*Acta Anaesthesiol Scand 2002; **46:** 393–397*
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ACTA ANAESTHESIOLOGICA SCANDINAVICA
0001-5172

Dynamic cerebral autoregulation in healthy adolescents

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Background: There is little information on the limits of cerebral autoregulation and the autoregulatory capacity in children. The aim of this study was to compare dynamic cerebral autoregulation between healthy adolescents and adults.
Methods: Seventeen healthy volunteers 12–17 years (n = 8) and 25–45 years ($n = 9$) were enrolled in this study. Bilateral mean middle cerebral artery flow velocities (Vmca; (cm/s)) were measured using transcranial Doppler ultrasonography (TCD). Mean arterial blood pressure (MAP) and end-tidal carbon dioxide were measured continuously during dynamic cerebral autoregulation studies. Blood pressure cuffs were placed around both thighs and inflated to 30 mmHg above the systolic blood pressure for 3 min and then rapidly deflated, resulting in transient systemic hypotension.
The change of Vmca to change in MAP constitutes the autoregulatory response, and the speed of this response was quantified using computer model parameter estimation. The dynamic autoregulatory index (ARI) was averaged between the two sides.
Results: Adolescents had significantly lower ARI (3.9 ± 2.1 vs. 5.3 ± 0.8; $P = 0.05$), and higher Vmca (75.2 ± 15.2 vs. 57.6 ± 15.0; $P < 0.001$) than adults.
Conclusion: The autoregulatory index is physiologically lower in normal adolescents 12–17 years of age than in adults.

Received 11 April, accepted for publication 17 July 2001

Key words: ARI; autoregulation; cerebral bloodflow; children; dynamic autoregulation.

USING TRANSCRANIAL Doppler (TCD), Bode conducted the first systematic, albeit indirect, study of cerebral blood flow (CBF) in 500 children 0–18 years of age (1). Mean middle cerebral artery blood flow velocity (Vmca) was found to increase linearly with age up to 2 years. After 2 years of age, Vmca increases more slowly to a maximum of four times the value measured at birth, and peaks at 6 years of age. After age 6, Vmca decreases linearly to reach adult values (approximately 70% of peak values). The specific reasons for increased Vmca cannot be explained definitively by differences in viscosity, cerebrovascular resistance, cerebral metabolic rate, or mechanism of vascular regulation, and therefore remain unclear (2, 3).

In healthy adults, cerebral autoregulation is said to be preserved between a mean arterial blood pressure (MAP) of approximately 60 and 160 mmHg (4, 5). To date, no study has assessed cerebral autoregulation in healthy adolescents and compared it to that in adults. Cerebral autoregulation testing can be performed using two methods: static and dynamic testing. Static measurements evaluate the change in cerebrovascular resistance (CVR) in response to steady-state manipulation of MAP. If CVR does not change with change in MAP, autoregulation is said to be impaired. Static testing provides a quantitative assessment of autoregulation and the index is scaled from 0–1 (6). The dynamic method of studying cerebral autoregulation yields information about the latency, as well as the magnitude, of the cerebral blood flow response to a decrease in MAP and is said to provide qualitative information (7). Despite methodological differences between static and dynamic autoregulation testing, good correlation between dynamic and static testing of autoregulation has been described (6). Dynamic autoregulation testing is non-invasive compared to static autoregulation testing, making it particularly appealing for use with children. There is no information describing dynamic cerebral autoregulation in the pediatric population. The aim of this study was to compare dynamic cerebral autoregulation between healthy adolescents and adults.

Materials and methods

After approval from the University of Washington Human Subjects Review Committee, eight healthy adolescents and nine healthy adult subjects were recruited over a two-year period. Exclusion criteria included cardiac, neurologic, pulmonary, peripheral/systemic vascular, hematologic, endocrine or renal disease.

Determination of middle cerebral artery blood flow velocity

The study was conducted in a clinical research laboratory at the hospital. In each participant, both middle cerebral arteries (MCAs) were identified by transcranial Doppler ultrasonography (TCD) (Multidop X; DWL Corp., Sipplingen, Germany) using standard protocols (6). The transducers were secured in place using a head band. Bilateral middle cerebral artery blood flow velocities (Vmca; cm/s) were continuously recorded. Continuous non-invasive pulsatile MAP measurements were made over one radial artery using a tonometric blood pressure monitor (N-Cat N-500; Nellcor Corp., Hayward, CA) (8, 9). End-tidal carbon dioxide (ET-CO_2) partial pressure was measured using nasal prongs connected to a CO_2 monitor (Datex 223; Puritan Bennett Corp; Tewksberry, MA) (9).

