Therapeutic Research (2009.04) 30巻4号:537～544.

Comparison of Blood Flow Velocity in the Middle Cerebral Artery between Men and Women at Rest and during Exercise
(男性及び女性の安静時及び運動時における中大脳動脈血流速度の比較)

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Comparison of Blood Flow Velocity in the Middle Cerebral Artery between Men and Women at Rest and during Exercise

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ABSTRACT

The differences in the middle cerebral artery blood flow velocity (MCA_V) and systemic arterial blood pressure (BP) between 10 healthy young males and 10 healthy young females were examined at rest and during 6 min of cycle exercise at an intensity of 100W for males and 50W for females. The systolic, diastolic, and mean MCA_V were continuously measured using a transcranial Doppler ultrasound velocimeter. The systolic, diastolic, and mean BP were also recorded by sphygmomanometry. The mean MCA_V (MCA_Vm) for both males and females was significantly (each $p<0.05$) increased by 18.7% and 17.3%, respectively, from rest to exercise. The mean values of MCA_Vm at rest and during exercise for females were significantly ($p<0.05$) greater than the corresponding values for males (rest 63.5±14.7 vs. 48.6±11.6 cm sec^{-1}, exercise 72.8±11.7 vs. 57.5±14.6 cm sec^{-1}). In contrast, the mean BP (MBP) was significantly ($p<0.05$) less in females than in males during exercise, whereas the MBP at rest was not significantly different between the two groups. Furthermore, to clarify the females' greater MCA_Vm in terms of physiological significance, we simulated the volumetric blood flow through the MCA and its potential for oxygen delivery to the downstream tissues by applying the physiological data available from the literature and from the experiments. The greater blood flow in the MCA in females compensates for the relatively lower arterial oxygen content, which is transported as oxyhemoglobin contained in a smaller number of red blood cells, to give a similar oxygen transport to that in males. These results suggest that the females' greater MCA_Vm, compensating for the lower arterial oxygen content, plays an important role in efficiently transporting oxygen through the bloodstream to tissues at a similar level to that of males.

Key words: Cerebral circulation, Transcranial Doppler, Oxygen transport, Shear stress, Blood viscosity

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INTRODUCTION

Although the adult human brain constitutes approximately only 2% of the body mass, it receives nearly 15% of cardiac output and consumes nearly 20% of the total oxygen utilization at rest[1]. With increases in cerebral tissue mass and its oxygen need, which have developed with the evolution of the human brain, relative to the body mass, such a large blood flow to the brain might be originally related to a delicate situation of or an adaptation of the vascular system to the orthostatic stress in the standing posture[2]. Since the brain tissues are extremely fragile in terms of oxygen deficiency, an adequate and continuous supply of oxygenated blood flow to the cerebral tissues is essential for the function of the brain as well as sustaining the tissues[3]. The blood flow in the middle cerebral artery (MCA) maintains about 80% of the flow volume arriving at the cerebral hemisphere[4]. Although there is a tight coupling between cerebral blood flow (CBF) and cerebral metabolism[3], the middle cerebral blood flow velocity (MCA_V) was reported to be significantly greater in females compared to males[5]. It has also been demonstrated that the diameter of MCA in females was 9% smaller than that in males[6]. When the calibers of MCA in both males and females are assumed to be constant within the normal range of systemic blood pressure (BP), the transport of oxygen via CBF is dependent on a change in MCA_V that is adjusted by perfusion pressure and vascular resistance. However, females have a lower blood oxygen capacity, because of a smaller number of red blood cells that contain hemoglobin compared with males. In contrast, females' lower blood viscosity (μ) associated with the smaller erythrocyte number (or lower hematocrit, Hct) is advantageous to decrease the mechanical energy loss of blood flow against viscous resistances[7]. Obviously, these differences have a crucial effect on the transport of oxygen in the circulation. However, few attempts to date have been made to ascertain how the differences in hemological and hemorheological factors, such as blood oxygen capacity, Hct, and μ, between males and females influence the regulation of MCA_V by tracing the contours of CBF both at rest and during exercise.

Therefore, the purpose of the present study was to examine the differences in MCA_V and the systemic artery BP between males and females at rest and during exercise and also to clarify the physiological significance of the hemological and hemorheological factors underlying the variation in MCA_V between males and females at rest and during exercise. To clarify the effects of these factors on the regulation of MCA_V, we simulated the blood flow with respect to oxygen transport through the MCA by applying the physiological data available from the literature and the data obtained in this study, and compared the results of numerical calculations between males and females.

