on a comfortable reclining seat of a specially designed cycle ergometer (Strength Ergo 240 BK-ERG-003, Mitsubishi Electric Engineering, Tokyo, Japan). The feet were placed on a shoe affixed at the pedal. The positions of the crank, pedal, and seat were adjusted so that the subjects remained in a comfortable and stable posture. Both torque against the wheel shaft and pedal displacement of the ergometer were continuously measured (16, 21). The subjects were instructed either to arbitrarily start cycling exercise without any cue or to abruptly start the exercise as soon as a cue voice was given. On a separate day prior to the main experiment, the subjects were acclimated to ergometer exercise under the laboratory environment.

Oxygenated- and deoxygenated-hemoglobin concentrations of the prefrontal cortex. The relative concentrations of the oxygenated- and deoxygenated-hemoglobin (Oxy- and Deoxy-Hb) of the bilateral prefrontal cortices were measured with NIRS in 19 of the 22 subjects. A pair of photoemission and photo-detection probes were placed on the forehead surface between Fp1 and F3 (left side) and between Fp2 and F4 (right side) (referring to the international EEG 10-20 system) (6, 13) and covered with a black cloth. The interprobe distance was 4 cm. The principle of NIRS is that near-infrared light from three laser photodiodes with different wavelengths (wavelength: 775, 810, and 850 nm) penetrates brain tissue and some of the light is absorbed by Hb, and that the remaining light scattered by the brain tissue is picked up with photodetectors (6). The reflected near-infrared light through brain tissue was sampled at a rate of 6 Hz and converted to optical densities with a near-infrared spectrometer (NIRO 200, Hamamatsu Photonics, Hamamatsu, Japan). Since the oxygenation signal of NIRS is dependent on a balance between oxygen supply and utilization in microcirculation within the illuminated tissue, the NIRS signal does not directly monitor regional blood flow. Nevertheless, since the Deoxy-Hb of the prefrontal areas remained at or near the baseline level throughout the interventions, the change in Oxy-Hb reflected the change in regional tissue blood flow, which may partly follow neural activity in the brain (5, 6, 7, 14, 15, 23, 34).

Another point to be considered was that the signals of the NIRS are influenced not only by regional cerebral blood flow but also skin blood flow in the illuminated tissue area (30). To clarify the possible contribution of skin blood flow to the Oxy- and Deoxy-Hb signals of the NIRS, a laser Doppler flow probe was placed at the middle of the forehead. Skin blood flow was monitored with a laser Doppler instrument (ALF21; ADVANCE, Tokyo, Japan) in 18 subjects, simultaneously with the NIRS measurements. Raw skin blood flow signal was integrated with a time constant of 0.1 s.

Cardiovascular recordings. An electrocardiogram (ECG) was monitored with a telemetry system (DynaScope DS-3140, Fukuda Denshi, Tokyo, Japan). Arterial pressure (AP) was noninvasively and continuously measured with a Finometer (Finapres Medical Systems BV, Arnhem, The Netherlands), with the cuff attached to the left middle or index finger. The AP waveform was sampled at 200 Hz. The beat-to-beat values of systolic AP (SAP), mean AP (MAP), diastolic AP (DAP), and HR were obtained throughout the experiments in 15 of the 22 subjects. Simultaneously, the beat-to-beat values of cardiac output (CO), stroke volume (SV), and total peripheral resistance (TPR) were calculated from the aortic pressure waveform by using a Modelflow software (BeatScope 1.1, Finapres Medical Systems BV, Arnhem, The Netherlands).

