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Cerebrovascular Response to CO_2 during Moderate-intensity Exercise Measured by Performing Transcranial Doppler Ultrasonography

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［Abstract］

Previous studies demonstrated that cerebral blood flow (CBF) changes during dynamic exercise and a physiological basis for this observation may be explained by the tight control of CBF by arterial carbon dioxide tension (P_aCO_2). This study examined whether the steady state of the middle cerebral artery blood flow velocity ($MCAV_{mean}$) and P_aCO_2 could be observed during constant work rate cycling exercise and to investigate the cerebrovascular reactivity (CVR) to CO_2. Seven young volunteers performed a 10-min exercise session with constant workload using a cycle ergometer, with intensities corresponding to the level below the lactate threshold. Respiratory gas analysis and $MCAV_{mean}$ were measured simultaneously using the transcranial Doppler (TCD) method. P_aCO_2 was estimated (eP_aCO_2) using the end-tidal pressure of CO_2 ($P_{ET}CO_2$) and the tidal volume (V_T). On-transient phase II of VO_2 and the corresponding responses of $MCAV_{mean}$ and eP_aCO_2 were investigated simultaneously with the monoexponential model. Since the responses in $\Delta MCAV_{mean}$ or eP_aCO_2 had the overshoot phase within 3min in some cases, analysis for the fitted curves of the monoexponential model was performed during the first 5 min as well as during the total 10 min. CVR to CO_2 during the dynamic cyclic exercise was 5.33 % $mmHg^{-1}$ and 4.78 % $mmHg^{-1}$ in the 5-min and the 10-min analysis, respectively. In the 5-min and the 10-min analysis, CVR to CO_2 significantly correlated with the exercise intensity during the 10-min bout (r^2 = 0.89 and 0.75, respectively). During the on-transient phase of dynamic exercise, CBF would be influenced by P_aCO_2 and other factors such as the neuronal activation and cardiac output would also be involved in changing CBF.

Key Words: cerebrovascular response to CO_2, cerebral blood flow, exercise

Introduction

Previous studies using the transcranial Doppler (TCD) method have shown that cerebral blood flow (CBF) in the internal carotid artery increases by almost 20% during dynamic exercise [1, 2]. A physiological basis for these deviating blood flow patterns may be explained, in part, by the tight control of CBF by arterial carbon dioxide tension (P_aCO_2), which fluctuates during dynamic exercise [3]. With respect to the role of P_aCO_2 in controlling CBF, numerous studies have investigated the cerebrovascular reactivity (CVR) to CO_2 with the steady state [4, 5] and rebreathing techniques [6, 7]. CVR to CO_2 has been widely applied in clinical practice to evaluate cerebral function, for example in ischemic cerebrovascular diseases or stroke [8, 9]. However, few studies have reported on CVR to CO_2 during dynamic exercise[10, 11]. Recently, we investigated changes in the middle cerebral artery blood flow velocity ($MCAV_{mean}$) during a moderate-intensity cycling exercise at a constant work rate (WR) and showed that $MCAV_{mean}$ remained stable in some

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subjects, as did the estimated P_aCO_2 (eP_aCO_2) [12]. During moderate-intensity exercise, pulmonary oxygen uptake ($\dot{V}O_2$) is in the steady-state phase that follows phase II of the $\dot{V}O_2$ kinetics [13]. Thus, we expect that CVR to CO_2 could be defined from 2 steady state conditions of rest and moderate intensity exercise if both P_aCO_2 and MCAV_{mean} are at the plateau phase.

Although CO_2 is one of major chemical factors that can affect cerebral vascular tone and alter CBF, neuronal activation has an effect on blood flow, and sympathetic innervation plays a role in the neurogenic control of CBF [14, 15]. Since previous studies have indicated that the mechanism of vascular response to neural activation is independent of that to P_aCO_2 [15], we would expect to see a greater increase in CBF during dynamic exercise compared with that during rest. The purpose of this study is to examine whether the steady state of MCAV_{mean} and eP_aCO_2 could be observed during 10 min of exercise at constant WR and to investigate CVR to CO_2 during a moderate-intensity cycling exercise at a constant WR.

