J. Exerc. Sci. 17 : 20—28, 2007

＜研究報告＞

Internal carotid artery blood flow and cerebrovascular resistance during dynamic exercise

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Abstract

The effect of the dynamic exercise on global cerebral blood flow (gCBF) has not yet been fully evaluated. There is controversy as to whether increasing mean arterial pressure (MAP), cardiac output (CO), arterial carbon dioxide tensions ($PaCO_2$), and sympathetic activity might compromise gCBF. To evaluate these effects, we studied internal carotid artery blood flow ($\dot{Q}_{ICA}$) and cerebrovascular resistance (CVR_{ICA}) in 7 healthy young adults at rest and during increasing levels of dynamic cycling exercise. We continuously monitored CO, MAP, end-tidal CO_2 ($P_{ET}CO_2$), and $\dot{Q}_{ICA}$ with a high-resolution Doppler ultrasound system at rest and stepwise cycle exercise at 30%, 50%, and 70% of the power of the upright $\dot{V}O_{2peak}$ with 5-min duration of each stage. CVR_{ICA} was calculated as MAP and divided by $\dot{Q}_{ICA}$. MAP, CO, and $P_{ET}CO_2$ increased significantly with increase exercise load, most likely related to increased sympathetic drive. Dynamic exercise also significantly increased $\dot{Q}_{ICA}$ during exercise. However, 70% $\dot{V}O_{2peak}$ exercise tended to reduced $\dot{Q}_{ICA}$ compared with 50% $\dot{V}O_{2peak}$, in contrast to continued increase in CVR_{ICA} throughout exercise. These data indicated that exercise-induced increase in sympathetic activity may have affected $\dot{Q}_{ICA}$ by change in CVR_{ICA}. Although cardiovascular responses and $PaCO_2$ contribute to an increase in gCBF during exercise, autonomic-dependent mechanisms may also play a role for cerebrovascular regulation during dynamic exercise with increasing exercise load, and e increase in CVR may be mechanism of protection for the brain against the large increase in cardiovascular responses during exercise.

Key words: intenal carotid artery, cerebrovascular resistance, sympathoexcitation, cardiovascular response, dynamic exercise

Introduction

Cerebral autoregulation normally ensure that cerebral blood flow (CBF) remains relatively constant despite fluctuations in arterial pressure provided that mean arterial pressure (MAP) remains within the range of autoregulation, usually from 50 to 170 mmHg (*Paulson et al.* 1990). However, recent studies reported that

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regional cerebral blood flow (rCBF) increases during exercise (*Jørgensen 1996 ; Ide and Secher 2000 ; Querido and Sheel* 2007). In addition, the Doppler ultrasound derived blood flow in internal carotid artery (ICA) increases indicated that global CBF (gCBF) does increases (*Huang et al. 1991 ; Huang et al. 1992 ; Hellstrom et al.* 1996). On review of the literature, there is a consistent support for an increase in CBF during exercise (*Querido and Sheel* 2007). A variety of factors might contribute to CBF regulation such as MAP, arterial carbon dioxide tensions ($PaCO_2$), metabolism, and neural innervations (*Querido and Sheel* 2007).

Recent data suggested that CO is an important determinant of rCBF during exercise. The effect of CO on the mean blood flow velocity of middle cerebral artery (MCA V_{mean}) was firstly demonstrated in patients with cardiac insufficiency (*Hellstrom et al.* 1997) or atrial fibrillation (*Ide et al.* 1999). These patients had an attenuated ability to increase CO and MCA V_{mean} during dynamic exercise. When the increase in CO was reduced by β-1 adrenergic blockade during exercise in healthy subjects, the increase in MCA V_{mean} during the dynamic exercise was reduced (*Ide et al.* 1998). In addition, decrease and increase in CO by lower body negative pressure and infusion of albumin, respectively, show a significant linear relationship between MCA V_{mean} and CO rest and during dynamic exercise (*Ogoh et al.* 2005).