Experimental protocols. The developed torque and pedal displacement of the ergometer and electromyogram (EMG) signals of the vastus lateralis muscles were measured throughout the experiments. Moreover, the cardiovascular responses, the NIRS signals of the bilateral prefrontal cortices, and forehead skin blood flow were simultaneously measured. Voluntary ergometer exercise was performed for 30 s with two different types of start (arbitrary vs. cued). In the case of cued start, exercise was suddenly started as soon as a cued voice was given. The exercise intensity was set at 100 W for males and 60 W for females, which corresponded to 41 ± 2% of the maximal voluntary exercise intensity (males, 234 ± 11 W; females, 157 ± 15 W). The responses in the cardiovascular variables and prefrontal NIRS signals during voluntary exercise were compared between the two start modes (arbitrary vs. cued). To determine feedback effects of limb mechanical movement on the cardiovascular variables and prefrontal NIRS signals, motor-driven passive cycling was performed for 30 s at 50 rpm in the same subjects. According to the Borg scale grade from 6 to 20 units (1), the rating of perceived exertion was asked immediately after each bout of voluntary or passive ergometer exercise.

Data and statistical analyses. The data of the developed torque and pedal displacement of the ergometer, AP, ECG, EMG, and NIRS signals were stored to computers at a sampling frequency of 1,000 Hz (MP150, BIOPACK Systems, Santa Barbara, CA, and PowerLab 16/35, ADInstruments-Japan, Nagoya, Japan) for off-line analysis. The onset of voluntary cycling exercise was precisely defined as “time = 0” according to the onset of pedal displacement. The absolute concentration of Oxy-Hb and Deoxy-Hb could not be obtained, because the path length of near-infrared light within tissue was unknown. The relative changes in the NIRS signals against the baseline were obtained in every bout of exercise. Then all relative changes of the cardiovascular variables, NIRS signals, and skin blood flow were aligned at the onset of exercise and they were sequentially averaged every 1 s. Furthermore, by using the time course data, the Oxy-Hb response with cued start (termed ΔOxy-Hb_cued) was subtracted from the response with arbitrary start (termed ΔOxy-Hb_arbitrary) in individual subjects. The differences of ΔOxy-Hb_arbitrary−cued (= ΔOxy-Hb_arbitrary−ΔOxy-Hb_cued) were used for estimating the preexercise component of the prefrontal Oxy-Hb during voluntary exercise. The differences in the prefrontal Deoxy-Hb (termed ΔDeoxy-Hb_arbitrary−cued) and forehead skin blood flow response (termed ΔSkin blood flow_arbitrary−cued) were similarly analyzed.

The baseline and peak values of the hemodynamics and skin blood flow during exercise were compared among the three exercise interventions (voluntary exercise with arbitrary start vs. voluntary exercise with cued start vs. passive exercise) by a one-way ANOVA with repeated measures and a Dunnett post hoc test, as shown in Table 1. If either normality or equal variance test failed, a Friedman repeated measures analysis of variance on ranks with the Dunnett test was performed. The cardiovascular responses at the initial period of exercise (from 0 to 15 s after the exercise onset) are expected to be
produced by central command (16, 17, 18). Thus the responses in the hemodynamics, prefrontal NIRS, and forehead skin blood flow prior to the exercise onset and at the initial period of exercise were analyzed between the exercise interventions by using a two-way ANOVA with repeated measures. If the main effect of exercise intervention and/or interaction between the interventions were significant, a pair-wise comparison with the Dunnett post hoc test was performed to analyze a significant difference between the exercise interventions at a given time. In each exercise intervention, the same data were analyzed by a one-way ANOVA with repeated measures to assess the significant changes from the baseline control. If a significant main effect of time was obtained, the Dunnett post hoc test was performed to assess significant changes from the control level taken more than 15 s before the exercise onset. The data of Oxy-Hb arbitrary-cued, Deoxy-Hb arbitrary-cued, and ΔSkin blood flow arbitrary-cued were similarly analyzed by a one-way ANOVA with repeated measures and the Dunnett post hoc test was performed to assess significant changes from the baseline control before exercise. †Significant difference (P < 0.05 by one-way ANOVA with repeated measures and Dunnett post hoc test) from the values during voluntary exercise with arbitrary start.

