Autoregulatory Response and CO₂ Reactivity of the Basilar Artery

Cheol Wan Park, MD, PhD; Mathias Sturzenegger, MD; Colleen M. Douville, BA, RVT; Rune Aaslid, PhD; David W. Newell, MD

Background and Purpose—Transcranial Doppler has been extensively used to measure cerebrovascular control mechanisms, including autoregulation in humans and in patients with cerebrovascular diseases. There have been sufficient reports on the measurement of normal autoregulatory response (AR) and CO₂ reactivity (CR) of the middle cerebral artery (MCA) but few reports of these indices for the basilar artery (BA). We measured AR and CR in the BA in healthy volunteers to determine normal values and compared them with simultaneous measurements made in the MCA.

Methods—Sixteen normal subjects were enrolled. Time-averaged mean velocities of maximum blood flow in the BA and MCA were continuously and simultaneously monitored by using transcranial Doppler along with continuous measurement of mean arterial blood pressure (MABP). Values were obtained during rest, alterations of end-tidal Pa CO₂ (ETCO₂), and acute decrease and recovery of MABP. AR was evaluated by using the thigh cuff method and graded by the standard dynamic autoregulatory index (ARI), with values between 0 and 9. CR was measured as percentage change in time-averaged mean velocity per mm Hg ETCO₂.

Results—The mean age of 16 subjects was 27.38±8.50 years. Average baseline values for MABP and ETCO₂ were 82.29±7.10 and 42.75±3.77 mm Hg, respectively. Mean ARI was 4.62±1.26 for the BA and was 4.77±1.23 for the MCA (n=15) (P=0.598). Average CR was 2.54±0.39%/mm Hg ETCO₂ for the BA and 2.51±0.29%/mm Hg ETCO₂ for the MCA (n=16) (P=0.686).

Conclusions—Our study demonstrates that ARI and CR values for the BA are similar to those for the MCA. (Stroke. 2003; 34:34-39.)

Key Words: autoregulation ■ basilar artery ■ blood flow velocity ■ carbon dioxide ■ ultrasonography, Doppler, transcranial

Cerebral autoregulation is a mechanism that allows cerebral blood vessels to maintain a constant cerebral blood flow (CBF) over a wide range of cerebral perfusion pressure.¹⁻³ The cerebral circulation is also profoundly affected by changes in PacO₂ and CO₂ reactivity (CR) defines the changes in CBF in response to changes in PacO₂.³⁻⁴ Transcranial Doppler (TCD) has been widely used to measure CBF velocity (BFV) and can be used to measure instantaneous changes in CBF in response to a variety of stimuli. TCD has recently been used to measure autoregulatory response (AR) and CR in various disease states that affect the brain.⁵⁻⁶ These measurements have led to an increased understanding of the effect of different pathological conditions on cerebrovascular function.

Numerous efforts have been made to establish normal criteria for AR and vasoactivity of the cerebral circulation by the use of TCD. Although there has been ample research involving normal values for the anterior half of the circle of Willis, mainly for the middle cerebral artery (MCA),⁷⁻⁻二十五 we have found few studies involving these values for the basilar artery (BA). To the best of our knowledge, no previous study has investigated AR in the human BA and both AR and CR for the BA in the same individuals. The objectives of the present study were to assess normal values of both the AR and CR for the BA and to compare them with simultaneously investigated values for the MCA in the same subjects. We also compared our results with previously reported normal values of CR for the BA with the use of TCD.

Subjects and Methods

Subjects
The present study involved 16 normal volunteers aged 19 to 46 years. TCD and carotid/vertebral duplex ultrasound findings were normal and symmetric in all volunteers. All subjects were healthy, were taking no medication, had no history of cardiovascular,
cerebrovascular, or other preexisting diseases, such as pulmonary or endocrine disease, and had no orthostatic symptoms. The subjects were not permitted to smoke or have caffeine or alcohol for at least 12 hours before the examination.

This present study was approved by the Institutional Review Board at the University of Washington, and informed consent was obtained for all subjects before examination.