During exercise, the competition for perfusion between active and inactive muscles, and other organs bed is regulated by the sympathetic nervous system (*Rowell* 1993). Similarly, cerebral perfusion is not only driven by increasing BP and CO but also has to adjust to high level of sympathetic activity (*Ogoh et al.* 2005). Previous studies reported that MCA V_{mean} and calculated index of cerebrovascular resistance increased from rest to dynamic exercise, and suggested that cerebral vasoconstriction was a result of the exercise-induced sympathoexcitation (*Ide et al.* 2000). Moreover, *Ogoh et al.* (2005) showed that the CO associated with the change in the central blood volume influence the MCA V_{mean} at rest and during dynamic exercise ; however, the relationship between MCA V_{mean} and CO was reduced from rest to dynamic exercise. These data indicated that the increase in sympathetic activity associated with dynamic exercise may have also affected rCBF by changing cerebrovascular resistance. However during dynamic exercise, it cannot be determined whether the cerebraovascular response in the restribution of the MCA reflect global cerebral effects, because discreet region of the brain may respond differently to change in sympathetic stimulation (*Ainslie et al.* 2005).

To date, the effect of the dynamic exercise on gCBF has not yet been fully evaluated. There is controversy as to whether increasing MAP, $PaCO_2$, CO and sympathetic activity might compromise gCBF during dynamic exercise. To evaluate these effects, we studied internal carotid artery blood flow ($\dot{Q}_{ICA}$), cardiorespiratory responses, and cerebrovascular resistance (CVR_{ICA}) at rest and during increasing levels of dynamic cycling exercise. Although cardiovascular responses and $PaCO_2$ contribute to an increase in CBF during exercise, we hypothesized that autonomic dependent mechanisms may also play a role for gCBF regulation with increasing exercise load.

Methods

Subjects.

Seven healthy young adults (1 men, 6 women) aged 21–25 yr (mean age 22.5 yr) participated in the study. Written, informed con-

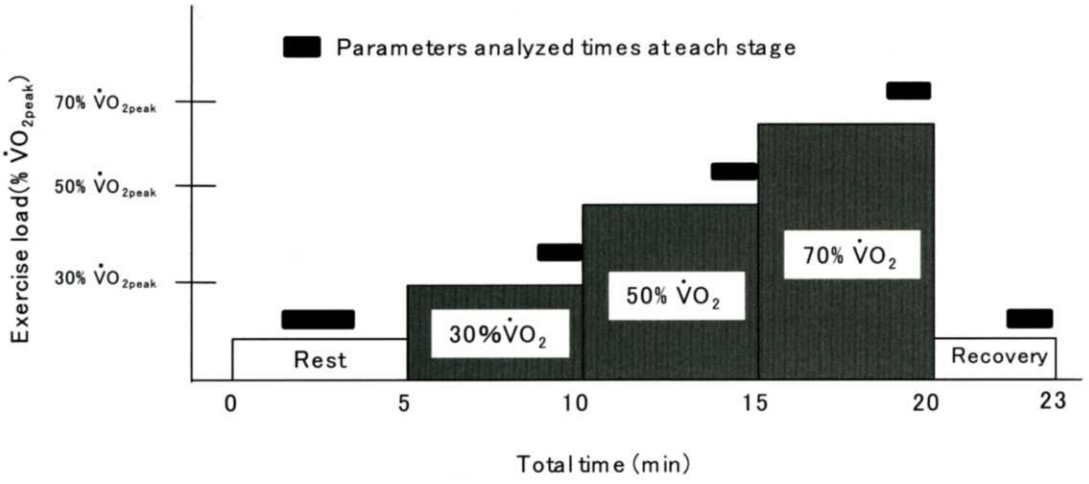

Fig. 1 Experimental design and parameter analyzed time at each stage.

sent was obtained according to the Ethics Committee of the Japan Women's College of Physical Education and the study was conducted in accordance with the Declaration of Helsinki. Subjects were requested to abstain from caffeinated beverages for 6 h and physical activity for at least 12 h before any experimental session.

$\dot{V}O_{2peak}$.

$\dot{V}O_{2peak}$ was determined in all subjects 1-wk before the experiments using incremental protocol on the cycle ergometer (AEROBIKE 800, Combi, Tokyo, Japan) in the upright (sitting) position. Subjects were exposed to an initial work rate of 30 W at the pace of 60 cycles/min. They were told to maintain the constant frequency, and the work rate was increased each following minute by 10–15 W up to volitional exhaustion. Volitional exhaustion occurred within 12–15 min in all subjects. Respiratory parameters at rest and during exercise were determined with an on-line system for breath-by-breath measurement. The gas fractions were analyzed by mass spectrometer (ARCO-1000, Arco system, Chiba, Japan). Expired gas volume was measured by a Fleisch pneumotachometer (WLCU-5201, Westron, Chiba, Japan). The highest value obtained for $\dot{V}O_2$ during the exercise protocol was used as the $\dot{V}O_{2peak}$.

