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# Kinetics of cerebral blood flow in the moderate and heavy exercise intensity domains estimated using the transcranial Doppler method

Mikio Hiura<sup>1)</sup>, Shigeki Izumi<sup>1)</sup>

[Abstract]

**Purpose:** The purpose of this study was to investigate the kinetics of cerebral blood flow (CBF) in conjunction with cardiopulmonary response during constant-work rate cycling exercise of moderate and heavy intensities. **Methods:** Seven subjects (6 males and 1 female; age,  $25.4 \pm 7.7$  yr; height,  $171.9 \pm 4.3$  cm; body mass,  $67.7 \pm 11.4$  kg) participated in the present study. The subjects completed incremental cycle ergometer test to assess  $VO_{2peak}$ , the gas exchange threshold (GET), and the respiratory compensation threshold (RCT). Secondary, the subjects performed two sets of constant workload of exercise bouts (10 min) by cycle ergometer corresponding to the level of 10% below GET (moderate intensity) and RCT (heavy intensity). Respiratory gas analysis and the middle cerebral blood flow mean velocity (MCA  $V_{mean}$ ) were measured simultaneously using the transcranial Doppler (TCD) method.  $P_aCO_2$  was estimated ( $eP_aCO_2$ ) using PETCO<sub>2</sub> and  $V_T$ . We assumed that MCA  $V_{mean}$  could be used as an index of the global CBF. **Results:**  $VO_2$  and  $eP_aCO_2$  remained stable after the onset at moderate intensity whereas  $VO_2$  increased throughout the trial and  $eP_aCO_2$  decreased after the onset at heavy intensity. The percentage change from baseline for MCA  $V_{mean}$  ( $\Delta MCA V_{mean}$ ) increased within 2 min to a peak value within 2 min by  $32.8 \pm 9.1\%$  and  $31.8 \pm 11.8\%$  at moderate and heavy intensity, respectively. In the heavy-intensity exercise  $\Delta MCA V_{mean}$  decreased further below the response to moderate exercise as time progressed prior to the recovery phase (trials  $\times$  time:  $F = 3.84$ ,  $P < 0.05$ ). **Conclusion:** The different kinetics of MCA  $V_{mean}$  between moderate and heavy-intensity exercise was identified during a constant work rate cycling exercise. We found that in heavy-intensity trials, the relationship between  $eP_aCO_2$  and MCA  $V_{mean}$  was different to that at moderate intensity during the recovery phase.

Key Words: Cerebral blood flow, transcranial Doppler, exercise

## Introduction

Perturbation of cerebral blood flow (CBF) should be a concern when the central command from the brain terminates exercise at volitional exhaustion<sup>1,2)</sup>. Previous studies have reported that the middle cerebral artery blood flow mean velocity (MCA  $V_{mean}$ ), measured using the transcranial Doppler (TCD) method, decreases during high-intensity exercise<sup>3, 4, 5)</sup>. Further, it has been suggested that MCA  $V_{mean}$  can be used as an index of

the global CBF rather than the regional CBF since the volume perfused by the middle cerebral artery between the cerebral hemispheres is quite large, although individual differences exist<sup>6)</sup>. This finding obtained during exercise suggests that hyperventilation-induced hypocapnia could affect CBF since carbon dioxide (CO<sub>2</sub>) plays an important role in regulating CBF.

Recently, we investigated MCA  $V_{mean}$  during incremental exercise tests<sup>7)</sup> and reported that MCA

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$V_{\text{mean}}$  peaked at the respiratory compensation threshold (RCT) where the end-tidal pressure of  $\text{CO}_2$  ( $P_{\text{ET}}\text{CO}_2$ ) began to decrease<sup>8)</sup>. In the present study, we investigated the kinetics of MCA  $V_{\text{mean}}$  during constant work rate cycling exercise. In moderate-intensity constant work rate exercise, during which oxygen uptake ( $\text{VO}_2$ ) remains in the steady state of phase III<sup>9)</sup>,  $P_{\text{ET}}\text{CO}_2$ , which reflects the arterial  $\text{CO}_2$  pressure ( $P_{\text{a}}\text{CO}_2$ ) to some extent, also has a steady phase. In contrast,  $P_{\text{ET}}\text{CO}_2$  could be affected during heavy-intensity constant work rate exercise. During steady-state exercise, it appears that the CBF could be stable if  $P_{\text{ET}}\text{CO}_2$  remained stable during low-intensity exercise but altered if  $P_{\text{ET}}\text{CO}_2$  changed during high-intensity exercise.