**TCD Examinations and Measurements**

TCD examinations were carried out with the subject in a supine position with the head elevated and rotated to the right slightly (15° to 30°) and with the eyes closed. BFVs were continuously recorded from the BA and left MCA simultaneously by using a multichannel TCD instrument (Multi-Dop X, DWL). A 2 MHz pulsed-wave Doppler transducer was fixed in position over the left MCA through the left temporal window with customized headgear. A second 2 MHz probe was held on the back of the neck, aiming upward through the foramen magnum throughout the test. A schematic drawing of simultaneous insonation on the BA and left MCA is given in Figure 1. The BA and left MCA were identified, and most suitable signals were obtained in a standard fashion. A continuous noninvasive vasopressor pressure and heart rate (HR) monitoring device (Continuous Blood Pressure Monitor, CBM 7000, Colin) maintained at the same level as the right atrium was used to record blood pressure. These data were transferred to the TCD instrument via a port and were simultaneously displayed with the BFVs. Software on the TCD instrument also provided continuous time-averaged mean velocity (TAMV) of the maximum velocity outline of the Doppler spectrum along with mean arterial blood pressure (MABP). These data were presented as mean ± SD. Statistical evaluation was conducted to compare values of the BA with those of the MCA by paired t test. A value of P<0.05 was considered to be significant.

**Data Analysis**

AR was determined by using the dynamic autoregulation index (ARI), ranging from 0 to 9 according to the method reported by Tiecks et al.14 and reflecting the change in cerebrovascular resistance per second in relation to the change in MABP. The responses of TAMVs to an abrupt drop in MABP were adjusted to 10 software-containing standard models, and the best fit was chosen. The critical closing pressure was manually modified to improve the curve fitting and to achieve the least possible error value through visual control of the fitting. The resulting ARI values were averaged on each subject, and the mean ARI of all available subjects was averaged again.

To calculate the CR, first we measured and added the percent changes in TAMV from baseline value to maximum and minimum value during hypercapnia and hypocapnia, respectively.18 The resulting percent change (vasomotor reactivity [VMR]) was then divided by the absolute change in ETCO2 (maximum ETCO2 during hypercapnia minus minimum ETCO2 during hypocapnia) to yield the percent change in TAMV per mm Hg ETCO2.

All the values of TAMV, ETCO2, and MABP were averaged values for 10 seconds through software-assisted processing. For analysis of ARI, signals were smoothed and filtered at 0.4 Hz. All data were presented as mean ± SD. Statistical evaluation was conducted to compare values of the BA with those of the MCA by paired t test. A value of P<0.05 was considered to be significant.

**Results**

Among 16 subjects, 9 were men and 7 were women. No significant differences were found in ARI or CR between the BA and left MCA in the same individuals. The ARI testing was attempted 3 to 7 times for each individual. A total of 68 thigh cuff tests were tried, and 6 tests were excluded from analysis. The authors’ exclusion criteria were as follows: an MABP drop <12 mm Hg, a prolonged MABP drop >5 seconds after cuff release, or an unstable state of MABP or TAMV before cuff release. A prerequisite for averaging ARI data was a minimum of 3 technically acceptable tests on each subject. As a result, 62 tests, ranging from 3 to 6 tests for each individual (4.13±1.13 per subject), were available for analysis for 15 of 16 subjects. The data for CR were available and considered as valid for all 16 subjects. Data for demographic and basic variables for 16 normal volunteers are presented in Table 1.

Principal variables and statistical significances for comparing AR of the BA with that of the MCA are contained in Table 2. The differences in MABP and HR between baseline and during cuff up were <2 mm Hg increase in MABP and <1 bpm in HR, as noted in Table 1. The magnitudes of drop on cuff release were 18.37±3.74 mm Hg in MABP, 12.64±2.56 cm/s in BA TAMV, and 15.16±4.25 cm/s in end-tidal Paco2 (ETCO2) was continuously and simultaneously recorded with TAMV and MABP. The BA and left MCA TAMV, MABP, and ETCO2 were observed until a steady state was reached, and baseline values (BA TAMV base, MCA TAMV base, MABP base, and ETCO2 base) were recorded and continuously monitored during normocapnia, hypercapnia, and hypocapnia. Artificial hypercapnia was achieved through 3-minute administration of 5.6% CO2 delivered from a 50-L rubber reservoir bag to the mouthpiece. A generous period of time was allowed for subjects to relax and breathe room air before the initiation of hyperventilation. Subjects were then asked to hyperventilate for 2 minutes in a controlled manner, breathing in a regular rhythm to lower ETCO2, to <25 mm Hg. The steady states of TAMV and ETCO2 at the end of hypercapnia and hypocapnia were used as maximum and minimum values, respectively.