METHODS

1 Subjects

Ten healthy young male and 10 healthy young female volunteers (males : age 21–24 years, height 1.69±0.05 m, weight 60.7±8.2 kg ; females : age 21–24 years, height 1.58±0.04 m, weight 49.8±4.4 kg) participated in the present study. All subjects were fully informed about the procedures, risk, and benefits of the study, and written informed consent was obtained from all subjects before the study. None of the subjects had any history of cardiovascular, cerebrovascular, or respiratory disease. None of the subjects were engaged in any regular physical activity or were involved in competitive sports. The study was approved by the university institutional review board.

2 Experimental design

Each subject was required to keep his body in an upright, seated position on an electromagnetically-braked cycle ergometer (EZ201, Combi Co. Ltd., Tokyo) during rest and exercise periods. The subject placed his feet on the footrest near the flywheel during the rest period. The subject rested for 15 min on the cycle ergometer and then exercised for 6 min, during which the work rate was maintained at 100 W for males and at 50 W for females. The braking system of the ergometer was externally controlled to ensure the desired work rate. During exercise, the subjects pedaled at a constant rate of 60 rpm paced by a metronome. The pedaling rate was monitored using an inductive revolution meter fitted to the ergometer.

Tests were initiated at approximately 10：00 a.m. in all subjects. Before the test, the subjects were not allowed to consume any beverages containing caffeine or alcohol after 9：00 p.m. the previous night and vigorous exercise was forbidden for 36 h before the day of testing. The subjects ate a small breakfast at least 3 h before exercising. All the subjects were familiarized with the test situation in several pilot experiments. All experiments were conducted at an ambient temperature between 21 and 22°C.

3 Measurement of cardio- and cerebro-vascular variables

The blood flow velocity in the right MCA was obtained using a 2-MH pulsed Doppler ultrasound system (Intra-view, Rimed, Tokyo). Its pulsed probe was located over the temporal bone and the Doppler signal was optimized through a change in the insonation angle. The probe attached to the skull at a fixed angle was held using commercially available headgear with an adjustable positioning system (MD350FC, Rimed, Tokyo). The probe position was maintained in all subjects to secure the insonation angle throughout the experiment. The blood flow velocity was assessed for 6 to 10 consecutive cardiac cycles recorded during the last minute before and during exercise. Systolic, diastolic, and mean blood flow velocity in MCA were represented by MCA_Vs, MCA_Vd, and MCA_Vm, respectively.

The brachial artery BP was sphygmomanometrically measured using a pneumatic arm cuff which was held at heart level. Mean arterial blood pressure (MBP) was calculated as diastolic blood pressure (DBP) plus one-third pulse pressure. The measurements of BP were made during the last minute before and during exercise.

4 Statistical analysis

A two-way analysis of variance was used to examine the effects of exercise and sex on mean values for all variables at rest before exercise and during exercise. When a significant F ratio was observed, the post-hoc Scheffé's test was used to identify significant differences. Differences were considered significant for all statistical analyses at $p<0.05$. All values are expressed as means±SD.

RESULTS

Fig. 1 shows the mean values for cardiovascular variables obtained from 10 male subjects and 10 female subjects at rest before exercise and during steady-state exercise at 100 W and 50 W, respectively. Each of the work loads was the stimulus to evoke the cardiovascular responses at a similar relative intensity between males and females because there was no significant difference in heart rate (HR) between the two groups (119.8±17.6 beats min^{-1} for males vs. 117.9±10.3 beats min^{-1} for females). There was no significant difference in systolic arterial blood pressure (SBP) between males