Experimental protocol.

Subjects were tested after a resting period of at least 20-min to ensure cerebrovascular and cardiovascular stability. The subjects were seated on a semirecumbent bicycle ergometer (Cateye-Ergociser, Cateye, Osaka, Japan) with a backrest inclination of 55 degree. The procedure consisted of a 5-min baseline (Rest) followed by levels of exercise load at 30%, 50%, and 70% of the power of the upright $\dot{V}O_{2peak}$, with 5-min duration of each stage (**Fig. 1**).

Measurement of internal carotid artery blood flow.

$\dot{Q}_{ICA}$ blood flow examination was performed with a high-resolution Doppler ultrasound system (VIVID 7 pro, GE Healthcare, Tokyo, Japan) equipped with a 10 MHz linear transducer. Measuremant were perfomed 1.0–1.5 cm distar to the carotid bifurcation on the right ICA. The subject's head was slightly elevated

and turned toward the opposite side by 20 degree for measurement of $\dot{Q}_{ICA}$.

The systolic and diastolic diameters in the ICA were measured based on a pulsed wave Doppler signal. The mean ICA diameter (D_{ICA}) was calculated in relation to the blood pressure curve according to the following formula: D_{ICA} = [(systolic diameter × 1/3)] + [(diastolic diameter × 2/3)]. Diameter measurements were obtained in the ultrasound B-mode, and the cursor was set perpendicular to the vessel wall. Each diameter was measured at least 3points and values were then averaged. Mean ICA blood flow ($\dot{Q}_{ICA}$) was calculated by multiplying the cross-sectional area of the ICA [area = $\pi \times (\text{diameter}/2)^2$] with the ICA mean blood flow velocity (V_{ICA} ; TAMEAN, m/sec) : $\dot{Q}_{ICA} = V_{ICA} \times \text{area} \times 60$ ($ml \cdot min^{-1}$). In all ICA measurements, special care was taken to ensure that the probe position was stable, that the insonation angle did not vary, and the sample volume was positioned in the center of the vessel and adjusted to cover the width of the vessel diameter.

Measurement of cardiorespiratory responses.

Mean arterial blood pressure (MAP) was measured non-invasively by photoelectric plethysmography with a Finometer (Finapres Medical Systems BV, Arnhem, Netherlands). Furthermore, the heart rate (HR), stroke volume (SV), and thus cardiac output (CO), were determined from the blood pressure wave form using the Modelflow software program, incorporating gender, age, height, and weight (Beat Scope 1.1, Finapres Medical Systems BV, Arnhem, Netherlands). CO was calculated as SV × HR.

Respiratory parameters were determined with an on-line system for the breath-by-breath method. Respiratory gas was sampled continuously from a face mask. The gas fractions were analyzed by a mass spectrometer (ARCO-1000, Arco system, Chiba, Japan) that was calibrated and confirmed before each test. The expired gas volume was measured by a Fleisch pneumotachometer (WLSU-5201, Westron, Chiba, Japan). Breath-by-breath data were analyzed using customized software on a computer (PC-9821, NEC, Tokyo, Japan), and the oxygen uptake ($\dot{V}O_2$), expiratory minute ventilation ($\dot{V}_E$), and end-tidal partial pressure of CO_2 ($P_{ET}CO_2$) were calculated.

Data processing and statistics.

In the present study, the ratio MAP/$\dot{Q}_{ICA}$ was calculated as indexes of cerebrovascular resistance (CVR_{ICA}). The cerebrovascular and cardiorespiratory responses during resting condition (Rest) were analyzed during 120-sec interval that ended 30 sec before the onset of cycle exercise. During dynamic exercise, these parameters were analyzed from the last 1-min of each of the 5-min exercise levels (**Fig. 1**).