Methods

Seven young volunteers (7 men; mean age, 23.0 ± 2.6 years; mean height, 1.71 ± 0.07 m; mean body mass, 67.0 ± 12.1 kg), having given written informed consent, participated in this study. All subjects were healthy, and none reported any history of neurological or cardiovascular disease. Subjects visited the laboratory on 2 occasions with a minimum of 2 days of recovery between each test, and all tests were performed within 4 weeks. At the first visit, the subjects followed a ramp protocol with an increase in WR of 25 W or 20 W/min, beginning from 0 W, for determining $\dot{V}O_{2peak}$, and the lactate threshold (LT) [13, 16] on an electromagnetically braked cycle ergometer (Lode Excalibur Sport, Groningen, The Netherlands). On subsequent occasions, subjects had a 10-min exercise session with constant workload using a cycle ergometer, with intensities corresponding to a level of at least 15% below LT. The exercise sessions were followed by 2-min rest for collecting the baseline data.

The subjects breathed through a facemask (Hans Rudolph, MO, USA) connected to an online gas analyzer (CPET; Cosmed, Rome, Italy). P_aCO_2 was estimated from measurements of the end-tidal pressure of CO_2 ($P_{ET}CO_2$) and the tidal volume (V_T) determined using the equation described by Jones et al. (eP_aCO_2) [17]. MCAV_{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 [18]. In this study, we determined MCA *V*mean as the time-averaged maximum velocity (TAV_{max}), which was calculated from the peak systolic and the end-diastolic velocity during each heart beat [19]. TAV_{max} was obtained using an A/D converter and the Power Lab ML840 and Chart software (version 7.0; AD Instruments, CO, USA).

Breath-by-breath data from measurements of pulmonary gas exchange were linearly interpolated to 1-s intervals, time-aligned, and ensemble-averaged to yield a single profile; the data were then time-averaged into 10-s bins to yield a single response for subsequent analysis for each subject. MCAV_{mean} was also determined as 10-s intervals of TAV_{max}. On-transient phase II of $\dot{V}O_2$ [13] and the corresponding responses of eP_aCO_2 and MCAV_{mean} were investigated simultaneously using the same kinetics model. The responses were then modeled using a monoexponential of the form:

$$Y(t) = Y(0) + Amp\{1 - e^{[-(t-TD)/\tau]}\}$$

where Y(t) represents the variable at any time (t), Y(0) is the relevant baseline control value, Amp is the amplitude (i.e., increase in Y above baseline), τ is the time constant (i.e., the time taken to reach 63% of the total increase in Y above baseline), and TD is the time delay. TD is 20 s in $\dot{V}O_2$ kinetics since the first 20 s of the ensemble dataset were removed [20]. TD is 0 s in eP_aCO_2 and $MCAV_{mean}$. Using the results of the monoexponential model, the relationship of the changes in $MCAV_{mean}$ and eP_aCO_2 are described as CVR to $CO_2 = (\Delta MCAV_{mean}/\Delta eP_aCO_2) \times 100$, where $\Delta MCAV_{mean}$ and ΔeP_aCO_2 correspond to the amplitudes of $MCAV_{mean}$ and eP_aCO_2, respectively.

The data were analyzed using the statistical package Prism 5.0 (GraphPad Software, CA, USA). Unless otherwise stated, all data are presented as the mean ± standard error (SE). The Wilcoxon matched pairs test was used to compare the intensity differences. A Pearson's product moment correlation coefficient was used to determine relationships between appropriate variables. The level of statistical significance was set at $P < 0.05$.

Results

$\dot{V}O_2$ and WR at the endpoint of the incremental tests ($\dot{V}O_{2peak}$ and P_{peak}), $\%VO_{2peak}$ at LT and WR at LT (P_{LT}) and WR for the 10-min cycling exercise (P_{EX}) at a constant WR, are shown for all participants in **Table 1**. Values of $MCAV_{mean}$ and eP_aCO_2 at rest were 54.9 ± 3.6 cm s^{-1} and 36.3 ± 0.6 mmHg, respectively. As $MCAV_{mean}$ varied among subjects, the relative change from the baseline (rest) ($\%\Delta MCAV_{mean}$) was determined for further analysis.

$\dot{V}O_{2peak}$, pulmonary oxygen uptake at the endpoint of the incremental tests; P_{peak}, work rate at the endpoint of the incremental tests; LT, lactate threshold; P_{EX}, work rate for the 10-min cycling exercise; P_{LT}, work rate at lactate threshold.