All the data were collected and saved on a hard drive for software-assisted offline analysis.

![Figure 1. Schematic drawing of simultaneous insonation on the BA and left MCA.](http://stroke.ahajournals.org/content/2017/07/14/hc9896/F1.large.jpg)
TABLE 1. Basic Data of 16 Normal Subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, y</td>
<td>27.38±8.50</td>
</tr>
<tr>
<td>Male-to-female</td>
<td>ratio</td>
</tr>
<tr>
<td>MABPbase, mm Hg</td>
<td>82.29±7.10 (n=15)</td>
</tr>
<tr>
<td>HRbase, beat/min</td>
<td>64.89±10.81 (n=15)</td>
</tr>
<tr>
<td>MABPcuff, mm Hg</td>
<td>84.05±8.21 (n=15)</td>
</tr>
<tr>
<td>HRcuff, beat/min</td>
<td>65.29±10.99 (n=15)</td>
</tr>
<tr>
<td>BA TAMVcuff, cm/s</td>
<td>46.39±8.86 (n=15)</td>
</tr>
<tr>
<td>MCA TAMVcuff, cm/s</td>
<td>65.24±16.39 (n=15)</td>
</tr>
<tr>
<td>MABPnorm, mm Hg</td>
<td>82.82±15.51</td>
</tr>
<tr>
<td>ETCO2norm, mm Hg</td>
<td>42.75±3.77</td>
</tr>
<tr>
<td>BA TAMVnorm, cm/s</td>
<td>48.38±8.74</td>
</tr>
<tr>
<td>MCA TAMVnorm, cm/s</td>
<td>70.00±14.39</td>
</tr>
</tbody>
</table>

Values are mean±SD. MABP indicates mean arterial blood pressure; HR, heart rate; BA, basilar artery; MCA, middle cerebral artery; ETCO2, end-tidal carbon dioxide; TAMV, time-averaged mean velocity.

MCA TAMV. These values were relevant to drops of corresponding values before cuff release of 21.90±3.75% in MABP, 27.52±4.48% in BA TAMV, and 23.25±3.65% in MCA TAMV. The time intervals for drops were 3.08±0.18 seconds in MABP, 2.33±0.18 seconds in BA TAMV, and 2.35±0.17 seconds in MCA TAMV. Recovery time intervals restoring cuff-up values were 17.05±2.70 seconds in MABP, 6.88±2.47 seconds in BA TAMV, and 6.88±2.96 seconds in MCA TAMV. A typical response of TAMVs to change in MABP is demonstrated in Figure 2. A paired t test comparing the BA with the MCA verified no significant difference in ARI or in other variables.

The MABPs during normocapnia, hypercapnia, and hypocapnia were 82.82±15.51, 89.00±12.18, and 83.25±9.02 mm Hg, respectively. These values corresponded to 8.99±12.32% and 3.28±18.70% increase during hypercapnia and hypocapnia, respectively. During hypercapnia and hypocapnia, ETCO2 increased and decreased by 20.81±7.37% (8.69±2.61 mm Hg) and by 51.52±6.54% (22.03±3.52 mm Hg), respectively, from normocapnia. The increased TAMVs during hypercapnia were 15.25±5.97 cm/s for the BA and 22.38±6.63 cm/s for the MCA. Decreased TAMVs during hypocapnia were 21.94±4.35 cm/s for the BA and 30.97±9.02 cm/s for the MCA. Main variables in CR for the BA and MCA are summarized in Table 3. Statistically, there was no significant difference in any main variable for CR between the BA and MCA. A model case of TAMV responses during ETCO2 changes is exhibited in Figure 3.

Discussion

During the last 2 decades, TCD has been one of the most valuable tools to estimate functional changes in the control of the cerebral circulation and to detect morphological alterations, such as stenosis in intracranial vessels. Measurements of AR and CR using TCD have provided reliable information about the physiological state of cerebrovascular reactivity and in various pathological situations. There is an increasing trend for AR and CR to be regarded as useful indices to measure the hemodynamic alterations that occur in cerebrovascular occlusive diseases.5,6,32 Alterations in AR and CR have also been described after brain injury.6,12,32

The BA is the only posterior axis supporting and supplying blood to the circle of Willis, providing a highly constant collateral blood flow system in physiological and many pathological conditions, although the efficiency of the circle of Willis in each individual is hard to predict.32 Nevertheless, AR and CR for the BA have received little attention, and most of the published data on AR and CR are for the anterior circle of Willis.7–25 We found a few reports on vasoreactivity for the BA,26–31 but we failed to find a report on AR for the human BA with the use of TCD. Using the thigh cuff method of AR testing and 5.6% CO2 inhalation and voluntary hyperventilation methods, we demonstrated that ARI and CR of the BA were 4.62±1.26%/mm Hg ETCO2 and 2.54±0.39%/mm Hg ETCO2, showing no significant difference from the MCAs in the same individuals.

