Developmental and Physiologic Changes in Cerebral Blood Flow Velocity

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ABSTRACT. Developmental change of mean blood flow velocity (MBFV) and resistance index of the basilar artery (BA), as well as the changes in MBFV of the BA and the middle cerebral artery (MCA) during sleep and hyperventilation, were studied using transcranial Doppler sonography in healthy Japanese subjects. The MBFV of the BA increased with age from infancy through early childhood, reaching the maximum (64.4 ± 2.6 cm/s) at the age of 5 y, and then gradually decreased. MBFV ratio of MCA to BA was almost stable between 1.57 to 1.64 in all age groups. The resistance index of the BA showed a maximum value in infants, decreased in 1- to 2-y-olds, and remained constant thereafter. The MBFV of both the MCA and BA were lower during non-rapid eye movement sleep than during wakefulness, whereas during rapid eye movement sleep they showed almost the same value as during wakefulness. They were also decreased during hyperventilation. At an expiratory CO_2 level of 25 mm Hg (33.33 kPa), the average decrease in MBFV in children ($n = 10$) was $-50.1 \pm 3.9\%$ in the BA, and $-46.2 \pm 7.4\%$ in the MCA, significantly ($p < 0.05$) more marked than that in adults ($n = 10$) ($-41.5 \pm 5.9\%$ and $-37.9 \pm 4.2\%$, respectively). Transcranial Doppler sonography is a noninvasive method that has a potentially wide range of applications in pediatric neurology. (*Pediatr Res* 34: 385–388, 1993)

Abbreviations

BFV, blood flow velocity
MBFV, mean blood flow velocity
RI, resistance index
MCA, middle cerebral artery
BA, basilar artery
PE_{CO_2}, expiratory carbon dioxide tension
Pa_{CO_2}, arterial carbon dioxide tension
ANOVA, analysis of variance
REM, rapid eye movement
CBF, cerebral blood flow

Transcranial Doppler, introduced by Aaslid *et al.* (1) in 1982, is a noninvasive method that can provide detailed information regarding cerebral blood flow. Because of these advantages, it can be applied in clinical measurement, repeatedly or continuously. It offers the additional advantage of real-time visualization of the blood flow.

Using this method, Murakami (2), found that developmental changes in MBFV of the MCA showed a maximum velocity at the age of 4 y, and that the RI of the MCA showed the most remarkable decrease at age 6 mo.

However, regarding the vertebral-basilar arterial system, especially developmental change of the MBFV of the BA, there has been only one reported study, by Bode and Wais (3), that did not include subjects in the 1st year of life. We therefore examined developmental changes of the MBFV of the BA from the 1st year of life through adulthood in an attempt to establish standard reference data. We also examined the changes in MBFV under various physiologic conditions to contribute to the diagnosis of cerebral vascular disease.

SUBJECTS AND METHODS

The subjects were 150 neurologically normal Japanese children and adults (75 males and 75 females) who had no history of any hematologic or cardiovascular diseases. Informed consents were obtained from all subjects. They were classified into nine age groups as shown in Table 1. In 72 of them, both BA and MCA were examined, and then the MBFV ratio of MCA to BA was investigated. A transcranial Doppler (EME TC2-64, Eden Medizinische Elektronik GmbH, Ueberlingen, Germany) was used for the measurement of the MBFV of the BA and MCA. For the detection of the MBFV of the BA, a 2-MHz probe was placed on the area between the 2nd cervical vertebra and occipital node. Then, ultrasound was applied to the BA, and reverse flow was recorded. For the detection of MBFV of the MCA, flow was detected using a probe placed on the right temporal area anterior to the auricle.

RI was calculated according to the following formula (4): RI = (systolic flow velocity − diastolic flow velocity)/systolic flow velocity.

The EME TC2-64 blood flowmeter, which operates on the pulsed Doppler principle, can measure BFV at depths ranging from 25 to 150 mm, at 5-mm intervals. In this study, the depth at which the BFV of the BA could be detected ranged from 35 to 90 mm, and each subject showed a specific range. In subjects who showed many depths at which maximum pulsed flow signal could be detected, the middle point was selected as the optimal depth.

We studied the relationship between head circumference and optimal pulsed signal depth, and there was a significant relationship between head circumference and optimal pulsed signal depth ($y = 1.606x − 22.78, r = 0.751$).