The purpose of this study was to investigate the kinetics of CBF detected by TCD during two trials that consisted of moderate and heavy constant work rate cycling exercise. The domains of moderate and heavy intensity have been described in previous studies based on  $\text{VO}_2$  and lactate response<sup>10)</sup>. As the phase III of  $\text{VO}_2$  kinetics occurs below the lactate threshold (LT) or the gas exchange threshold (GET)<sup>8,9)</sup>, the power output at the GET in the incremental test was defined as the criterion for constant work rate at moderate intensity. Considering that the exercise intensity at the RCT can be regarded as the cut-off point where volitional exhaustion begins in incremental tests, we selected the power output at the RCT as the criterion for constant work rate at heavy intensity. We hypothesized that the kinetics of CBF would be different between the two trials and investigated whether the kinetics of CBF would be similar to that of systematic  $P_{\text{a}}\text{CO}_2$  estimated from pulmonary gas exchange. Since systematic  $P_{\text{a}}\text{CO}_2$  changes in response to increased metabolic demand of energy consumption for working muscles and hyperventilation during exercise,  $P_{\text{a}}\text{CO}_2$  was

estimated using the formula that was proposed and applied in previous studies<sup>11, 12)</sup> using  $P_{\text{ET}}\text{CO}_2$  and tidal volume ( $V_{\text{T}}$ ) during the trials.

## METHODS

### Subjects

Seven volunteers (6 males and 1 female; age,  $25.4 \pm 7.7$  yr; height,  $171.9 \pm 4.3$  cm; body mass,  $67.7 \pm 11.4$  kg), having given written informed consent, took part in this study, which conformed to the standards set by the *Declaration of Helsinki*. All subjects were healthy and none reported any history of neurological or cardiovascular diseases. All subjects had abstained from exercise and caffeine for at least 12 h before the day of the experiment. Prior to any data collection, the subjects were familiarized with all procedures and measurements.

### Experimental design

Subjects visited the laboratory on two occasions, with a minimum of two days of recovery between each test, and all tests were performed within four weeks. On the first visit, the subjects followed a ramp protocol for the determination of  $\text{VO}_{2\text{peak}}$ , GET, and RCT on an electromagnetically braked cycle ergometer (Lode Excalibur Sport, Groningen, The Netherlands). On the second visit, subjects performed two trials of different constant work rate cycling exercise with sufficient rest for recovery between each trial. On the second visit, MCA  $V_{\text{mean}}$  was measured using TCD.

### Determination of $\text{VO}_{2\text{peak}}$ , GET, and RCT

Each subject adjusted the ergometer for comfort and the seat height was adjusted so that there was a slight bend in the knee joint when the pedal was at its lowest point.  $\text{VO}_{2\text{peak}}$ , GET, and RCT were determined using a ramp protocol that consisted of 1 min of unloaded baseline pedaling and then a 25 W exercise started with a  $30 \text{ W} \cdot \text{min}^{-1}$  or

25 W·min<sup>-1</sup> increase in work rate until volitional exhaustion. Subjects were instructed to maintain their preferred cadence (60–80 r.p.m.) for as long as possible. The test was terminated when the subjects could no longer maintain the pedaling frequency above 60 r.p.m. for more than 10 s despite strong verbal encouragement. Throughout the test, pulmonary gas exchange was measured breath-by-breath as described below.  $VO_{2peak}$  was determined as the highest average  $VO_2$  over a 30-s period. Data were reduced to 10-s averages for the estimation of GET and RCT.

### Constant work rate tests

These tests were performed after 1-min unloaded pedaling of the preferred cadence (60–80 r.p.m.). The first trial was of moderate intensity corresponding to approximately 10% below the GET; the second trial was of heavy intensity approximately 10% below the RCT. Between each trial, the subjects rested for at least 3 h so that the baseline state was not different among trials. Pulmonary gas exchange was measured breath-by-breath throughout the tests. During the tests, measurements of the middle cerebral artery blood flow velocity (MCA  $V_{mean}$ ) were performed using TCD ultrasound.