Individual $\dot{V}O_2$ kinetics during the 10-min exercise is shown in **Fig. 1.** For all sessions, $\dot{V}O_2$ was in steady state, and the estimated values for the plateau phase of $\dot{V}O_2$ varied from 19.7 to 32.2 ml min^{-1} kg^{-1} (37.4–54.7% of $\dot{V}O_{2peak}$). The τ for $\dot{V}O_2$ was 30.0 ± 2.4 s. Individual kinetics of $\%\Delta MCAV_{mean}$ and eP_aCO_2 during the 10-min exercise are showed in **Fig. 2.** In subjects A, B, and F, $\%\Delta MCAV_{mean}$ and eP_aCO_2 seemed to have reached the plateau phase.

Table 1. Individual values of pulmonary oxygen uptake and power output derived from the incremental tests and the power output determined during an exercise session with a constant workload.

Subject	VO_{2peak} (ml/kg/min)	P_{peak} (watt)	$\%VO_{2peak}$ at LT	P_{LT} (watt)	P_{EX} (watt)	$\%P_{LT}$ during exercise
A	60.2	370	73.5	240	100	41.7
B	43.3	265	56.4	125	70	56.0
C	47.0	230	55.2	95	80	84.2
D	47.6	350	70.4	200	150	75.0
E	48.6	300	67.6	180	130	72.2
F	55.2	285	68.2	160	100	62.5
G	59.2	345	62.4	205	150	73.2
Mean ± SE	51.6 ± 2.5	306 ± 19	64.8 ± 2.7	172 ± 19	111 ± 12	66.4 ± 5.4

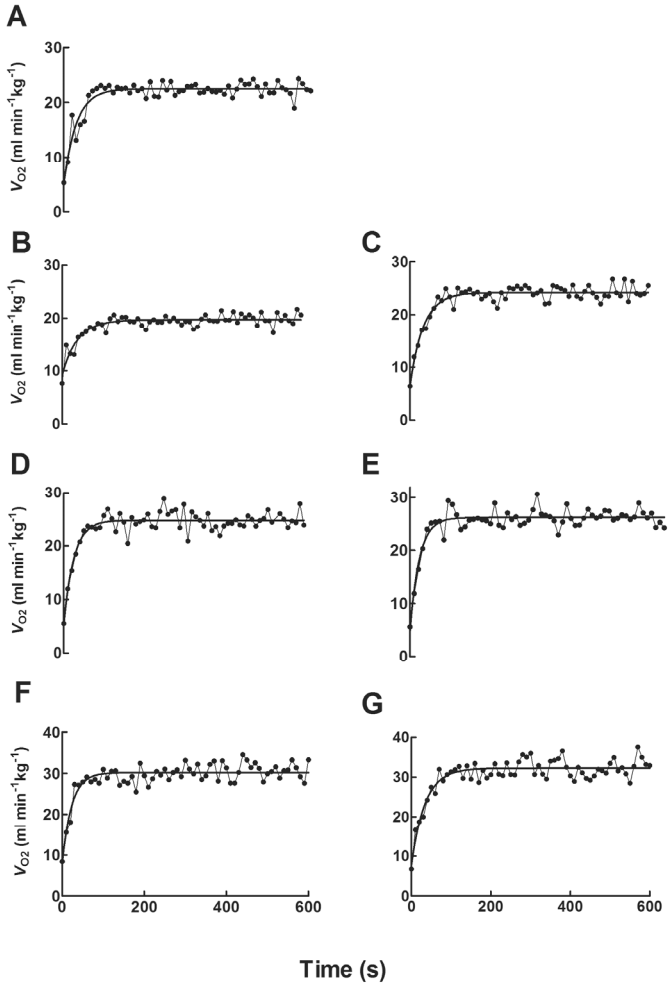

Figure 1. Individual VO_2 kinetics during an exercise session with a constant workload (● and line-of-best-fit).

However, in subjects C, D, E, and G, the overshoot phase of the fitting curves was observed within 3 min in either %ΔMCAV_{mean} or eP_aCO_2.