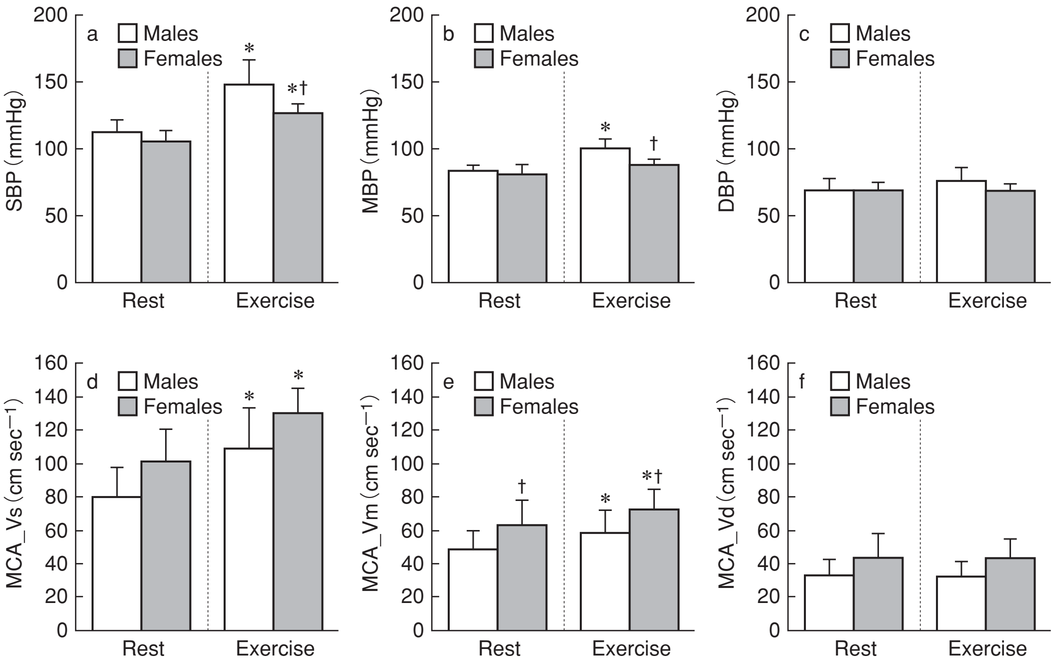

Fig. 1 cardiovascular variables at rest and during exercise for males and females
a: systolic arterial blood pressure (SBP), **b**: mean arterial blood pressure (MBP), **c**: diastolic arterial blood pressure (DBP), **d**: systolic blood flow velocity in the middle cerebral artery (MCA_Vs), **e**: mean blood flow velocity in the middle cerebral artery (MCA_Vm), **f**: diastolic blood flow velocity in the middle cerebral artery (MCA_Vd) at rest and during exercise for males (n=10) and females (n=10).
Values are means±SD.
*: significantly different from rest ($p<0.05$), †: significantly different from males ($p<0.05$).

and females at rest. The SBP in both males and females during exercise was significantly (each $p<0.05$) increased from that at rest, while it was significantly greater for males than for females during exercise. The MBP for males increased significantly ($p<0.05$) from rest to exercise, whereas the corresponding increase in MBP for females was not statistically significant. The MCA_Vs and MCA_Vm in both males and females were significantly ($p<0.05$ each) increased from rest to exercise. The mean values of MCA_Vm at rest and during exercise for females (63.5±14.7 and 72.8±11.7 cm sec^{-1}, respectively) were significantly ($p<0.05$) greater than the corresponding values for males (48.6±11.6 and 57.5±14.6 cm sec^{-1}, respectively), whereas the mean values of MCA_Vs at rest and during exercise for females were slightly, but insignificantly, greater than those for males. However, there were no significant differences in the DBP or MCA_Vd between males and females, or between rest and exercise in each of the groups.

DISCUSSION

The increased MBP in response to exercise from a similar resting baseline level was significantly greater for males than for females in the seated upright position. However, a significantly greater MCA_Vm was observed in females compared to males both at rest and during exercise. These results were in agreement with those of a study demonstrating that the MCA_Vm in females was significantly greater than that in males at rest in the supine position[5].

The regulation of CBF, especially its autoregulation, has been extensively studied in humans as well as in animals with respect to the influences of neurogenic, chemical, and physical factors[3]. Since little was found regarding autoregulation of CBF in response to exercise in this study, we attempted to explain the physiological significance of the greater MCA_V for females by simulating the transport of oxygen for the cerebral circulation and by comparing the results of simulation analysis between females and males. The numerical simulation analysis was performed using the data obtained from this study and the literature and a set of formulas as follows：