Many methods have been proposed for the evaluation of static or dynamic AR. Although the thigh cuff method has been the most common approach for dynamic AR, other studies have used techniques involving vasoactive drugs, the Valsalva maneuver, cold pressor, isometric hand grip, and lower body negative pressure, carotid artery compression, and spontaneous fluctuations in arterial blood pressure,7,13,14 Each technique has its own merits and limitations. Advantages and limitations of the thigh cuff test that we used have been described,7,9,10,14 and we tried to reduce the drawbacks of determining ARI using this method during examination and analysis. For instance, we performed the thigh cuff testing at least 3 times to obtain a mean ARI for each subject, and we permitted sufficient breaks between each thigh cuff test for the return of MABP and TAMV to baseline values. We conducted recordings in a single session for each individual to remove possible day-to-day variance, adjusted critical closing pressure manually to diminish the error, and monitored MABP continuously throughout the examination. We thought that the effect of MABP on ARI was negligible because baseline MABP was normotensive in all subjects, and the mean difference between baseline and during cuff up MABP was only <2 mm Hg, as stated above.

In the present study, there was no significant difference in ARI or in other variables between the BA and MCA, as shown in Table 2. Interestingly, the mean recovery time interval of the BA to recover TAMVcuff was identical to that of the MCA. To our knowledge, there is no reported reference to compare ARI for the BA with our results. Our value of ARI
for the MCA (4.77±1.23) was similar to that in a previously published study using the thigh cuff technique by Tiecks et al14 (4.8±1.0), by Jung et al2 (4.7±1.0), and by Mahony et al9 (4.98±1.06). These reports also included mean ages of normal subjects and mean MABP drops on cuff release that were similar to those of our study (Tiecks et al, 35±10 years and 20±4 mm Hg drop; Jung et al, 38±16 years and 22±5 mm Hg drop; Mahony et al, 31.8±8.5 years and 26.4±7.1 mm Hg drop; and our result, 27.38±8.50 years and 18.37±3.74 mm Hg drop). Some studies using the same thigh cuff technique reported an ARI for the MCA that was higher than that in our study (Dawson et al,8 6.18±2.34; White and Markus,11 6.3±1.1). These discrepancies could be explained by use of a correlation coefficient instead of adjustment of critical closing pressure for the best model fitting and by use of an MABP drop on cuff release that was relatively smaller than ours.

In the present study, CR for the BA (2.54±0.39%/mm Hg ETCO2) also showed no significant disparity from the MCAs (2.51±0.29%/mm Hg ETCO2). Our results of CR for the BA and MCA are hard to compare with the results of earlier reports11,15,18–31 because of methodological differences in the evaluation of CR. The major dissimilarities are equations to calculate CR, techniques to induce change in ETCO2, concentrations of inhaled CO2, kinds of capnic stimuli used (hypercapnia, hypocapnia, or both), positions of subjects during examination, and mean ages of the subjects. When compared with reports that were conducted under a method relatively similar to ours, the CR values in our study are similar to the data reported by Hida et al31 (BA CR, 2.8±0.2%/mm Hg ETCO2; MCA CR, 2.7±0.3%/mm Hg ETCO2), and our result of VMR for the MCA (76.51±9.08%) is similar to but a little lower than VMR for the MCA documented by Ringelstein et al18 (85.63±15.96%) and by Weiller et al15 (87±15%). This relatively lower value of our VMR for the MCA than found in the studies described above might be accounted for by lower maximum ETCO2 and/or lower concentrations of inhaled CO2 in the present study.

There have long been debates about the mechanisms that govern the CBF.1–3,17,31–33 Principal techniques to determine VMR of cerebral vessels by TCD have made use of the administration of acetazolamide or CO2 and the breath-holding method.16,18,25,34 Each of these methods has limitations and advantages. However, discussions about CBF mechanisms and VMR techniques are beyond the scope of the present study.