As responses of MCAV_{mean} or eP_aCO_2 differed from the VO_2 kinetics, which were in the steady-state phase, the kinetics for these 2 variables were analyzed during 5-min (gray lines for the best-fit curve) and 10-min (black lines for the best-fit curve) periods. Using the 2 plateau phases of ΔMCAV_{mean} and eP_aCO_2, CVR to CO_2 for each subject was determined in both the 5-min and the 10-min analysis. Individual parameter estimates for the responses of %ΔMCAV_{mean}, eP_aCO_2, and CVR to CO2 over 5 min and 10 min are presented in **Table 2**. ΔMCAV_{mean} in the 5-min analysis tended to be higher than that in the 10-min analysis with mean values of 27.2% vs. 24.7%, although there was no statistical difference.

During the plateau phase in the 5-min analysis, eP_aCO_2 level was significantly higher than that in the 10-min analysis (41.6 mmHg vs. 41.3 mmHg). From the perspective of the goodness of fit for the monoexponential model of the kinetics, R^2 in the 5-min analysis was higher than that in the 10-min analysis for both ΔMCAV_{mean} and eP_aCO_2. The τ values for ΔMCAV_{mean} and eP_aCO_2 in the 10-min analysis were 36.3 ± 5.3 s and 20.1 ± 5.2 s, respectively, and in the 5-min analysis were 44.7 ± 8.2 s and 25.1 ± 5.8 s, respectively. The τ for ΔMCAV_{mean} was significantly longer than that for eP_aCO_2 both in the 10-min and in the 5-min analysis ($P < 0.05$). The τ for ePaCO2 in the 5-min analysis

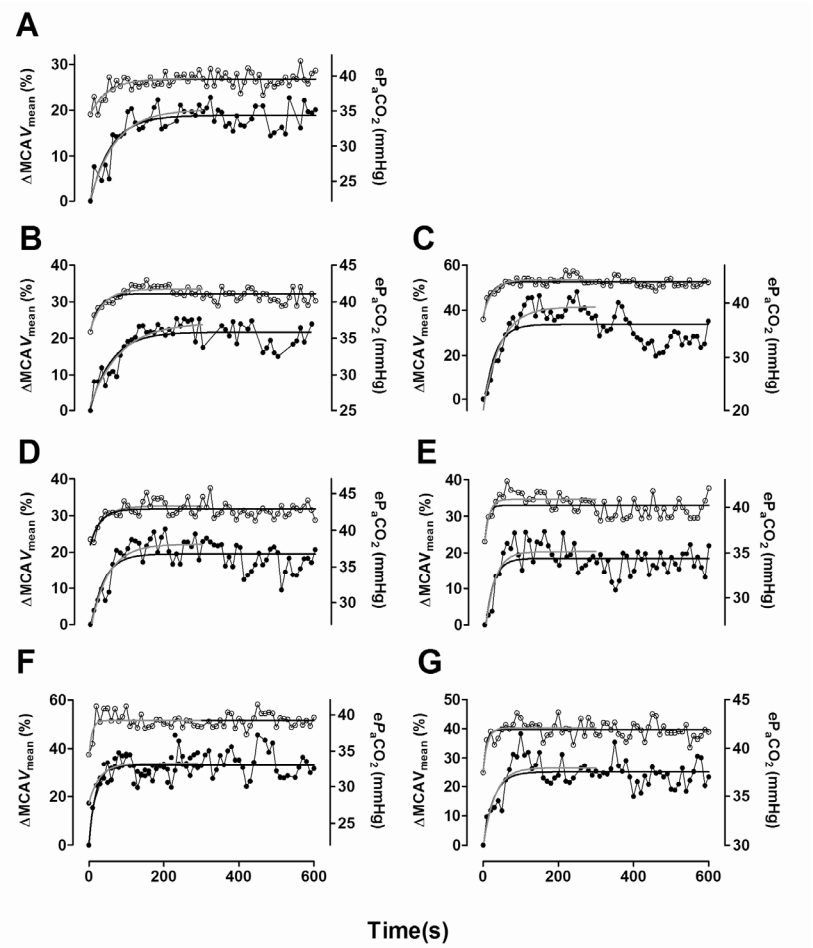

Figure 2. Individual kinetics of %ΔMCAV_{mean} (● and line-of-best-fit) and eP_aCO_2 (○ and line-of-best-fit) during an exercise session with a constant workload. The kinetics for these 2variables were analyzed during 5-min (gray lines for the best-fit curve) and 10-min (black lines for the best-fit curve).

was significantly longer than that in the 10-min analysis, whereas the τ for ΔMCAV_{mean} was similar in the 5-min and the 10-min analyses. CVR to CO_2 during the dynamic cycling exercise were 5.33% $mmHg^{-1}$ and 4.78% $mmHg^{-1}$ in the 5-min and the 10-min analysis, respectively. CVR to CO_2 in the 5-min analysis tended to be higher than that in the 10-min analysis but there was no statistical difference.