### Table 1. Summary of the cardiovascular variables before and during exercise

<table>
<thead>
<tr>
<th></th>
<th>Voluntary Exercise with Arbitrary Start</th>
<th>Voluntary Exercise with Cued Start</th>
<th>Motor-Driven Passive Exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>During</td>
<td>Change</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>70 ± 2</td>
<td>103 ± 2*</td>
<td>33 ± 2</td>
</tr>
<tr>
<td>SV, ml</td>
<td>84 ± 5</td>
<td>103 ± 6*</td>
<td>19 ± 2</td>
</tr>
<tr>
<td>CO, liters/min</td>
<td>5.8 ± 0.4</td>
<td>10.2 ± 0.6*</td>
<td>4.4 ± 0.3</td>
</tr>
<tr>
<td>SAP, mmHg</td>
<td>136 ± 5</td>
<td>131 ± 4*</td>
<td>−6 ± 2</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>101 ± 3</td>
<td>92 ± 3*</td>
<td>−9 ± 2</td>
</tr>
<tr>
<td>DAP, mmHg</td>
<td>78 ± 3</td>
<td>70 ± 2.4*</td>
<td>−8 ± 2</td>
</tr>
<tr>
<td>TPR, MU</td>
<td>1.10 ± 0.07</td>
<td>0.59 ± 0.04*</td>
<td>−0.51 ± 0.04</td>
</tr>
<tr>
<td>Skin blood flow, ml·min⁻¹·100 g⁻¹</td>
<td>5.9 ± 1.1</td>
<td>6.8 ± 1.1*</td>
<td>0.9 ± 0.4</td>
</tr>
<tr>
<td>Borg scale, unit</td>
<td>—</td>
<td>11 ± 0.4</td>
<td>—</td>
</tr>
</tbody>
</table>

Values are means ± SE (n = 15 subjects). HR, heart rate; SV, stroke volume; CO, cardiac output; SAP, systolic arterial pressure; MAP, mean arterial pressure; DAP, diastolic arterial pressure; TPR, total peripheral resistance; MU, medical unit (mmHg·ml⁻¹·s⁻¹). *Significant difference (P < 0.05 by paired t-test) from the baseline control before exercise. †Significant difference (P < 0.05 by one-way ANOVA with repeated measures and Dunnett post hoc test) from the values during voluntary exercise with arbitrary start.

Fig. 1. Representative recordings of angle displacement, developed torque, concentrations of oxygenated- and deoxygenated-hemoglobin (Oxy-Hb and Deoxy-Hb) of the left prefrontal cortex, forehead skin blood flow, arterial pressure (AP), and heart rate (HR) during voluntary exercise with arbitrary start (A) or with cued start (B). Prefrontal Oxy-Hb increased prior to the onset of exercise with arbitrary start (A), whereas an increase in the Oxy-Hb appeared immediately after the onset of exercise with cued start (B).
post hoc test. If either normality or equal variance test failed in the one-way ANOVA, a Friedman repeated measures analysis of variance on ranks with the Dunnett test was performed. The comparison of the Borg scales among the exercise interventions was conducted with a Friedman singed rank test. A level of statistical significance was defined at $P < 0.05$ in all cases. All statistical analyses were performed by SigmaPlot version 12.5 (Systat Software, San Jose, CA). All variables are expressed as means ± SE.

RESULTS

The baseline values of the cardiovascular variables and forehead skin blood flow were approximately the same among the exercise interventions (voluntary exercise with arbitrary or cued start and motor-driven passive exercise), although there were slight differences in HR, CO, and blood pressures as demonstrated in Table 1.

The prefrontal NIRS, skin blood flow, and cardiovascular responses prior to and during voluntary exercise with arbitrary or cued start. Figure 1 represents an example of the NIRS and cardiovascular responses during voluntary ergometer exercise with arbitrary or cued start in the same subject. The Oxy-Hb concentration of the prefrontal cortex increased prior to the onset of exercise with the arbitrary start and peaked a few