Determination of dynamic cerebral autoregulation and study protocol

Details of the methodology have been described (6). In brief, subjects were supine with the upper body raised 10–15 degrees. Baseline blood pressure was recorded at the radial artery with patients' arms at their sides. Appropriately sized blood pressure cuffs were placed around each thigh and inflated to 30 mmHg above systolic blood-pressure (SBP) for 3 min The cuffs were then rapidly and simultaneously deflated, causing an instantaneous drop in MAP. A decrease in MAP of more than 12 mmHg was considered adequate dynamic cerebral autoregulatory stimulus (7, 10). Change in MAP and Vmca were simultaneously recorded and analyzed offline. The test was repeated three times in each subject with 8 min between each test. The average of the three bilateral responses was used in the final analysis.

Calculation of autoregulatory index

Values for each MCA were analyzed separately and a dynamic cerebral autoregulatory index (ARI) was calculated using a previously described computer program (6). Briefly, dynamic cerebral autoregulation involves a transient decrease in MAP and a comparison of the return of Vmca and MAP to baseline. MAP normally remains low after thigh cuff deflation for approximately 20 to 40 s before returning to normal. Because of cerebral autoregulation, Vmca generally returns to baseline more quickly. The Vmca and MAP values after thigh cuff release are used to calculate an ARI that reflects the change in CVR per s in relation to the change in MAP. A family of hypothetical Vmca curves with different degrees of autoregulation are plotted by the computer and compared to the actual Vmca curve for a given test. A hypothetical Vmca curve based on absent autoregulation is derived by the computer. If the actual curve has a perfect fit with the hypothetical curve, the ARI is zero. Values for ARI are, accordingly, calculated based on a scale of 0–9, with 0 representing absent autoregulation and 9 representing the fastest autoregulatory response possible in adults. The ARI value has a normal distribution in healthy adults with a mean of approximately 5 (9). Higher ARI values indicate better autoregulation (Appendix).

Statistical analysis

Statistical analysis was conducted using the Fisher's Exact test, Student's *t*-test, and linear regression analysis where appropriate. Significance was set at $P<0.05$. All values are expressed as mean ± SD unless otherwise indicated.

Results

Subjects were grouped into two age categories: group 1 (12–17 years; n = 8) and group 2 (25–45 years; n = 9). The age of the patients in groups 1 and 2 was 13 ± 1 and 37 ± 6, respectively (mean ± standard deviation). Seven of the eight subjects in group 1 were male; there were five males and four females in group 2. The two groups had similar heart rate and ET-CO_2 measurements before and during testing. There was no difference in baseline MAP between group 1 and group 2 (Table 1).

There was an inverse relationship of mean Vmca with age. Vmca was examined by group (group (1) 75 ± 15 vs. group (2) 58 ± 11; $P<0.001$) and as a continu-

Table 1

Differences in autoregulation between adolescents (group 1) and adults (group 2)

	Group 1 (n = 8)	Group 2 (n = 9)	*P*-value
Baseline			
Heart rate (beats/min)	72 ± 14	66 ± 9	0.15
ET-CO_2 (mmHg)	33 ± 5	33 ± 4	0.2
MAP (mmHg)	77 ± 11	80 ± 8	0.3
Vmca (cm/s)	75 ± 15	58 ± 15	0.0009*
After thigh cuff deflation			
MAP drop (mmHg)	20 ± 4	20 ± 6	0.34
MAP (mmHg)	57 ± 8	61 ± 8	0.26
ARI	3.9 ± 2.1	5.3 ± 0.8	0.05*

Group (1) 12–17 years, (2) 25–45 years. Values are expressed as mean ± SD. $P<0.05$ is significant.
*AR1 is significantly lower in group 1. Vmca is significantly lower in group 2.

ous variable using linear regression ($R^2 = 0.5$). There was no relationship between Vmca and MAP.