Δ MCAV_{mean}, the relative change from the baseline; eP_aCO_2, the estimated arterial carbon dioxide tension; CVR to CO_2, cerebrovascular reactivity to carbon dioxide; R, correlation coefficient.

The exercise intensity during the 10-min session was expressed as the percentage of VO_2 at the plateau phase in the fitted monoexponential model compared with VO_{2peak} (%VO_{2peak} EX), and the relationships between %VO_{2peak} EX and CVR to CO_2 in the 5-min and 10-min analyses are shown in **Fig. 3.** In the 5-min and 10-min analyses, CVR to CO_2 significantly correlated with %VO_{2peak} EX (r^2 = 0.89 and 0.75, respectively). The exercise intensity during the 10-min session was expressed as the percentage of VO_2 at the plateau phase in the fitted monoexponential model compared with VO_{2peak} (%VO_{2peak} EX), and the relationships between %VO_{2peak} EX and CVR to CO_2 in the 5-min and 10-min analyses are shown in **Fig. 3.** In the 5-min and 10-min analyses, CVR to CO_2 significantly correlated with %VO_{2peak} EX (r^2 = 0.89 and 0.75, respectively).

Table 2. Summary of the parameter estimates for the responses of %ΔMCAV_{mean} and eP_aCO_2 during 5 min and 10 min.

Subject	Plateau of ΔMCAV mean (95% CI) (%)	R^2	Plateau of eP_aCO_2 (95% CI) (mmHg)	R^2	CVR to CO_2 (% $mmHg^{-1}$)
		10 min analyzed			
A	18.9 (17.9 – 19.8)	0.71	39.6 (39.3 – 39.9)	0.51	3.73
B	21.7 (20.5 – 22.9)	0.72	41.1 (40.9 – 41.3)	0.49	4.16
C	33.7 (31.6 – 35.9)	0.47	43.9 (43.7 – 44.1)	0.65	4.87
D	19.6 (18.5 – 20.7)	0.53	42.9 (42.7 – 43.2)	0.43	4.71
E	18.5 (17.4 – 19.5)	0.46	40.2 (42.7 – 43.2)	0.20	4.66
F	35.7 (34.2 – 37.3)	0.51	39.2 (39.9 – 40.5)	0.33	5.75
G	25.0 (23.7 – 26.3)	0.49	41.9 (41.7 – 42.2)	0.36	5.56
Mean ± SE	24.7 ± 2.7	0.56 ± 0.04	41.3 ± 0.66	0.42 ± 0.05	4.78 ± 0.27
		5 min analyzed			
A	20.1 (18.0 – 22.3)	0.83	39.7 (39.1 – 40.2)	0.88	3.57
B	24.2 (21.7 – 26.7)	0.86	41.7 (41.4 – 42.0)	0.83	4.14
C	41.5 (39.2 – 43,8)	0.90	44.3 (44.0 – 44.6)	0.81	5.68
D	22.2 (20.5 – 24.0)	0.81	43.3 (42.9 – 43.8)	0.65	5.50
E	22.3 (20.5 – 24.1)	0.68	40.9 (40.5 – 41.2)	0.83	6.49
F	33.6 (31.7 – 35.5)	0.72	39.2 (38.8 – 39.6)	0.46	6.28
G	26.5 (24.1 – 28.9)	0.66	42.1 (41.8 – 42.5)	0.53	5.66
Mean ± SE	27.2 ± 2.9	0.78 ± 0.04*	41.6 ± 0.70*	0.71 ± 0.06*	5.33 ± 0.41

* $P < 0.05$ compared with10 min analyses.

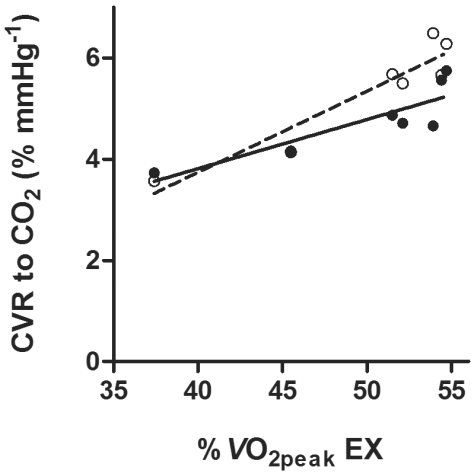

Figure 3. Relationship between exercise intensity (% $VO2_{peak}$ EX) and cerebrovascular reactivity to carbon dioxide (CVR to CO_2) in the 5-min (○) and 10-min (●) analyses.