---

**Fig. 2.** The time courses of the average changes in HR, stroke volume (SV), cardiac output (CO), systolic arterial pressure (SAP), mean arterial pressure (MAP), diastolic arterial pressure (DAP), and total peripheral resistance (TPR) from the baseline during voluntary exercise with arbitrary (○) or cued start (●) in the same 15 subjects. MU, medical unit (mmHg·ml⁻¹·s⁻¹). *Significant differences ($P < 0.05$ by two-way ANOVA with repeated measures and Dunnett post hoc test) between the arbitrary and cued starts at a given time; N.S., not significant ($P > 0.05$).
seconds after the exercise onset. When exercise was started immediately after a verbal cue was given, the preexercise increase in the prefrontal Oxy-Hb was absent but the prefrontal Oxy-Hb increased quickly following the exercise onset. Thereafter, the prefrontal Oxy-Hb decreased during the later period of exercise, irrespective of either arbitrary or cued start. The decrease in the Oxy-Hb lasted even following the cessation of exercise. On the other hand, the prefrontal Deoxy-Hb did not change throughout exercise but increased after exercise. Forehead skin blood flow seemed unchanged throughout voluntary exercise, irrespectively of arbitrary or cued start. It was of interest that the increase in HR preceded the onset of voluntary exercise with the arbitrary start, whereas the tachycardia lagged behind the exercise onset in the case of the cued start.

The time courses of the average cardiovascular responses during voluntary ergometer exercise are compared between the arbitrary and cued start in Fig. 2. Their peak responses are summarized in Table 1. The increases in HR, SV, and CO during voluntary exercise were similar ($P > 0.05$ by two-way ANOVA) between the start modes (arbitrary vs. cued), despite some significant differences in the HR and CO responses around the onset of exercise. SAP, MAP, and DAP decreased by 6–9 mmHg ($P < 0.05$ by one-way ANOVA) at the initial period of exercise with arbitrary start, whereas the depressor responses were attenuated or disappeared ($P < 0.05$ by two-way ANOVA) at the initial period of exercise with the cued start. TPR started to decrease at 4–5 s from the onset of exercise ($P < 0.05$ by one-way ANOVA), and the decrease in TPR continued throughout exercise. There were no main effect and interaction on the TPR responses between the arbitrary and cued start mode ($P > 0.05$ by two-way ANOVA).

The time courses of the average prefrontal NIRS responses are shown in Fig. 3. With arbitrary start, the prefrontal Oxy-Hb increased ($P < 0.05$ by two-way ANOVA) 2–4 s prior to the onset of voluntary exercise, compared with the Oxy-Hb response with cued start, and peaked at 3–6 s following the onset, whereas the Deoxy-Hb remained unchanged at that period. The time courses and response magnitudes of the Oxy- and Deoxy-Hb matched approximately between the bilateral prefrontal cortices. When voluntary exercise was abruptly started by a cued signal, such preexercise increase in the Oxy-Hb was never seen. With the cued start, an increase in the prefrontal Oxy-Hb developed immediately after the exercise onset and peaked at 5 s after the exercise onset. The peak increase in the Oxy-Hb with the cued start was 74–78% of the peak increase with the arbitrary start (left side, 0.63 ± 0.14 μmol/cm; right side, 0.53 ± 0.22 μmol/cm), although there were no significant differences between them. Subsequently,
the Oxy-Hb gradually decreased during the later period of and after exercise, irrespective of either arbitrary or cued start. In contrast, the Deoxy-Hb increased at the end of and after exercise with both start modes. Forehead skin blood flow did not change prior to the exercise onset but increased slightly ($P < 0.05$ by one-way ANOVA) at the initial period of exercise. However, the two-way ANOVA about the changes in forehead skin blood flow indicated neither significant main effect of the start mode nor significant interaction. The peak response of the skin blood flow during exercise was not significantly different between the two start modes (Table 1).

The preexercise components of the prefrontal NIRS and skin blood flow responses. To estimate the preexercise components of the prefrontal NIRS and skin blood flow responses, their responses during exercise with the cued start were subtracted from the corresponding responses with the arbitrary start, as shown in Fig. 4. Before subtraction, bilateral Oxy-Hb and Deoxy-Hb responses were pooled, respectively, because they showed the similar response on both sides. The subtracted value ($\Delta$Oxy-Hb$_{arbitrary-cued}$) of the Oxy-Hb concentration increased ($P < 0.05$ by one-way ANOVA) from 5 s prior to the onset of exercise to 3 s after the exercise onset. In contrast, both $\Delta$Deoxy-Hb$_{arbitrary-cued}$ and $\Delta$Skin blood flow$_{arbitrary-cued}$ showed no significant changes during exercise.