The ARI was significantly lower in group 1 than in group 2 (3.9 ± 2.1 vs. 5.3 ± 0.8; $P = 0.05$; Table 1; Fig. 1). ARI did not differ with comparison of right to left MCA. ARI was not related to the magnitude of postdeflation drop in MAP. There was no difference in the drop in MAP or postcuff deflation MAP between the two groups (Table 1). There was no difference in ARI between males and females in either group 1 or group 2.

Discussion

The results of this study suggest that adolescents aged 12–17 years have a lower ARI compared to adults when given a dynamic autoregulatory stimulus. Using TCD, we have also demonstrated that these adolescents have a significantly higher Vmca than adults. The average Vmca for group 1 in this study (75 ± 15 cm/s) was comparable to that described by Bode (l) (81 ± 11 cm/s). As expected, baseline MAP was lower in adolescents compared to adults.

Transcranial Doppler ultrasonography has been used to assess CBF in healthy children and in children with various medical conditions (11–13). There are other methods of studying CBF. Compared to TCD, however, they are more invasive, time consuming, and assume more risk, thereby constraining the study of cerebral hemodynamics. These considerations make TCD particularly well suited for the study of cerebral autoregulation in children.

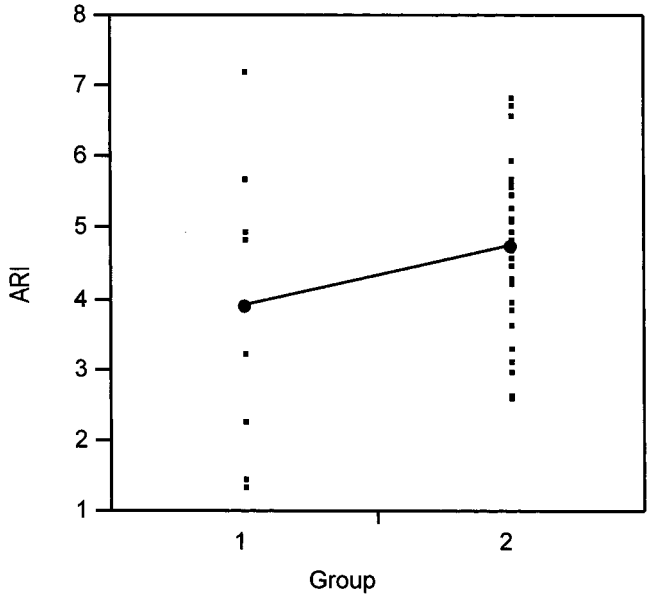

Fig. 1 Age versus ARI by groups. Group (1) 12–17 years; (2) 25–45 years. Horizontal line connects means of two groups. Difference in means is statistically significant; P=0.05.

The clinical methodology of and rationale for using dynamic autoregulation testing deserves comment. Dynamic autoregulation testing considers the rate of restoration of Vmca (cm/s) during transient hypotension. The ARI is derived from a mathematical model and reflects how quickly Vmca returns to baseline while the MAP remains low (14). In patients with intact autoregulation, cerebral vascular resistance decreases after thigh cuff deflation, allowing for a timely compensatory increase in CBF. An abnormal ARI reflects a decrease in the rate of recovery and/or capacity of the autoregulatory response. In 1997, Junger et al. described an ARI of 4.7 ± 1.0 and, more recently, Engelhard et al. reported ARI values of 5.4 ± 1.2 in healthy adults (9, 15). Based on previously published data, we considered a 12-mmHg decrease in MAP to be the minimum autoregulatory stimulus. During this study, the mean decrease in MAP in each of our groups was actually approximately 20 mmHg (7, 10).

Although cerebral autoregulation has classically been studied using the static method, this necessitates pharmacological manipulation of blood pressure, with its inherent risk and confounding pharmacological effects. In contrast, dynamic testing offers the advantage of quantifying the speed of the response without use of any pharmacologic agents, as well as testing the response to hypotension instead of hypertension. Despite these differences, there is excellent correlation between ARI determined using both methods under conditions of both intact and impaired autoregulation (11, 16). The use of dynamic autoregulatory testing in this study can be justified by the following reasons: (i) it requires no pharmacologic manipulation, making it ethically feasible to study healthy children, (ii) studies of autoregulation have been performed using dynamic testing in normal adults and adults with head injury, which gives us points of reference and comparison, and (iii) similar studies have not been performed in children.