$$\mu = 1.09 \times Exp\,(0.024 \times Hct) \qquad (1)$$

$$\dot{\gamma}_w = \frac{4MCA\_Vm}{R} \qquad (2)$$

$$\tau_w = 0.01 \times \mu \times \dot{\gamma}_w \qquad (3)$$

$$CaO_2 = SaO_2/100 \times 1.306 \times Hb + 0.003 \times 95 \qquad (4)$$

$$MCA\_Fm = \pi R^2 \times MCA\_Vm \qquad (5)$$

$$O_2\ Transport = MCA\_Fm \times CaO_2 \qquad (6)$$

$$\eta = O_2\ Transport/\mu \qquad (7)$$

where μ (cP) is the apparent viscosity at a shear rate of 1000 s^{-1} with respect to Hct (%)[8], $\dot{\gamma}_w$ (s^{-1}) is the wall shear rate (WSR), τ_w (dyn cm^{-2}) is the wall shear stress (WSS), CaO_2 (mL O_2 mL^{-1} blood) is the O_2 content flowing to the MCA, SaO_2 (%) is the O_2 saturation in the MCA, Hb (g dL^{-1} blood) is the hemoglobin concentration of blood[9,10], MCA_Fm (mL min^{-1}) is the mean volumetric flow rate, R (cm) is the radius of MCA[6], O_2 transport (mL O_2 min^{-1}) is the rate of the delivery of oxygen through MCA to the dependent brain tissues, η (mL O_2 min^{-1} $Poise^{-1}$) is the efficiency of O_2 transport through the MCA. The constant 1.306 in Eq. 4 is the O_2 capacity of hemoglobin in mL g^{-1} Hb[11]. The constant 0.003 in Eq. 4 is the solubility coefficient of plasma per O_2 pressure in mL dL^{-1} $mmHg^{-1}$ (Ref. 12) and the O_2 pressure in the MCA was assumed to be 95 mmHg[13]. The SaO_2 at MCA was estimated to be 96.8% from Hill's equation with a half-saturation pressure of 27 mmHg[14] and an index of 2.7 for humans[12]. The efficiency (η) of O_2 transport was evaluated by the ratio of O_2 transport to μ, which was analogous to the relationship between the optimum Hct and μ[7]. The results of the simulation with the numerical parameters used for the calculation are summarized in **Table 1**.

It has been reported in the literature[6,9,10,15] that the caliber of MCA, Hct, and Hb were significantly lower in females compared to in males as listed in **Table 1**. Despite the narrower caliber of female MCA, the volumetric flow rate was greater in females than in males at rest and during exercise because of the significantly greater MCA_Vm of females. The greater MCA_Vm of females may be in part associated with their lower Hct and lower μ, which is consistent with the inverse relationships between CBF and Hct and between CBF and μ[16]. Although the lower Hct is favorable for draining of the CBF, the decrease in Hct, with which the concentration of Hb decreases in blood, is undesirably accompanied by a decrease in blood O_2 content. However, the increase in volumetric flow rate with the greater MCA_Vm in females offset the lower O_2 content of blood, and the O_2 transport in females (49.7 mL O_2 min^{-1} at rest and 57 mL O_2 min^{-1} during exercise) became comparable to that in males (52.0 and 61.6 mL O_2 min^{-1}, respectively). Accordingly, the efficiency of O_2 transport to the brain tissues for males

Table 1 Oxygen transport and physiological data used for calculations

Variables	Unit	Male		Female		Sources
		Rest	Exercise	Rest	Exercise	
MCA_Vm	cm sec^{-1}	48.6	57.5	63.5	72.8	
R	cm	0.168	0.168	0.153	0.153	Ref. 6
MCA_Fm	mL min^{-1}	257	304	278	319	Eq. (5)
Hct	%	45	45	42	42	Ref. 10
μ	cP	3.2	3.2	3.0	3.0	Eq. (1)
WSR	L sec^{-1}	1160	1374	1666	1909	Eq. (2)
WSS	dyn cm^{-2}	37.5	44.4	50.1	57.4	Eq. (3)
Hb	g dL^{-1} blood	15.8	15.8	13.9	13.9	Ref. 9
O_2 content	mL O_2 mL^{-1} blood	0.203	0.203	0.179	0.179	Eq. (4)
O_2 transport	mL O_2 min^{-1}	52.0	61.6	49.7	57.0	Eq. (6)
η	mL O_2 min^{-1} $Poise^{-1}$	16.1	19.1	16.5	18.9	Eq. (7)
Re	dimensionless	533	632	683	782	Ref. 1

MCA_Vm：mean blood flow velocity in the middle cerebral artery, R：radius of the middle cerebral artery, MCA_Fm：blood flow in the middle cerebral artery, Hct：hematocrit, WSR：wall shear rate at MCA, WSS：wall shear stress at MCA, Hb：hemoglobin, η：efficiency, Re：Reynolds number, oxygen saturation at MCA：96.8%, oxygen tension at MCA：95 mmHg (Ref. 13), half-saturation oxygen pressure：27 mmHg (Ref. 14)

and females was very similar under the resting and exercising conditions.