Developed torque at the initial period of exercise. When the peak and average values of torque developed against the wheel shaft at the initial 15-s period of exercise were compared between the arbitrary and cued start, the peak and average

\begin{figure}
\centering
\includegraphics[width=0.8\textwidth]{figure4}
\caption{The preexercise components of the responses in the prefrontal Oxy-Hb and Deoxy-Hb and forehead skin blood flow during voluntary exercise are estimated as a subtraction of the response during exercise with cued start from the corresponding response with arbitrary start in the same 18 subjects. The bilateral Oxy-Hb and Deoxy-Hb responses were pooled, respectively, before subtraction. The subtracted value of the Oxy-Hb concentration (termed $\Delta$Oxy-Hb$_{arbitrary-cued}$) increased ($P < 0.05$) 5 s prior to the exercise onset. In contrast, $\Delta$Deoxy-Hb$_{arbitrary-cued}$ and $\Delta$Skin blood flow$_{arbitrary-cued}$ showed no significant changes ($P > 0.05$) during exercise. *Significant differences from the baseline control ($P < 0.05$ by one-way ANOVA with repeated measures and Dunnett post hoc test); N.S., not significant ($P > 0.05$).}
\end{figure}
values of developed torque were not different \((P > 0.05\) by paired \(t\)-test) between the two start modes (Fig. 5).

The prefrontal NIRS, skin blood flow, and cardiovascular responses during passive exercise. The average cardiovascular responses during motor-driven passive exercise are compared with the responses during voluntary exercise with the arbitrary start in Fig. 6. Their peak responses during passive exercise are summarized in Table 1. Compared with the baseline control before passive exercise, HR and CO slightly increased \((P < 0.05\) by one-way ANOVA) during passive exercise, while SAP, MAP, and DAP increased \((P < 0.05)\) by 6–10 mmHg at the initial period of passive exercise. TPR decreased by 12 ± 3% of the baseline \((P < 0.05)\) during the later period of passive exercise. Compared with the responses during voluntary exercise with the arbitrary start, all cardiovascular responses to passive exercise were considerably smaller.

The average responses of the prefrontal NIRS and forehead skin blood flow during passive exercise are shown in Fig. 7. Compared with the baseline control before passive exercise, bilateral prefrontal Oxy-Hb showed a gradual decrease \((P < 0.05\) by one-way ANOVA) during the later period of passive exercise, while the Oxy-Hb remained unchanged throughout the exercise. Compared with the responses during voluntary exercise with the arbitrary start, significant differences in the prefrontal Oxy-Hb response were found at most phases of exercise (prior to exercise, at the initial period of, and after exercise). However, the time course of the decrease in prefrontal Oxy-Hb during the later period of exercise was not different between passive and voluntary exercise \((P > 0.05\) by two-way ANOVA and Dunnett post hoc analysis). In addition, the peak decreases in prefrontal Oxy-Hb during the later period of passive exercise were 0.96 ± 0.29 \(\mu\)mol/cm (left side) and 0.72 ± 0.17 \(\mu\)mol/cm (right side), which were the same with the decreases during voluntary exercise with arbitrary start [1.00 ± 0.31 \(\mu\)mol/cm (left side) and 0.94 ± 0.29 \(\mu\)mol/cm (right side)]. With respect to the prefrontal Deoxy-Hb response, the significant differences between the exercise interventions were not found mostly during the exercise but found at the end of and following exercise. Forehead skin blood flow did not change from the baseline control \((P > 0.05\) by one-way ANOVA) throughout passive exercise. Accordingly, there were significant differences in the skin blood flow response between passive and voluntary exercise.