The present study bears some limitations and possible sources of error. Although we assumed that the variations in BFV can be used to precisely pursue concomitant changes in CBF and that the diameters of the BA and MCA remain unaffected during examinations, whether the changes in BFV measured with TCD can accurately reflect the relative changes in CBF and whether the diameter of the BA and MCA are relatively constant throughout acute blood pressure perturbations and capnic stimuli have long been argued.17,20,35–40

Panerai et al7,10 and Mahony et al9 pointed out several problems with autoregulation testing by use of the thigh cuff method. We made efforts to minimize these problems as stated above, but potential errors might not be entirely eliminated. During CR testing, capnic challenges could cause fluctuation of MABP and HR, which, in turn, might lead to

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**TABLE 3. CO2 Reactivity in the BA Versus MCA (n=16)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>BA</th>
<th>MCA</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR, %/mm Hg ETCO2</td>
<td>2.54±0.39</td>
<td>2.51±0.29</td>
<td>0.686</td>
</tr>
<tr>
<td>VMR, %</td>
<td>77.69±12.57</td>
<td>76.51±9.08</td>
<td>0.663</td>
</tr>
<tr>
<td>Increased TAMV, %*</td>
<td>32.02±12.65</td>
<td>32.84±9.95</td>
<td>0.748</td>
</tr>
<tr>
<td>Decreased TAMV, %†</td>
<td>45.66±7.56</td>
<td>43.67±5.59</td>
<td>0.403</td>
</tr>
</tbody>
</table>

Values are mean±SD. CR indicates carbon dioxide reactivity; VMR, vaso-motor reactivity.

*Represents % increased velocity during hypercapnia from normocapnic value.

†Represents % decreased velocity during hypercapnia from normocapnic value.

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**Figure 2.** Illustration of dynamic AR (filtered at 0.4 Hz) in a 46-year-old male, demonstrating time-averaged mean velocities (TAMVs) for the basilar artery (BA) and left middle cerebral artery (MCA) react to a stepwise drop in mean arterial blood pressure (MABP) apparently in identical fashion.
deviations in the estimation of CR.\textsuperscript{19} Other reported factors may have an impact on the reliability of CR as representative of vasoreactivity for cerebral vessels, including reproducibility of CR,\textsuperscript{41} age and sex dependency,\textsuperscript{21,22} variability with posture and time,\textsuperscript{23,24} extent of collaterals with completeness of the circle of Willis,\textsuperscript{42} and food (such as that containing caffeine) just before the examination.\textsuperscript{43} Factors such as those described above could also influence the ARI.

Previous reports have indicated equal responses in BFVs and autoregulatory functions for the right and left MCA.\textsuperscript{7,8,12} We presumed that there was little error in using the left MCA BFV as a representative of BFV for both the MCAs. We insonated the BA with a handheld probe, whereas the MCA probe was fixed by the use of headgear. Therefore, BFV recording from the BA might have less constant placement of sample volume and/or angle of insonation than recording from the MCA. However, in the present study, because time-averaged spectral outline velocity (TAMV) was used as BFV, we thought that some movement of sample volume would have little, if any, effect on BFV for the BA.\textsuperscript{40} Other factors are also relevant to our finding. In the present study, the mean MABP alteration during hypercapnia was 8.99±12.32\% and 3.28±18.70\% during hypocapnia from the baseline value as described above. Blood pressure alterations may affect the calculation of CR if they are severe. The values of ARI and CR for the BA and MCA in the present study are insufficient as normal values of the whole normal population because the mean age in the present study was 8.50 years.\textsuperscript{8.99}

We are also aware that besides anatomic inequality, there are conflicting observations through human and animal studies on functional differences, including AR and CR between vertebrobasilar and carotid systems.\textsuperscript{26,28,30,31,33,44,45} We could not find any significant functional dissimilarity between the BA and MCA in the aspect of ARI and CR in normal subjects. However, this similarity may be disturbed in patients with cerebrovascular disorders.

Several indices (including ARI, CR, and VMR) using TCD are increasingly being used as indispensable parameters to manage patients with cerebrovascular diseases. It is important to continue to establish standards of testing methods and normal values for vascular reactivity in the anterior and posterior circulation to compare these values with the values in patients with disease states.

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References


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