According to Eqs. (2) and (3), the increases in WSR and WSS for females at rest and during exercise compared with males resulted from both the greater MCA_Vm and the smaller radius. As a result, the WSR and WSS at the MCA were markedly greater in females than in males at rest and during exercise. The estimated values of 37.5 to 50.1 dyn cm^{-2} for WSS at rest were in agreement with the results in our previous study on the vascular system based on its fractal nature[17]. The relatively higher WSS in the MCA of females with the lower Hct may play an important role in reducing the incidence of cerebral infarction and cerebrovascular incidents, including spasms and hemorrhages[18], because the lower WSR and WSS inversely correlated with an increase in carotid intima-media thickness, reflecting arteriosclerosis[19,20]. The remodeling of vascular walls has also been reported to be associated with the degree of WSS to endothelial cells[21]. However, the physiological implication of the difference in WSS due to gender for the vessel wall is as yet unknown and requires further study.

In contrast to the results of this study, WSS in the common carotid artery was significantly greater in males than in females, and the difference declined with age[15]. The WSS rising in the common carotid artery of males resulted not only from a higher μ, but also from higher blood flow velocity compared to females. The distinction between the common carotid artery and the MCA with respect to the gender difference in blood flow velocity remains unclear.

Limitations

In this study, MCA_V measured by transcranial Doppler velocimetry was used to assess the blood flow change in the MCA at rest and during exercise, while the systemic artery BP was significantly increased from the resting to exercising states. A previous study demonstrated that the relative changes in MCA_V recorded using a transcranical Doppler velocimeter closely correlated with those of blood flow in the internal carotid artery (ICA) recorded using an electromagnetic flowmeter in response to dynamic changes in systemic BP[22]. The direct proportion of MCA_V to the changed blood flow in the ICA indicated that the cross-sectional area of the MCA did not change significantly. Furthermore, it has been reported that the walls of human cerebral arteries are very stiff in terms of mechanical properties[23]. These results strongly support the idea that the MCA_V is valid to assess the blood flow in the MCA, even under conditions in which the perfusion pressure changes in response to exercise. Accordingly, in this study, the calibers of the MCA in males and females at rest and during exercise were assumed to be constants in the calculations of hemodynamic and hemorheologic parameters. The validity of the vessel caliber sizes used in the simulation was indirectly supported by estimating that the amount of both the right and left MCA_F ($257 \times 2 = 514$ mL min^{-1}, see **Table 1**) was comparable to the fraction of the systemic circulation ($5000 \times 0.13 \times 0.8 = 520$ mL min^{-1}) as follows:

Brain Flow＝13% *Cardiac output* and

MCA_F＝80% *Brain flow*

where cardiac output is 5.0 L min^{-1} (Ref. 4).

A change in arterial carbon dioxide tension is known to have a marked influence on MCA_V[24]. Moreover, the influences of the different phases of the menstrual cycle on the MCA_V and the cardiorespiratory system remain unclear. Thus, further studies are necessary to elucidate these issues.

CONCLUSIONS

When compared with males, females had a significantly higher MCA_V despite a lower perfusion pressure. As a result, the MCA_F of females was greater than that of males at rest and during exercise. The greater MCA_F in females compensates for the lower arterial oxygen content, which is due to the smaller quantities of Hct and Hb, to give substantial oxygen transport at the same level as the arterial O_2 transport to the brain tissues in males.

ACKNOWLEDGEMENT

The authors thank Messrs. Yuji Ohta, Mizuta Kanda, and Yuji Namekawa (Kanagawa Institute of Technology) for their assistance. This study was supported in part by a research grant from the Ministry of Education, Culture, Sports, Science and Technology (Kiban C_H20-H22).

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＜Received on February 3, 2009＞