Differences between values at Rest, during the three load of exercise, and recovery were tested by analysis of variance for repeated measures (RANOVA). If significance was detected, Scheffe's post-hoc analysis was performed to determine specific differences for pair-wise comparison. A pearson correlation was used to assess the relationship between cardiorespiratory responses and $\dot{Q}_{ICA}$. P value of <0.05 were considered significant.

Results

All subjects completed the 30% to 70% $\dot{V}O_{2peak}$ exercise levels. With increasing exercise load, there was significant increase in $\dot{Q}_{ICA}$ from baseline values (Rest) (*RANOVA* and *post-hoc*, $P<0.01$; **Table 1** and **Fig. 2A**). $\dot{Q}_{ICA}$ at 50% $\dot{V}O_{2peak}$ exercise was significantly higher than 30% $\dot{V}O_{2peak}$ $\dot{Q}_{ICA}$ values (*post-hoc*, $P<0.01$).

Table 1. Cerebrovascular and cardiorespiratory responses at rest, during dynamic exercise, and recovery

		Rest	30% $\dot{V}O_{2peak}$	50% $\dot{V}O_{2peak}$	70% $\dot{V}O_{2peak}$	Recovery	RANOVA *P*
Q_{ICA}	(ml/min)	295 ± 64	336 ± 73	363 ± 79	353 ± 73	317 ± 79	< 0.01
D_{ICA}	(cm)	0.477 ± 0.065	0.482 ± 0.070	0.488 ± 0.062	0.485 ± 0.065	0.478 ± 0.060	> 0.05
$\dot{V}_{ICA}$	(cm/sec)	28.4 ± 8.8	32.1 ± 11.2	33.2 ± 9.3	33.6 ± 9.7	30.8 ± 9.8	< 0.01
$\dot{V}O_2$	(ml/min)	239 ± 32	902 ± 108	1333 ± 258	1698 ± 293	403 ± 81	< 0.01
MAP	(mmHg)	77 ± 5	91 ± 8	104 ± 8	111 ± 10	80 ± 2	< 0.01
HR	(beats/min)	59 ± 7	91 ± 8	115 ± 5	143 ± 8	75 ± 6	< 0.01
SV	(ml)	75 ± 7	94 ± 7	102 ± 9	104 ± 10	84 ± 9	< 0.01
CO	(l/min)	4.4 ± 0.5	8.5 ± 1.0	11.7 ± 1.2	14.9 ± 1.4	6.2 ± 0.4	< 0.01
$P_{ET}CO_2$	(mmHg)	37.9 ± 1.1	41.0 ± 4.7	45.8 ± 5.3	45.9 ± 5.5	38.9 ± 2.1	< 0.01
CVR_{ICA}	(mmHg/ml/min)	0.276 ± 0.081	0.288 ± 0.092	0.305 ± 0.099	0.330 ± 0.097	0.268 ± 0.080	< 0.01

Data are presented as means ± SD. Q_{ICA} : mean ICA blood flow, D_{ICA} : mean ICA diameter, V_{ICA} : mean ICA blood flow velocity, VO_2 : oxygen uptake, MAP : mean arterial pressure, HR : heart rate, SV : stroke volume, CO : cardiac output, $P_{ET}CO_2$: end-tidal partial pressure of CO_2, CVR_{ICA} : index of cerebrovascular resistance.