To evaluate changes in the MBFV of the MCA and BA during natural sleep, all-night sleep polygraph (EEG, electro-oculogram, geniohyoid muscle electromyogram, pneumogram, and ECG) recordings were obtained in 10 subjects (six males and four females) ranging in age from 10 to 32 y, and the MBFV of the BA and MCA were recorded during each sleep stage estimated according to the Association for the Psychophysiological Study of Sleep criteria (5). MBFV showed fluctuation when respiration became irregular. Therefore, MBFV were measured during the stable MBFV period, *i.e.* at least 5 min later when respiration is estimated regular.

Hypocapnia was induced by hyperventilation in 10 children (five males and five females), ranging in age from 6 to 15 y, and

Table 1. *Subjects and MCA/BA ratio**

Age	BA	BA and MCA	MCA/BA ratio (SD)
0–4 mo	10 (M5, F5)	5 (M3, F2)	1.60 (0.08)
4–8 mo	12 (M6, F6)	7 (M2, F5)	1.62 (0.11)
8–12 mo	10 (M5, F5)	5 (M3, F2)	1.64 (0.13)
1–4 y	15 (M8, F7)	9 (M2, F7)	1.63 (0.11)
4–7 y	19 (M10, F9)	8 (M4, F4)	1.59 (0.13)
7–10 y	17 (M8, F9)	7 (M4, F3)	1.57 (0.14)
10–15 y	17 (M10, F7)	6 (M3, F3)	1.62 (0.17)
15–20 y	23 (M9, F14)	10 (M4, F6)	1.64 (0.08)
20–30 y	27 (M14, F13)	15 (M8, F7)	1.57 (0.12)
Total	150 (M75, F75)	72 (M33, F39)	

* M, male; F, female.

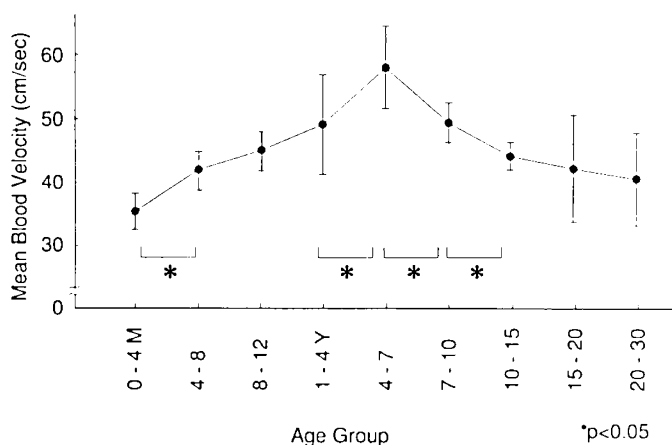Fig. 2. Developmental change of the RI of the BA.

Fig. 1. Developmental change of the MBFV of the BA.

10 adults (five males and five females), ranging in age from 18 to 32 y. PE_{CO_2}, which is considered to be almost the same as Pa_{CO_2}, was measured with a Respina 1H26 (NEC-Sanei, Tokyo, Japan). The subjects were instructed to breathe 20 times/min, as indicated by a metronome, so that the mean PE_{CO_2} level was reduced from 40 mm Hg (53.33 kPa) to 25 mm Hg (33.33 kPa) in 30 s. When the PE_{CO_2} level had stabilized at 25 mm Hg (33.33 kPa) for 5 s, MBFV measurement was begun. RI was calculated afterwards.

Statistical analyses of these results were performed by ANOVA and *t* test.

RESULTS

Developmental change in MBFV of BA. The MBFV of the BA measured at the optimal pulsed signal depth for each age group is shown in Figure 1. MBFV was 35.5 ± 2.9 cm/s in subjects 0 to 4 mo of age, and increased with age thereafter until reaching its maximum value in the 4- to 7-y age group. To be more precise, we examined this group by year, and at the age of 5 y, it showed maximum velocity. MBFV then gradually decreased with age. ANOVA revealed a significant relationship between age group and the MBFV of the BA, and *t* test of each consecutive age group revealed significant differences among the 0 to 4 and 4 to 8 mo, 1 to 4 and 4 to 7 y, and 4 to 7 and 7 to 10 y age groups, as indicated by asterisks in Figure 1. There was no significant difference in MBFV value of the BA between males and females within each age group.

MCA/BA ratio was almost stable between 1.57 and 1.64 in all age groups as shown in Table 1.