### Equipment

The subjects breathed through a facemask (Hans Rudolph, MO, USA) connected to an online gas analyzer (CPET; Cosmed, Rome, Italy). The inspired and expired gas volume and gas concentration signals were continuously sampled at 100 Hz, the latter using paramagnetic ( $O_2$ ) and infrared ( $CO_2$ ) analyzers via a capillary line connected to the facemask. These analyzers were calibrated before each test with gases of known concentration, and the turbine volume transducer was calibrated using a 3-L syringe (Hans Rudolph,

MO, USA). The volume and concentration signals were time aligned by accounting for the delay in capillary gas transit and analyzer rise time relative to the volume signal.  $VO_2$ ,  $CO_2$  production ( $VCO_2$ ),  $V_T$ , minute ventilation ( $V_E$ ), and  $P_{ET}CO_2$  were calculated and displayed breath-by-breath. Heart rate (HR) was monitored every 5 s by short range radio telemetry (Polar S-610; Polar Electro, Kempele, Finland). MCA  $V_{mean}$  was determined using TCD (Companion III, Nicolet Vascular, CO, USA). The proximal segment of the middle cerebral artery was insonated at a depth of 50–54 mm from the temporal bone depending on the position with the best signal-to-noise ratio<sup>13)</sup>. Once the optimal signal-to-noise ratio was obtained, the probe was covered with an adhesive ultrasonic gel and secured with headbands because the probes of the TCD should be accurately insonated with an appropriate volume of the sample to be detected.

### Data Analysis

Measurements of pulmonary gas exchange were averaged over 10-s intervals for subsequent analysis.  $P_aCO_2$  was estimated from measurements of  $P_{ET}CO_2$  and  $V_T$  (in liters) using the equation described by Jones and colleagues<sup>11)</sup>. The estimated  $P_aCO_2$  ( $eP_aCO_2$ ) was calculated as  $5.5 + (0.9 \times P_{ET}CO_2) - (0.0021 \times V_T)$ . MCA  $V_{mean}$  was computed as the time average of continuously sampled maximum frequency Doppler shift for each heart beat, which thereafter were averaged over 10-s intervals. In this study, we determined MCA  $V_{mean}$  as the time-averaged maximum velocity ( $TAV_{max}$ ) that was calculated from the peak systolic velocity (PSV) and the end-diastolic velocity (EDV) during each heart beat as  $TAV_{max} = (PSV + 2 \times EDV)/3$ <sup>14)</sup>.  $TAV_{max}$  was obtained by an A/D converter and the softwares Power Lab ML840 and Chart version 7.0 (ADInstruments, CO, USA).

## Statistical Analysis

Unless otherwise stated, all data are presented as the mean  $\pm$  SD. Normality of the data was checked using the Shapiro-Wilk test, and homogeneity of variance was checked using the Levene test. Baseline variables for the two trials were compared using a paired t-test. One-way repeated-measures analysis of variance (ANOVA) was performed to evaluate the differences within trials. For the differences between trials and time, two-way repeated-measures ANOVA was performed. The source of any significant main effect was examined using Bonferroni post hoc analysis. The data were analyzed using the statistical package Prism 5.0 (GraphPad Software, CA, USA) and Medcalc 10.0 (Medcalc Software bvba, Mariakerke, Belgium). The level of statistical significance was set at  $P < 0.05$ .

## RESULTS

### Incremental tests and baseline measurements in the two trials

Peak values of oxygen uptake ( $VO_{2peak}$ ) and percentage values relative to  $VO_{2peak}$  at the GET and RCT are presented in Table 1. On the basis of the results of the incremental tests, the power output for constant work rate trials at moderate intensity

and heavy intensity were determined for each subject (Table 2). The individual baseline values of respiratory and cerebral hemodynamic variables for the two trials are presented in Table 2.  $eP_aCO_2$  and  $MCA V_{mean}$  were similar at rest before the two trials.

### Cardiopulmonary responses

The  $VO_2$  and  $eP_aCO_2$  recorded during exercise and recovery are presented in Fig. 1.  $VO_2$  increased at the onset and did not change during exercise in the moderate-intensity trial, whereas it increased gradually in the heavy-intensity trial.  $eP_aCO_2$  increased at the onset and began to decrease toward the end of exercise in the heavy-intensity trial, whereas it did not change until the end of exercise in the moderate-intensity trial.  $eP_aCO_2$  decreased in the recovery phase of both trials, but with lower values in the heavy-intensity trials than in the moderate-intensity trials at 11 min and 14 min. Cardiopulmonary data at the end of the trials (10 min) were significantly higher in heavy-intensity trials than in the moderate-intensity trials (Table 3).