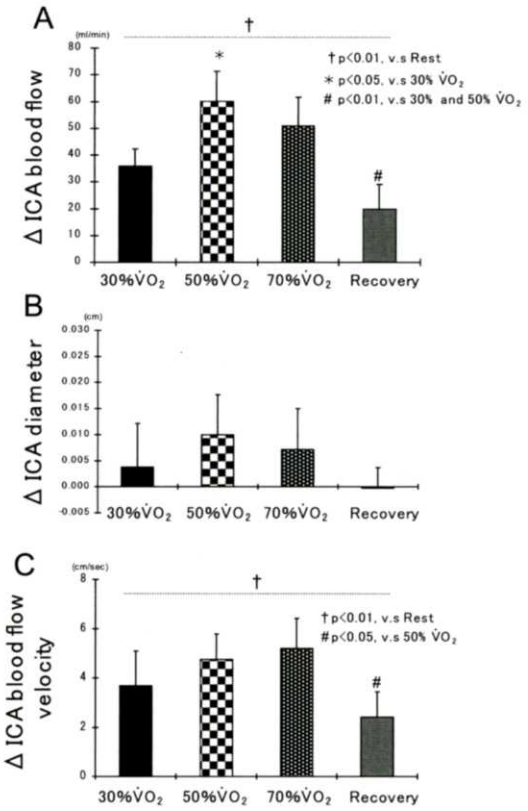

Fig. 2 Changes (Δ ; exercise minus rest) in cerebrovascular parameters during dynamic exercise. (A) ICA blood flow volume, (B) ICA diameter, (C) ICA blood flow velocity. Values are means±SE.

However, 70% $\dot{V}O_{2peak}$ exercise tended to reduced $\dot{Q}_{ICA}$ compared with 50% $\dot{V}O_{2peak}$ exercise. There was no significant differences between the increase in D_{ICA} at Rest, 30%, 50%, 70% $\dot{V}O_{2peak}$ exercise, and Recovery (*RANOVA*, P>0.05 ; **Table 1** and **Fig. 2B**). Therefore, the increase in $\dot{Q}_{ICA}$ during dynamic exercise was mainly induced by increase in the V_{ICA}. There was significant increase in V_{ICA} at during dynamic exercise (*RANOVA*, *P*<0.01 ; **Tabla 1** and **Fig. 2C**).

With increasing exercise load, there was a significant increase in $\dot{V}O_2$, MAP, HR, SV, CO, and $P_{ET}CO_2$ levels (*RANOVA*, *P*<0.01 ; **Table 1**). CVR_{ICA} at 50% $\dot{V}O_{2peak}$ exercise, and 70% $\dot{V}O_{2peak}$ exercise were significantly higher than Rest (*RANOVA* and *post-hoc*, *P*<0.01 ; **Table 1** and **Fig. 3**). CVR_{ICA} at 70% $\dot{V}O_{2peak}$ exercise was significantly higher than 30% and 50% $\dot{V}O_{2peak}$ exercise.

The mean responses of $\dot{Q}_{ICA}$ to change in CO are showed **Fig. 4**. The linear relationships between $\dot{Q}_{ICA}$ and CO was statistically significant at Rest, during exercise and Recovery (r = 0.93, *P*<0.05).

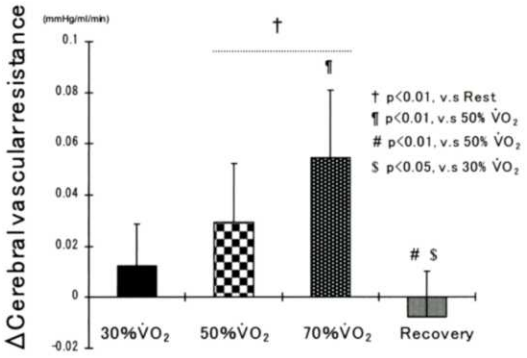

Fig. 3 Change (Δ ; exercise minus rest) in cerebrovascular resistance during dynamic exercise. Values are means±SE. CVR_{ICA} increased with increasing exercise load.

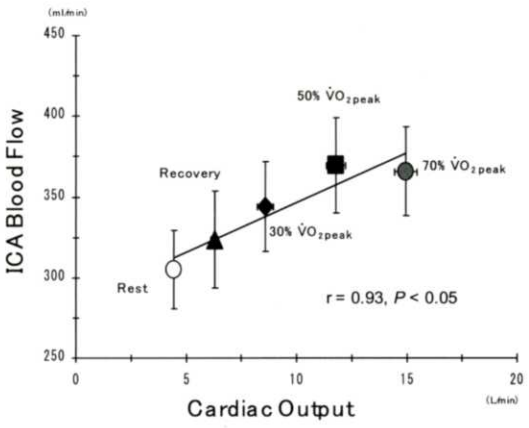

Fig. 4 Change in ICA blood flow and cardiac output at rest, during exercise, recovery. Values are means±SE. The lines represent the linear regression calculated from the group average data. The significant relationship between ICA blood flow and CO was linear.

Discussion

Major findings.