Developmental change in RI. As shown in Figure 2, RI showed a fairly constant value of 0.57–0.58 during the 1st year of life. RI then decreased in 1- to 4-y-olds, and was constant thereafter. To determine the critical age of decrease in RI, we examined the
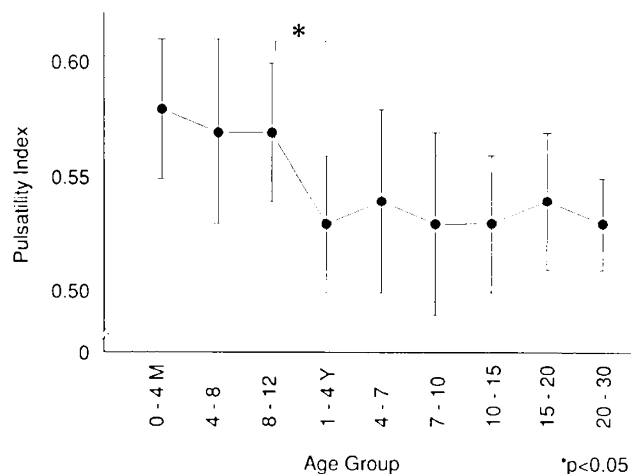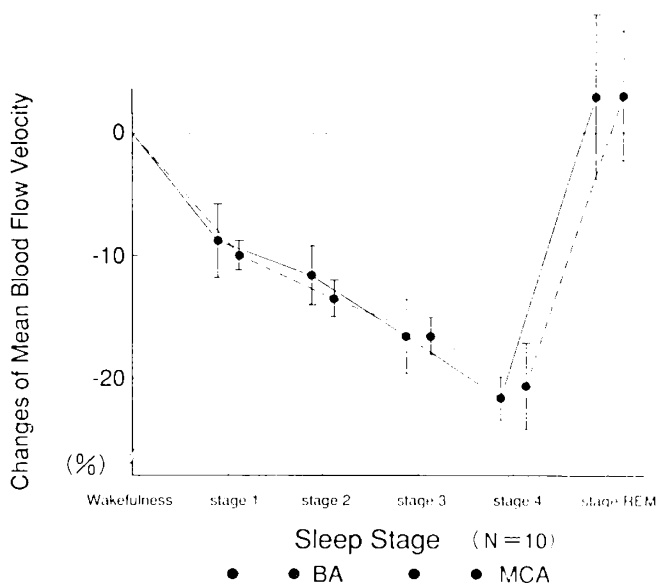

Fig. 3. Changes in the MBFV of the BA and MCA during sleep stages.

RI values of 1- to 4-y-olds; RI was found to show the most marked decrease at the age of 1 y. There was a significant relationship between age and RI value (ANOVA).

Changes in MBFV of BA and MCA during sleep. The changes in MBFV of the BA and MCA during stages of natural sleep in comparison with mean value during wakefulness are shown in Figure 3. MBFV during non-REM sleep were lower than those during wakefulness. There were significant relationships between the MBFV of the BA and MCA and stages of non-REM sleep (ANOVA). On the other hand, there was no significant difference between REM-period and wakeful MBFV in the BA and MCA.

During each REM period, which lasted 10 to 30 min, one to three episodes of apnea of 5 to 10 s duration each were observed. During these episodes, MBFV were increased by 10 to 30% compared with those during the wakeful state; the MBFV during these periods were excluded from the estimation of MBFV during REM sleep. Concerning the difference between MBFV of the BA and the MCA during natural sleep, they showed no significant difference in change.

Changes in MBFV of BA and MCA during hyperventilation. The BFV of the BA and MCA decreased with hyperventilation (Fig. 4). The average decreases in the MBFV of the BA and MCA in children were significantly ($p < 0.05$) greater than those in adults. There was no significant difference between the groups in relative response to CO_2 in the BA and MCA.

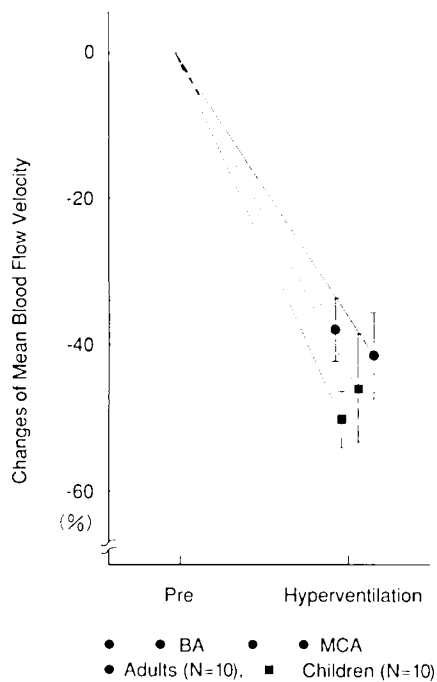The RI of the BA and MCA increased significantly during

Fig. 4. Changes in the MBFV of the BA and MCA during hyperventilation.

hyperventilation. There was no significant difference between children and adults or between the BA and MCA in change in RI. There was no significant difference between males and females in MBFV values or RI values during hyperventilation.