### Cerebral hemodynamics

TCD measurements of  $MCA V_{mean}$  were performed bilaterally; however, there were discrepant results between the sides in three subjects that may have been attributable to head

**Table 1. Individual values of oxygen uptake and power output for selected intensities derived from the incremental tests.**

subject	$VO_{2peak}$ (ml/kg/min)	% $VO_{2peak}$ at GET	% $VO_{2peak}$ at RCT	$P_{peak}$ (watt)	% $P_{peak}$ at GET	% $P_{peak}$ at RCT
1	49.8	62.0	80.3	235	59.6	76.6
2	54.2	69.6	82.8	355	59.2	73.2
3	42.2	60.7	80.3	355	53.5	78.9
4	36.6	56.3	74.3	230	43.5	73.9
5	56.2	70.1	82.2	345	60.9	78.3
6	43.0	51.2	74.9	230	43.5	73.9
7	47.1	66.0	77.1	245	55.1	75.5

**Table 2. Individual power output for constant work load ( $P_{\text{const}}$ ) and baseline values of respiratory and cerebral hemodynamic variables for moderate-intensity (MI) and heavy-intensity (HI) trial.**

subject	$P_{\text{const}}$ (watt)		$eP_a\text{CO}_2^a$ (mmHg)		MCA $FV^b$ (cm /sec)	
	MI	HI	MI	HI	MI	HI
1	115	160	33.3	33.4	60.6	60.0
2	150	250	32.4	37.3	61.9	67.2
3	150	260	38.1	38.0	52.9	60.5
4	80	160	39.4	32.9	52.4	57.6
5	150	250	39.7	38.8	61.1	60.7
6	80	150	37.6	39.2	41.2	41.4
7	125	170	42.4	35.8	67.3	57.5

<sup>a</sup> $eP_a\text{CO}_2$ , <sup>b</sup> MCA $FV$  were not significantly different between the two trials.

**Table 3. Cardiopulmonary data at 10 min in moderate-intensity ( $Ex_{\text{MI}}$ ) and heavy-intensity ( $Ex_{\text{HI}}$ ) trial.**

	$Ex_{\text{MI}}$ at 10 min	$Ex_{\text{HI}}$ at 10 min <sup>a</sup>
$\dot{V}_E$ (L/min)	42.7 ± 6.0	94.0 ± 28.4
$\dot{V} O_2$ (ml · min <sup>-1</sup> · kg <sup>-1</sup> )	27.7 ± 4.1	44.5 ± 8.3
% $\dot{V} O_{2\text{peak}}$	58.9 ± 1.8	94.9 ± 11.1
RER	0.88 ± 0.04	0.94 ± 0.06
fb (breaths per minute)	24.4 ± 4.6	41.5 ± 5.7
$V_T$ (L)	1.82 ± 0.53	2.27 ± 0.62
HR (beats per minute)	121 ± 18	169 ± 17
pet $\text{CO}_2$ (mmHg)	43.6 ± 2.9	36.3 ± 2.8

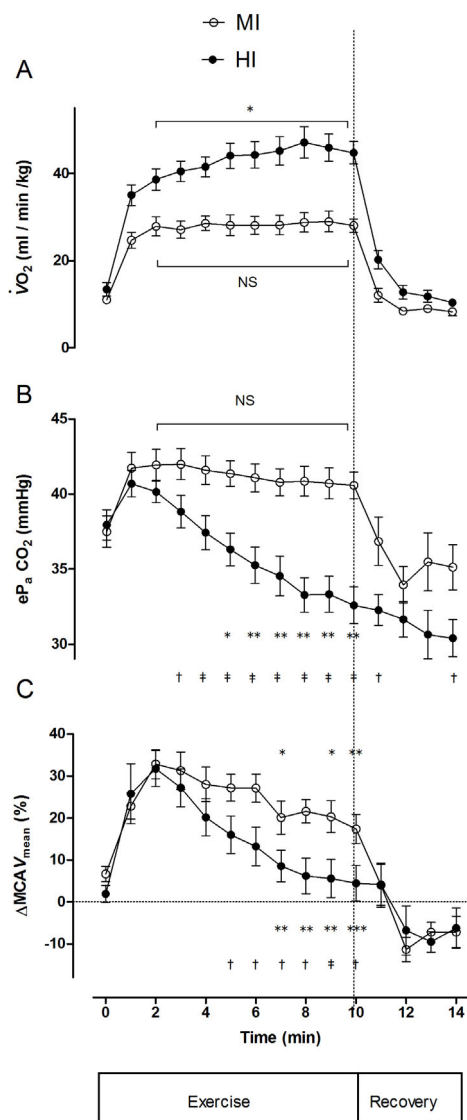
<sup>a</sup>All variables in  $Ex_{\text{HI}}$  at 10 min were significantly higher than those in  $Ex_{\text{MI}}$ .