discussion

The present study has examined by using NIRS whether prefrontal cerebral oxygenation increases prior to the onset of voluntary ergometer exercise for 30 s in humans. The Oxy- and Deoxy-Hb concentrations of the bilateral prefrontal cortices were measured as an index of rCBF during voluntary exercise. The major findings are that 1) the Oxy-Hb concentrations of the bilateral prefrontal cortices increased 5 s prior to the onset of exercise with the arbitrary start, whereas such increase of the prefrontal Oxy-Hb was absent when exercise was started by a verbal cue; 2) the increase in the prefrontal Oxy-Hb at the initial period of exercise was greater with the arbitrary start than the Oxy-Hb increase with the cued start; 3) motor-driven passive cycling did not cause any changes in the prefrontal Oxy-Hb at the initial period of exercise; 4) the decreases in the prefrontal Oxy-Hb during the later period of and after exercise had almost the same time course between voluntary exercise with either arbitrary or cued start and motor-driven passive exercise; and 5), on the other hand, the prefrontal Deoxy-Hb remained unchanged throughout any exercise intervention. Taken together, it is likely that the increase in the prefrontal Oxy-Hb observed prior to the onset of voluntary exercise may be in association with central command, whereas the later decrease in the prefrontal Oxy-Hb during voluntary exercise may be in association with feedback from mechanical events of cyclic limb motion.

Increased oxygenation in the prefrontal cortex prior to voluntary exercise. The preexercise increase in prefrontal Oxy-Hb was evoked neither by voluntary exercise with the cued start nor by passive exercise, suggesting that the Oxy-Hb response prior to the onset of exercise with arbitrary start is not a startle and/or emotionally evoked response under the present experimental environment. Furt-
thermore, no significant changes in oxygen utilization are suggested, because the prefrontal Deoxy-Hb remained unchanged at or near the baseline throughout any experimental intervention (Figs. 3 and 7). Thus the increase in the prefrontal Oxy-Hb may reflect the increase in regional oxygen supply due to increased rCBF (6, 16, 17, 18). In addition, skin blood flow involved in the illuminated tissue area might influence the Oxy-Hb signal of the NIRS (30). In fact, forehead skin blood flow did not change prior to the onset of voluntary exercise but increased slightly at the initial period of exercise with both arbitrary and cued starts (Fig. 3). Thus forehead skin blood flow cannot explain the increased prefrontal oxygenation prior to the onset of voluntary exercise. Taken together, the prefrontal blood flow may follow

Fig. 6. The time courses of the average cardiovascular changes from the baseline during motor-driven passive exercise (○) in 15 subjects. The responses during voluntary exercise with arbitrary start (the data taken from Fig. 2, ○) in the same subjects are superimposed. *Significant differences (P < 0.05 by two-way ANOVA with repeated measures and Dunnett post hoc test) between the arbitrary and cued starts at a given time.
augmented neural activity in the cortical areas as indicated by transcranial magnetic stimulation (8).

The start modes of voluntary exercise (arbitrary vs. cued) and the cardiovascular responses. The cardiac responses to voluntary exercise were almost similar between the two start modes (arbitrary vs. cued). On the other hand, substantial differences in the blood pressure responses were found between the start modes. The depressor response observed at the initial period of exercise was more pronounced with arbitrary start than cued start (Fig. 2), despite slight differences in HR and CO around the onset of exercise. Although the augmented depressor response might be caused by greater vasodilatation due to stronger muscle contraction in association with the arbitrary start, this was not the case because torque development at the initial period of exercise was identical between the two start modes (Fig. 5). Instead, this finding leads us to an attractive hypothesis that greater peripheral vasodilatation may occur in association with central command rather than muscle contraction-evoked local mechanisms. Ishii et al. (17, 18) and Viana et al. (40) reported that muscarinic blockade blunted a decrease in TPR observed during one-legged exercise and during static arm or leg exercise. Moreover, Ishii et al. (16, 17, 18) reported that the Oxy-Hb in the contracting and noncontracting vastus lateralis muscles, as an index of muscle tissue blood flow, increases at the initial period of voluntary exercise with the arbitrary start and that the increases in the Oxy-Hb are blunted by atropine. Thus it is likely that cholinergic vasodilatation elicited by a central feedforward mechanism plays a role in the initial vasodilatation of skeletal muscle. The aforementioned findings about the blood pressure responses in this study may support this hypothesis, although there was no statistical difference in the TPR response between the arbitrary and cued modes (Fig. 2).