In the present study, we observed an increase in MAP and CO with increasing exercise load, most likely related to increased sympathetic drive. Dynamic exercise also significantly increased $\dot{Q}_{ICA}$ during exercise. However, 70% $\dot{V}O_{2peak}$ exercise tended to reduced $\dot{Q}_{ICA}$ compared with 50% $\dot{V}O_{2peak}$ exercise, in contrast to continued increase in CVR_{ICA} throughout exercise. Our data suggested that importance of CO and/or MAP for the gCBF may be reduced with increasing exercise intensity due to evidence showing no increase in $\dot{Q}_{ICA}$ with a simultaneous increase in MAP and CO at 70% $\dot{V}O_{2peak}$ exercise, and exercise-induced increase in sympathetic activity may have affected $\dot{Q}_{ICA}$ by change in CVR_{ICA}.

ICA blood flow and cardiovascular responses.

The carotid blood flow studies using Doppler ultrasound measurement have been used to evaluate change in the gCBF (*Hellstrom et al.* 1996). Such measurement might be of value when estimating blood flow change in the ICA. In the present study, $\dot{Q}_{ICA}$ increases suggesting an increase in cerebral blood flow to large part of the brain during dynamic exercise. We observed that $\dot{Q}_{ICA}$ increased by 14% during 30% $\dot{V}O_{2peak}$ exercise and reached a maximum of 23% during 50% $\dot{V}O_{2peak}$ exercise. In addition, 70% $\dot{V}O_{2peak}$ exercise load tend to reduce $\dot{Q}_{ICA}$ compared with 50% $\dot{V}O_{2peak}$ exercise. The magnitude and time course of changes in $\dot{Q}_{ICA}$ during step exercise were similar to those in the ICA blood flow measurement in *Hellstrom et al.* (1996).

In general, MAP and arterial $PaCO_2$, which are commonly measured, are thought to be important factors in regulation of CBF during exercise. In addition, recent findings suggested that CO is an important factor in establishing rCBF at rest and during dynamic exercise (*Ide et al. 1998 ; Ide et al. 1999 ; Ide and Secher 2000 ; Ogoh et al. 2005 ; Ogoh et al.* 2007). When the increase in CO was reduced by β-1 adrenergic blockade, or arterial fibrillation, the increase in mean blood flow velocity of tMCA V_{mean} during

the dynamic exercise was reduced (*Ide et al. 1998 ; Ide et al.* 1999). Moreover, *Ogoh et al.* (2005) reported that the CO associated with the change in the central blood volume influence the MCA V_{mean} at rest and during dynamic exercise. The findings of the present study provide information regarding the relationship between $\dot{Q}_{ICA}$ and CO during dynamic exercise (**Fig. 4**). The relationship between the change in $\dot{Q}_{ICA}$ and the change in CO at Rest, during dynamic exercise, and Recovery were linear and significant (**Fig. 4**). These findings indicated that CO is an important factor in establishing the gCBF during from light to modelate dynamic exercise, as well as rCBF (*Ide et al.* 1998).

In the present study, we observed that cardiovascular responses were lineally related from Rest to 70% $\dot{V}O_{2peak}$ exercise. On the other hand, 70% $\dot{V}O_{2peak}$ exercise tended to reduced $\dot{Q}_{ICA}$ compared with 50% $\dot{V}O_{2peak}$ exercise. Our data suggested that importance of CO and/or MAP for the gCBF may be reduced with increasing exercise intensity due to evidence showing no increase in $\dot{Q}_{ICA}$ with a simultaneous increase in MAP and CO at 70% $\dot{V}O_{2peak}$ exercise. In the previous study, there have been suggestions that there is no correlation between MAP and rCBF at heavy dynamic exercise (*Moraine et al.* 1993). In addition, *Ogoh et al.* (2005) showed that the change in MCA V_{mean} that occurred in responses to central blood volume-induced change in CO was decreased from rest to moderate dynamic exercise. The author suggested that one possible explanation is the presence of a decrease the distribution of CO to brain at moderate and heavy exercise (*Ogoh et al.* 2005). The distribution of CO to the brain was decreased from rest (14%) to exercise (3%) and this reduction may be dependent on the exercise intensity (*Rowell* 1993). Thus in the present study, it is possible that the importance of CO for the gCBF may be reduced with increasing exercise intensity may be explained by the reduced proportion of CO distributed to brain (*Ogoh et al.* 2005).