movement artifacts. Accordingly, in the cases of discrepancy, the side yielding higher values was selected for further investigation. As the baseline values of MCA  $V_{\text{mean}}$  were different among subjects (Table 2), the percentage change from baseline ( $\Delta\text{MCA } V_{\text{mean}}$ ) for each subject was used for investigation in both trials. The  $\Delta\text{MCA } V_{\text{mean}}$  values recorded during exercise and recovery are presented in Fig. 1 in conjunction with cardiopulmonary variables.  $\Delta\text{MCA } V_{\text{mean}}$  increased within 2 min to a peak value by  $32.8 \pm 9.1\%$  and  $31.8 \pm 11.8\%$  at moderate and heavy intensity, respectively. In the heavy-intensity exercise  $\Delta\text{MCA}$

$V_{\text{mean}}$  decreased further below the response to moderate exercise as time progressed prior to the recovery phase (trials  $\times$  time:  $F = 3.84$ ,  $P < 0.05$ ). During the recovery phase, there was no significant difference in  $\Delta\text{MCA } V_{\text{mean}}$  between the moderate- and heavy-intensity trials.

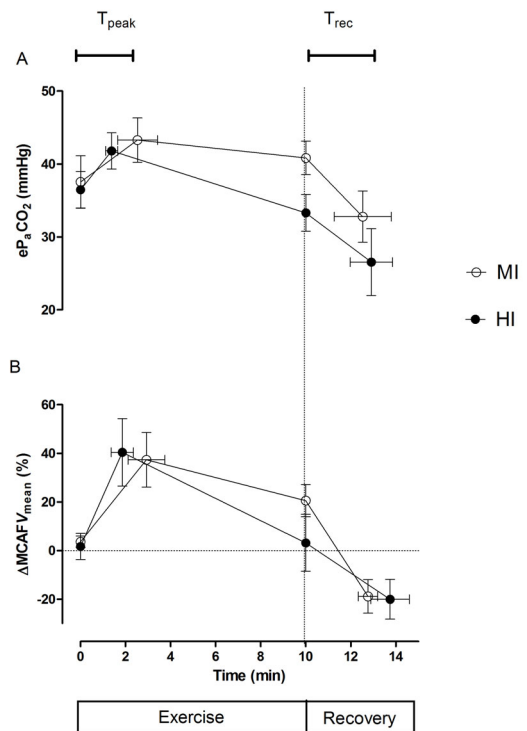
#### Time course of $eP_a\text{CO}_2$ and $\Delta\text{MCA } V_{\text{mean}}$

Individual values of  $eP_a\text{CO}_2$  and  $\Delta\text{MCA } V_{\text{mean}}$  were observed in relation to the duration from start to peak and from end to nadir, and expressed as  $T_{\text{peak}}$  and  $T_{\text{rec}}$ , respectively (Fig. 2). As shown in Fig. 3, for both  $eP_a\text{CO}_2$  and  $\Delta\text{MCA } V_{\text{mean}}$ ,  $T_{\text{peak}}$  was shorter in