DISCUSSION

Our results clarified that MBFV of the BA shows developmental change with a single peak at age 5 y. Kety (6) reviewed the literature regarding CBF volume measured by the N_2O method and concluded that CBF volume shows maximum value at the age of 5 y. This conclusion is compatible with the results obtained by Chiron *et al.* (7) by single photon emission computerized tomography using ^{133}Xe, which showed the highest value between the ages of 4 and 8 y. Chugani *et al.* (8), using positron emission tomography, also found that cerebral glucose metabolism shows a peak between the ages of 3 and 9 y and hypothesized that the development of myelination and maintenance of membrane potentials of developing synapses and dendritic processes in this age group requires active glucose metabolism. These extensive maturational changes apparently require ample supplies of blood.

In our study, a significant decrease in the RI of the BA was observed between the ages of 1 and 2 y, which is later than the decrease in the RI of MCA reported at 6 mo by Murakami (2). Accordingly, the age period at which RI reaches a constant value can be presumed to vary for different vascular systems. RI is considered to reflect cerebrovascular resistance, and Bode and Wais (3) speculated that increase of capillary density in the brain might be the reason for the decrease in RI observed during infancy. In addition, Otto and Liese (9) found that developmental change of the percentage volume of the cerebellar cortex and occipital pole, which are irrigated by the BA, increased later than that of MCA-irrigated regions. These topographical differences in brain capillary development are presumed to account for the different ages during which stabilization of RI in different vascular systems takes place.

A few studies of CBF during sleep using various methods have been reported (10-13), and cerebral hemodynamic changes during non-REM sleep have also been studied (14) using transcranial Doppler. Consistent with our results, a gradual decrease in CBF

during sleep stages 1 to 4 of non-REM sleep has been reported (12-14). Concerning the CBF during REM sleep, Townsend *et al.* (13) found an 8% increase in cortical CBF compared with that during the wakeful state using the ^{133}Xe inhalation regional CBF measurement method. In our study, the MBFV of both the BA and MCA during REM sleep were higher than those of non-REM sleep, but, compared with those during the wakeful state, the difference was about 3%, which was not significant. The specificity of the ^{133}Xe inhalation regional CBF method that predominantly reflects the CBF of the cortical surface rather than the deeper cortex might be one factor in the difference between our results and those of Townsend *et al.*

Several studies of the changes in cerebral hemodynamics during hyperventilation have been reported (15-19), but changes in the MBFV of the BA in childhood have not yet been reported. Markwalder *et al.* (17) reported that decrease in the MBFV of the MCA was in accordance with the decrease of PE_{CO_2}, and that response to hyperventilation decreases with age. The findings in our study that the MBFV of the MCA decreased with the decrease of PE_{CO_2} and that the rate of decrease in children was greater than that in adults corresponds well with the results reported Markwalder *et al.*

In addition, we found that the response of the MBFV of the BA to change in PE_{CO_2} is also more marked in children than in adults. The rate of change in MBFV found in this study (2.5–3.3% per 1 mm Hg, *i.e.* 1.33 kPa) is smaller than that reported by Lassen (20), *i.e.* a decrease of CBF volume of 4% as Pa_{CO_2} decreases 1 mm Hg (1.33 kPa), in a physiologic state. Huber and Handa (21) demonstrated using angiography that the diameters of the main cerebral arteries are constant regardless of Pa_{CO_2} changes. Taylor *et al.* (22), however, suggested on the basis of the study in lamb that an enlargement in mean vessel diameter as CBF increases causes underestimation of the degree of change in MBFV by Doppler measurement in comparison with that of CBF volume by the radiolabeled microsphere technique. The smaller degree of change in MBFV in our study than in that by Lassen supports this suggestion (22).

Transcranial Doppler has been clinically applied for perinatal brain damage, hydrocephalus (23), and brain death (24). In recent years, the examination of cerebrovascular response to the administration of CO_2 and O_2 and to hyperventilation have been considered useful in the diagnosis of cerebrovascular disorders, such as arteriovenous malformation (25), moyamoya disease (26), and stenosis and occlusions (27) of main cerebral arteries. Meanwhile, in our study, the MCA/BA ratio was stable through infancy to adulthood; therefore, this ratio is considered useful for estimation of the distribution of intracranial hemodynamics irrespective of age. The method used in this study is noninvasive, and can therefore be expected to be useful in a wide range of clinical applications in the field of pediatrics and child neurology.

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