Discussion

This study showed the kinetics of MCAV_{mean} during moderate-intensity cycling exercise with a constant workload in which the VO_2 kinetics were in the steady-state phase (**Figs. 1 and 2**). Although the TCD method helps measure flow velocity, and not CBF, MCAV_{mean} is a reliable and valid index of CBF [21, 22]. MCAV_{mean} overshot at the on-transient phase in some subjects (subjects C, D, E, and G) and remained stable in others (subjects A, B, and F) (**Fig. 2**). This finding is attributable to the varying exercise intensities among subjects during the 10-min exercise, with %VO_{2peak} EX ranging from 37.4% to 54.7%; the extent of changes in cardiac output would also affect MCAV_{mean}. In order to reveal whether MCAV_{mean} remains stable, further investigation is required with similar exercise intensity among subjects, and several steps of exercise intensities should be investigated.

In this study, the CVR to CO_2 during dynamic exercise was 5.33% $mmHg^{-1}$ and 4.78% $mmHg^{-1}$ in the 5-min and the 10-min analysis, respectively, and no significant difference was observed between the analysis of 2 trials. Previous studies involving CO_2 inhalation and the measurement of MCAV_{mean} among young healthy volunteers have reported the CVR to CO_2 (mean ± SD) to be 4.5 ± 1% $mmHg^{-1}$ [23], 4.8 ±

0.5% $mmHg^{-1}$ [24], and 2.9 ± 1.8% $mmHg^{-1}$ [25]. These data were collected in 4 or 5 steps of the steady hypercapnic conditions obtained by inhalation of CO_2, assuming a linear relationship between MCAV_{mean} and $P_{ET}CO_2$, with $P_{ET}CO_2$ ranging from 35 mmHg to 55 mmHg. In contrast, in this study, the data for CVR to CO_2 were collected using 2 baseline points and the plateau phase during dynamic exercise, with eP_aCO_2 ranging from 36.3 mmHg to 44.3 mmHg. In other words, changes in eP_aCO_2 were manipulated as a result of voluntary dynamic exercise itself and metabolic processes, mainly in working muscles, are involved. Since the methods for determining CVR to CO_2 were different and since there was marked variability in the "normal" CVR to CO_2 [14], whether data in the present study are comparable to those in the previous study could not be elucidated. Thus, further modified investigation comprising a session of 3–4 steps of steady exercise is required for the precise evaluation of CVR to CO_2.

The finding that CVR to CO_2 in the 5-min analysis tended to be higher than that in the 10-min analysis is attributable to the changes in CBF during the on-transient phase of dynamic exercise. Since the increase in CBF would be accompanied by the neuronal activation resulting from central command [26] and the exercise pressor reflex arising from skeletal muscles [27], the neuronal activation during the on-transient phase of exercise could be postulated if the increase in CVR to CO_2 is specific to the initial phase. In this study, cardiac output increased during the on-transient phase of dynamic exercise and remained stable during the steady-state phase of VO_2. Since it has been recently established that CBF is also dependent on cardiac output [14, 28, 29], the findings in the present study show that changes in cardiac output contribute to CBF.

Considering the findings of the positive correlation between exercise intensity and CVR to CO_2 (**Fig. 3**), it is tempting to speculate that exercise intensity would affect the extent of change in CBF, surpassing the effect of P_aCO_2 or independent of P_aCO_2. However, individual difference in CVR to CO_2 was not considered in the present study as the relationship was examined among different subjects. Thus, the intra-individual evaluation of CVR to CO_2 for several steps of exercise intensity is required to determine the accurate relationship between exercise intensity and CVR to CO_2.

In conclusion, we reported the kinetics of MCAV_{mean} during moderate-intensity cycling exercise at a constant WR in which the VO_2 kinetics were in the steady-state phase. There was a positive correlation between exercise intensity and CVR to CO_2. Further investigation with a modified experimental design is required to confirm the effect of the inter-individual differences in CVR to CO_2.

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