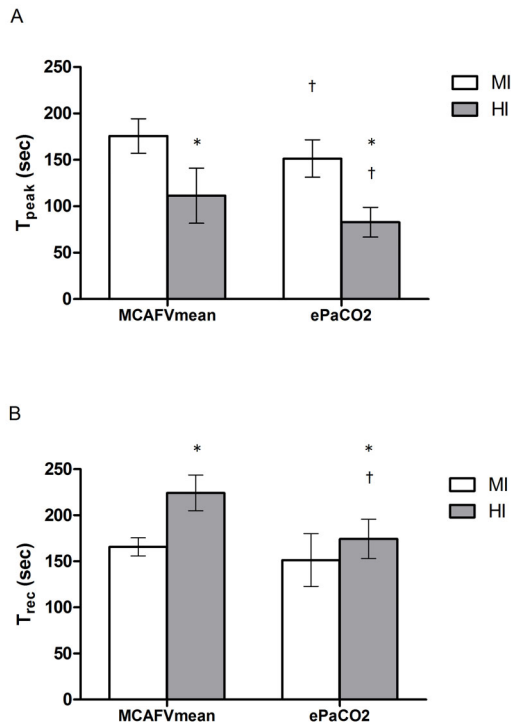
**Figure 1.**  $VO_2$  (A),  $eP_aCO_2$  (B), and  $\Delta MCA V_{mean}$  (C) during 10 min of cycling exercise and recovery at moderate intensity ( $\circ$ ) and heavy intensity ( $\bullet$ ) trial. Values are mean  $\pm$  SEM;  $n=7$ . Significantly different from 1 min for  $VO_2$  (A),  $eP_aCO_2$  (B) and from 2 min for  $\Delta MCA V_{mean}$  (C) within trial:  $P < 0.05$  and  $** P < 0.01$ . Significantly different from moderate-intensity trial:  $\dagger P < 0.05$  and  $\ddagger P < 0.01$ . NS: Not significantly changed.

heavy-intensity trials than in moderate-intensity trials and  $T_{rec}$  in high-intensity trials was longer than in moderate-intensity trials.  $T_{peak}$  in  $MCA V_{mean}$



**Figure 2.**  $eP_aCO_2$  (A) and  $\Delta MCA V_{mean}$  (B) in relation to the duration from start to peak ( $T_{peak}$ ) and from end to nadir ( $T_{rec}$ ) during 10 min of cycling exercise and recovery at moderate intensity ( $\circ$ ) and heavy intensity ( $\bullet$ ) trial. Values are mean  $\pm$  SEM;  $n=7$ .

lagged that in  $eP_aCO_2$  by 28.6 s ( $P < 0.05$ ) at heavy intensity and by 32.9 s ( $P < 0.05$ ) at moderate intensity as well. During the recovery phase,  $T_{rec}$  in  $MCA V_{mean}$  lagged that in  $eP_aCO_2$  by 50.0 s ( $P < 0.05$ ) at heavy intensity, whereas  $T_{rec}$  in  $MCA V_{mean}$  did not differ from that in  $eP_aCO_2$  ( $P = 0.67$ ) at moderate intensity. Furthermore, values of  $eP_aCO_2$  and  $\Delta MCA V_{mean}$  at 0 min,  $T_{peak}$ , 10 min and  $T_{rec}$  beyond 10 min were investigated as time-aligned data, including the onset and endpoint (Fig. 4). There was a significant difference between the moderate- and heavy-intensity trials (trial  $\times$  time  $F = 3.41$  and  $6.43$ ,  $P < 0.05$  and  $0.001$  for  $eP_aCO_2$  and  $\Delta MCA V_{mean}$ , respectively). It was commonly found



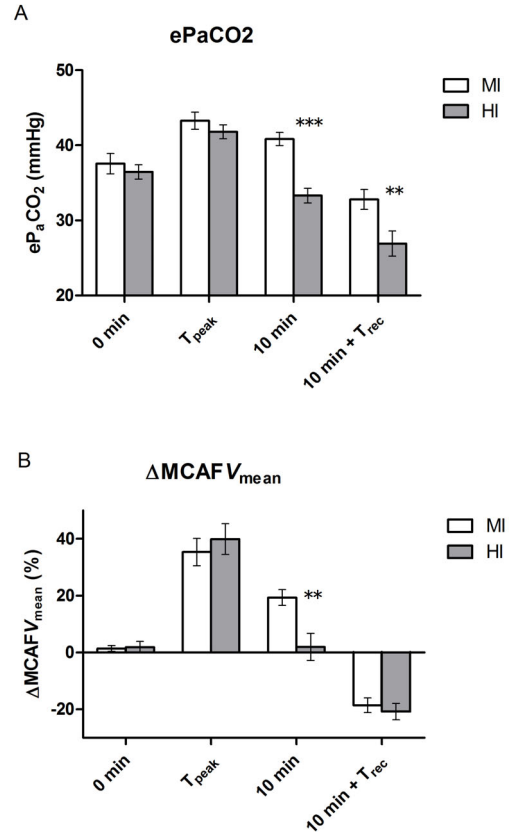
**Figure 3.**

$T_{peak}$  (A) and  $T_{rec}$  (B) of MCA  $V_{mean}$  and  $ePaCO_2$  during 10 min of cycling exercise and recovery at moderate-intensity (MI) and heavy-intensity (HI) trial. Values are mean  $\pm$  SEM; n=7. \*Significantly different from MI trial ( $P < 0.05$ ). †Significantly different from MCA  $V_{mean}$  ( $P < 0.05$ ).