Effects of feedback from mechanoreceptors stimulated by limb motion. Motor-driven passive exercise caused no changes in the Oxy- and Deoxy-Hb signals at the initial period of the exercise, suggesting that the NIRS signals involved no mechanical artifacts by limb movement. Moreover, forehead skin blood flow remained unchanged throughout passive exercise, suggesting that the skin blood flow signal also involved no mechanical artifacts. As a result, any feedback from mechanoreceptors stimulated by cyclic limb motion does not affect the prefrontal Oxy-Hb and skin blood flow at the initial period of passive exercise. These findings are in good agreement with the changes in blood flow velocity of the cerebral arteries, demonstrating that increased cerebral blood flow during voluntary exercise is due to central command rather than feedback from muscle afferents (31, 38, 43).
In contrast to the initial period, the prefrontal Oxy-Hb decreased during the later period of passive exercise (Fig. 7). Since the prefrontal Deoxy-Hb, forehead skin blood flow, and MAP was unchanged at that period, the later decrease in prefrontal Oxy-Hb may reflect a reduction in rCBF, which is not due to decreased perfusion pressure. Instead, it is speculated that the reduction in rCBF may be caused by a decrease in neural activity in the cerebral region and/or redistribution of cerebral blood flow to other active cerebral regions. Similarly, the prefrontal Oxy-Hb decreased during the later period of voluntary exercise, irrespectively of arbitrary or cued start (Fig. 3). Since the time course and response magnitude of the Oxy-Hb decrease during voluntary exercise matched those of the Oxy-Hb decrease during passive exercise, it can be speculated that a feedback from mechanoreceptors in association with cyclic limb motion may decrease prefrontal Oxy-Hb not only during passive exercise but also during volitional exercise. Otherwise, hyperventilation during the volitional and passive exercise, if any, may induce a decrease in partial pressure of arterial carbon dioxide, which may in turn reduce rCBF. The rCBF decrease in the prefrontal region is supported by the data during exercise in fMRI studies (37, 39, 48), in which passive mechanical stimulation of muscle was not performed. However, blood flow velocity of the cerebral arteries remained unchanged during passive exercise (38, 43). The dissociation between the responses in cerebral artery blood velocity and rCBF remains unknown. Curiously, the prefrontal Oxy-Hb augments again above the baseline level when voluntary exercise is sustained for more than 5 min (6, 32, 35). A mechanism responsible for the second and sustained increase of the prefrontal oxygogenation during exercise also remains unknown.

In conclusion, the Oxy-Hb of the bilateral prefrontal cortices exhibited the increase 5 s prior to voluntary exercise. The prefrontal cortical activation is just early enough to control the cardiovascular system at the initial period of exercise, even if a large time lag of cardiovascular effectors is taken into account. Interestingly, the prefrontal activation may precede considerable activity of the motor regions such as the supplementary and primary motor cortices (29). According to the NIRS probe placement, the Oxy-Hb signal may detect regional cerebral oxygenation in the bilateral dorsolateral prefrontal cortex (DLPFC) and its vicinities (6). The DLPFC plays a role in multiple higher functions including cognitive function (6, 22), selective judgment and attention (20, 27), and long-term memory (33). Thus it is not always explicit which physiological function the prefrontal activation prior to exercise excursion should be linked with, although we speculate that the prefrontal cortex may play a role in triggering causal neural circuits responsible for central command generation. Accordingly, a more comprehensive study including NIRS recordings from multiple cortical sites will be needed to answer the question.

ACKNOWLEDGMENTS

We thank Ms. Tomoko Ishida for her excellent technical assistance.

GRANTS

Support for this study was provided by Grants-in-Aid for Scientific Research (B) and for Exploratory Research from the Japan Society for the Promotion of Science (JSPS) and partially supported by the Center of Innovation Program from Japan Science and Technology Agency (JST). K. Ishii was supported as a JSPS research fellow.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS


REFERENCES