It is well known that $PaCO_2$ is the most powerful regulator of cerebrovascular tone (*Ainslie et al.* 2005). Although we did not direct measure $PaCO_2$, $P_{ET}CO_2$ have been shown to be appropriate estimates arterial values in individuals. $P_{ET}CO_2$ levels during from light to moderate exercise were significantly higher than resting value. However, $P_{ET}CO_2$ levels at 70% $\dot{V}O_{2peak}$ exercise did not decrease from 50% $\dot{V}O_{2peak}$. Therefore, $PaCO_2$ is not also important factor for the tendency toward a reduction of $\dot{Q}_{ICA}$ at 70% $\dot{V}O_{2peak}$ exercise and may be more likely due to other contributing factors.

Cerebrovascular resistance during dynamic exercise.

Vascular resistance is estimated as the ratio of the pressure drop to flow across the vascular bed. In the case of CVR, calculation is complicated by unknown values intracranial and venous pressure. During dynamic exercise, we observed an increase in CVR_{ICA} with increasing exercise load. During dynamic exercise with change in exercise load, progressive sympathoexcitation may occur resulting in an increasing proportional distribution of CO to exercising muscles (*Rowell* 1993 ; *Ogoh et al.* 2005). It is considered that sympathoexcitation associated with exercise may affect $\dot{Q}_{ICA}$ by changing CVR_{ICA} in this study. *Ide et al.* (1999) previously suggested that cerebral vasoconstriction during exercise was induced by sympathoexcitation. *Ogoh et al.* (2005) observed that the change in cerebrovascular resistance during exercise, calculated by MCA V_{mean}, was greater than in the forearm at the same perfusion pressure. It is possible that an increase in CVR_{ICA} with increasing exercise load may serve to maintain a

constant cerebral blood flow in the face of a large increase in CO and/or blood pressure during exercise. However, from the present study, we cannot determine whether this cerebral vasoconstriction was caused by sympathoexcitation or was a myogenic response elicit by the dynamic exercise induced rise in arterial pressure. The mechanism underlying this finding requires further investigation.

In contrast to our findings, *Brys et al.* (2003) reported that there was no difference between the CVR at rest and during steady state cycling exercise at HR of 90,120, and 150 beats/min. The possible reason why our results are not consistent with the previous report of Brys et al. are that they calculated for CVR by MCA V_{mean} and MAP values. In this point, we speculated that cerebrovascular resistance during dynamic exercise may differ between intracranial and extracranial artery or rCBF and gCBF. However, the differences between the two studies remain unclear. It seems to be difficult to determine whether the CVR in MCA reflect global cerebralvascular effects. The novel approach in the present study is the use of a blood flow volume in ICA in order to account for any change in global cerebrovascular resistance.

Several animal studies demonstrated that cerebral arteries are richly innervated with sympathetic nerve fibers. In animal study, cerebrovascular responses to haemorrhage were balance between autoregulatory vasodilatation and sympathetic vasoconstriction (Pearce and D'Alecy 1980). In human studies, several researchers reported a direct effect of sympathoexcitation on CBF in pathophysiology (*Ide et al.* 2000 ; *Jordan et al.* 1998). Moreover, during isocapnic handgrip exercise, increase in sympathetic activity was associated with increase in CVR (*Ainslie et al.* 2005). Therefore, autonomic neural control of the cerebral circulation plays a important role for CBF.

Conclusion.

During from light to moderate dynamic exercise, we observed an increase in CVR_{ICA} along with decrease in $\dot{Q}_{ICA}$. Although cardiovascular responses and $PaCO_2$ contribute to an increase in CBF during exercise, our data indicated that autonomic-dependent mechanisms may also play a role for cerebrovascular regulation with increasing exercise load, and the increase in CVR may be mechanism of protection for the brain against the large increase in cardiovascular responses during exercise (*Ogoh et al.* 2005).

The authors appreciate the time and effort expended by all the volunteer subjects. We thanks Hiroyuiki Yamamoto (GE Yokogawa medical systems, Tokyo, Japan) for his expert technical assistance. This study was supported by a research grant from the Academic Frontier Project at the Japan Women's College of Physical Education.

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(Received 2007, 12, 15)