that  $ePaCO_2$  and  $\Delta MCA V_{mean}$  at  $T_{peak}$  did not differ between the moderate- and heavy-intensity trials. At heavy intensity,  $ePaCO_2$  decreased further below the response to moderate exercise as time progressed at the endpoint. In the heavy-intensity trial,  $\Delta MCA V_{mean}$  was lower than in the moderate-intensity trial only at the end of exercise (10 min), but was similar at  $T_{rec}$ .

## DISCUSSION

The main finding of the present study is that



**Figure 4.**

$ePaCO_2$  (A) and  $\Delta MCA V_{mean}$  (B) at 0 min,  $T_{peak}$ , 10 min and 10 min plus  $T_{rec}$  at moderate-intensity (MI) and heavy-intensity (HI) trial. Values are mean  $\pm$  SEM; n=7. Significantly different from MI trial at a given time point: \* $P < 0.05$  and \*\* $P < 0.01$ .

the time course of the MCA  $V_{mean}$  change in heavy-intensity trials differed from that at moderate intensity during a constant work rate cycling exercise. As shown in Figs. 1, 2, and 4, there was also a difference between the two trials in terms of the kinetics of  $VO_2$  and  $ePaCO_2$ . In the moderate-intensity trials, MCA  $V_{mean}$  decreased during exercise, whereas the kinetics of  $VO_2$  and  $ePaCO_2$  remained stable after the onset. In heavy-intensity trials, the decrease in MCA  $V_{mean}$  during exercise was steeper than that in the



moderate-intensity trials. This enhanced change in MCA  $V_{\text{mean}}$  is similar to that observed in extreme conditions such as during heat stress, where MCA  $V_{\text{mean}}$  has been demonstrated to decrease during intense exercise by 20%–30% due to hyperventilation-induced hypocapnia<sup>1,12, 15)</sup>. The finding that MCA  $V_{\text{mean}}$  was closely correlated with  $eP_a\text{CO}_2$  confirms that  $\text{CO}_2$  plays an important role in regulating CBF<sup>16, 17)</sup>. However, in the moderate-intensity trials of the present study, MCA  $V_{\text{mean}}$  decreased without a change in  $eP_a\text{CO}_2$  and this finding suggests that factors other than  $\text{CO}_2$  regulate CBF. Although arterial blood pressure, cardiac output, and sympathetic activation could influence the regulation of CBF<sup>1,3,18)</sup>, these factors were not investigated in the present study. Whereas the range of  $eP_a\text{CO}_2$  differed between the two trials, that of MCA  $V_{\text{mean}}$  was similar (Fig. 4). This discrepancy was identified during the recovery phase, during which MCA  $V_{\text{mean}}$  did not decrease in the heavy-intensity trials as much as expected from the cerebral vascular response (CVR) to  $\text{CO}_2$  recorded in the moderate-intensity trials. Accordingly, it is speculated that CBF would not decrease beyond a certain extent under circumstances where hypoperfusion disturbs the homeostasis of the central nerve system. In the present study, CBF was approximately 20% below the baseline where MCA  $V_{\text{mean}}$  decreased to a nadir during the recovery phase in heavy-intensity trials. If the CVR to  $\text{CO}_2$  in the moderate-intensity trials was applied at the endpoint in the heavy-intensity trials, the MCA  $V_{\text{mean}}$  would decrease to nearly 50% below the baseline. Considering that a previous study reported that presyncopal symptoms occur when MCA  $V_{\text{mean}}$  decreased by approximately 50% from the resting value<sup>19)</sup>, it is likely that factors other than  $\text{CO}_2$  play a role in regulating CBF in order to prevent hypoperfusion during heavy-intensity exercise. Differences between the