There have been few studies examining cerebral autoregulation in the pediatric population. Many studies examining cerebral autoregulation in critically ill preterm infants show a loss or absence of autoregulation (17–19). The absence of smooth muscle in the cerebral vasculature in infants <30 weeks has been implicated as a factor responsible for impaired cerebral autoregulation, increased CBF, and the increased incidence of intraventricular hemorrhage. Healthy neonates appear to have some autoregulatory capacity, but the effect of increasing age on complete maturation of the autoregulation process is unknown (20).

Our results suggest that adolescents have a lower ARI compared to adults. This, however, does not mean that autoregulation is impaired. Rather, the ARI represents normal distribution for the age group. The autoregulatory response is different, but physiologically normal. Both anatomic and physiological maturation might play a role in the development of the fully developed autoregulatory response. Compared to healthy adults, healthy adolescents might have a slightly delayed return of CBF in response to transient hypotension. In adults, when the cerebrovascular resistance is lowered and the Vmca is increased by CO_2 administration, dynamic autoregulation response has been shown to be slowed down significantly (14). This is secondary to a lower baseline cerebrovascular resistance. Therefore, it is conceivable that the decrease in autoregulatory response rate in children reflects a normal but lower level of cerebrovascular tone as compared to adults. The finding of an increase in baseline Vmca in group 1 is consistent with this reasoning. Mahoney et al. demonstrated a correlation between ARI and baseline MAP in healthy adults using dynamic cuff autoregulation testing. Their observations suggest that subjects with lower ARI are close to maximal autoregulatory vasodilation and to their lower limit of autoregulation (7). When subjects are given an autoregulatory stimulus that is inadequate without sufficient decrease in MAP, the ARI would be falsely high. Consequently, only a decrease in MAP of at least 12 mmHg was accepted as the minimum autoregulatory stimulus (7, 10). On the other hand, if the decrease in MAP is excessive, the ARI may be falsely low. The decrease in MAP cannot be controlled. Although the extent of decrease in MAP during dynamic autoregulation testing cannot be controlled, there was no difference in MAP decrease between the two groups. Thus, the difference in ARI between adolescents and adults may arise from a difference in cerebrovascular tone in the resistance vessels, or that adolescents have a baseline MAP closer to the lower limit of autoregulation than adults. We, however, found no relationship between baseline MAP and ARI in our series of children.

Since the number of subjects in both groups is relatively small, we are unable to delineate any specific relationship between age and autoregulation on a continuous scale. Nor can we comment on the influence of gender, because only one female was enrolled in group 1. Although the standard deviation for mean ARI in group 1 is twice that of group 2, suggesting an overlap in ARI between the two groups, the variance of the means is incorporated into the *t*-test for the significance level of 0.05. Therefore, we believe the difference in ARI between group 1 and group 2 is valid. These findings do not necessarily imply that adolescents have impairment in cerebral autoregulation. Rather, they suggest the ARI has a different distribution in children compared to adults, as attested to by the greater standard deviation.

To the best of our knowledge, this is the first study of cerebral autoregulation in healthy children outside the neonatal period. We have demonstrated that healthy adolescents between the ages of 12–17 years have a slightly lower physiological ARI compared to adults during dynamic autoregulation testing. At the same time, adolescents have increased Vmca compared to adults. We believe that these findings are age appropriate and may reflect normal physiological distribution. The issue of optimal autoregulatory stimulus for pediatric patients of different ages, however, may warrant further investigation.

Acknowledgements

This project was supported in part by National Institutes of Health Grant no: R49CCR002570-14.

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Appendix

Table A1

Dynamic cerebral autoregulation was calculated by the computer using the following algorithm.

$$dP = (MAP - cMAP)/cMAP - CCP)$$
$$\times 2 = \times 2 + (\times 1 - 2D.\times 2)/f\ T)$$
$$\times I = \times I + (dP - \times 2)/(f.T)$$
$$mV = cVmca.(1 + dP - k.\times 2)$$

dP = change in MAP due to cuff release; cMAP = baseline MAP value before cuff release; CCP = critical closing pressure (calculated by the computer); $\times 1$ and $\times 2$ = variables that were assumed to be zero during the control period; D = damping factor; f = sampling rate; T = time constant; mV = mean velocity; cVmca = mean middle flow velocity before cuff deflation; K = autoregulatory dynamic gain.