two trials with respect to  $eP_a\text{CO}_2$  and MCA  $V_{\text{mean}}$  were also suggested by the temporal changes (Fig. 3). In both  $T_{\text{peak}}$  and  $T_{\text{rec}}$ , changes in MCA  $V_{\text{mean}}$  lagged behind those in  $eP_a\text{CO}_2$  in the heavy-intensity trials, whereas synchronized change between MCA  $V_{\text{mean}}$  and  $eP_a\text{CO}_2$  was identified in the moderate-intensity trials. These findings suggest that CBF reacts rapidly to a change in  $eP_a\text{CO}_2$  in moderate-intensity trials but that this was not the case in the heavy-intensity trails. During constant work rate exercise, the kinetics of  $P_a\text{CO}_2$  differed between heavy- and moderate-intensity domains during both the onset and recovery<sup>20)</sup>. With regards to  $eP_a\text{CO}_2$ , these findings were confirmed in the present study and, additionally, we made a new discovery concerning MCA  $V_{\text{mean}}$ .

Secondly, we suggest the possibility that the kinetics of MCA  $V_{\text{mean}}$  could indicate a boundary between the moderate- and heavy-intensity domains, i.e., the LT or GET that is identified using pulmonary gas exchange criteria or analysis of blood lactate response during the staged protocol of the incremental tests<sup>8)</sup>. This boundary could not be detected using the kinetics of  $\text{VO}_2$  and  $eP_a\text{CO}_2$  with a single bout of constant work rate exercise and could reflect the fitness status of the observed subjects<sup>21)</sup>. In one study of prolonged exercise<sup>12)</sup>, which was carried out for 60 min in a thermoneutral environment at a constant work rate of approximately 57%  $\text{VO}_{2\text{max}}$ , MCA  $V_{\text{mean}}$  increased at the onset by 20% and remained stable, and the kinetics of  $eP_a\text{CO}_2$  were similar to those of MCA  $V_{\text{mean}}$ . In the present study, the steady state of  $\text{VO}_2$  was identified in the moderate-intensity trials with a mean of 58.9%  $\text{VO}_{2\text{peak}}$  at the end of trials, but MCA  $V_{\text{mean}}$  decreased. The heterogeneous characteristics of subjects with a  $\text{VO}_{2\text{peak}}$  of  $47.0 \pm 7.0 \text{ ml}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$  in the present study (Table 1) were quite different from the homogeneous characteristics of subjects with a  $\text{VO}_{2\text{max}}$  of  $70 \pm 1$

ml·min<sup>-1</sup>·kg<sup>-1</sup> in the previous study. The intensity of 57%  $VO_{2max}$  observed among highly trained subjects in the previous study is expected to be sufficiently below the GET, whereas the moderate intensity of 58.9%  $VO_{2peak}$  recorded in the present study was close to the mean of 62.3%  $VO_{2peak}$  at the GET. From a comparison of our data with those from the previous study described above, we speculated that MCA  $V_{mean}$  would remain stable after the onset phase if the constant work rate is sufficiently below the GET for subjects. It is likely that the kinetics of MCA  $V_{mean}$  could be determined by the relationship between the given intensity and fitness status of the subjects. Consequently, from a single bout of constant-work rate exercise of moderate intensity, in which  $VO_2$  remains stable after the onset, one could obtain further information relevant to the GET from the kinetics of MCA  $V_{mean}$ . It is notable that in only one bout of constant work rate exercise with measurements for pulmonary gas exchange and MCA  $V_{mean}$  were we able to detect the GET or the boundary between the moderate- and heavy-intensity domains without an additional incremental test. However, we should investigate other constant work rate tests at an intensity sufficiently below the GET in order to examine this possibility. Simultaneous analysis for response of blood lactate could confirm the domain of exercise intensity. Furthermore, it should be taken into consideration that head movement during the trials may have yielded artifacts that suggested a tendency of decreasing MCA  $V_{mean}$  values. With respect to this issue, we could estimate whether measurements were valid or not by comparing values obtained from both sides of the head.

In conclusion, the different kinetics of MCA  $V_{mean}$  between moderate and heavy exercise intensity was identified during a constant work rate cycling exercise. We found that in heavy-intensity

trials, the relationship between  $eP_aCO_2$  and MCA  $V_{mean}$  was different to that at moderate intensity during the recovery phase. The additional finding that MCA  $V_{mean}$  decreased without a change in  $eP_aCO_2$  implies that CBF is regulated by factors other than  $CO_2$ . Furthermore, we suggest the possibility that the kinetics of MCA  $V_{mean}$  during constant work rate cycling exercise could represent a threshold related to the fitness level of subjects.

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