Comparison of the Autoregulatory Mechanisms between Middle Cerebral Artery and Ophthalmic Artery after Thigh Cuff Deflation in Healthy Subjects

Julia Kolodjascbna, Fatmire Berisha, Solveig Lung, Heinrich Schima, Elzbieta Polska, and Leopold Schmetterer

PURPOSE. To compare dynamic autoregulation in the middle cerebral artery (MCA) and the ophthalmic artery (OA) after a step decrease in systemic blood pressure.

METHODS. Eighteen healthy male young subjects were studied. Ultrasound parameters and systemic blood pressures were recorded in each subject before, during, and after a step decrease in blood pressure. Continuous blood pressure recordings were made with a finger plethysmograph system, and flow velocities in the MCA and the OA were continuously measured with Doppler ultrasound. Large bilateral thigh cuffs were inflated and a pressure approximately 20 mm Hg above peak systolic blood pressure was maintained for 3 minutes. A decrease in blood pressure was induced by rapid deflation of bilateral thigh cuffs. Experiments were performed separately for the OA and the MCA.

RESULTS. Systemic blood pressure showed a step decrease immediately after thigh cuff release (9%–15%) and returned to baseline 7 to 10 pulse cycles later. Flow velocities in the MCA returned to baseline earlier than systemic blood pressure, indicating peripheral vasodilation, with a maximum of five to six pulse cycles after the blood pressure decrease. By contrast, flow velocities in the OA returned to baseline later than systemic blood pressure, reflecting peripheral vasoconstriction with a maximum 10 to 15 pulse cycles after cuff release. There was a statistically significant difference in the time course of the resistance changes in the two selected arteries after thigh cuff release (P < 0.001).

CONCLUSIONS. The results of the present study suggest substantial differences in the autoregulatory behavior of the vascular beds peripheral to the MCA and the OA. Results in the MCA would be compatible with either metabolic or myogenic vasodilation, whereas the results in the OA could reflect sympathetic vasoconstriction. Further studies are needed to support this hypothesis. The thigh cuff technique may represent an interesting approach to the study of autoregulation in patients with ocular vascular disease. (Invest Ophthalmol Vis Sci. 2005; 46:636–640) DOI:10.1167/iovs.04-0717

Blood flow autoregulation is defined as the ability of a tissue to maintain a relatively constant flow, despite moderate alterations in perfusion pressure. Similar to the cerebral, renal, coronary, and skeletal muscle circulations, the ocular vascular beds show the property of flow autoregulation. This homeostatic mechanism allows blood supply to the eye to match metabolic demands during daily activities such as changes in posture. Autoregulation has been found to be a complex phenomenon, showing heterogeneity in site and time course of action. Because metabolic, neurogenic, myogenic, and possibly endothelium-related mechanisms are involved, several factors may contribute to the autoregulatory process, depending on the challenging stimulus or the vessel tone.

Static and dynamic testing of autoregulation assess some different aspects of the ocular response to changes in perfusion pressure. During static testing, interventions are introduced to change perfusion pressure, and measurement of local hemodynamics and blood pressure are performed when a new perfusion pressure level is established at discrete time points and at best leads to a pressure/flow curve when autoregulatory processes have occurred to their fullest extent. By contrast, dynamic autoregulation assesses the full time course of the autoregulatory process by analyzing beat-to-beat changes in both perfusion pressure and ocular blood flow parameters. To study the dynamics of ocular autoregulation, it is necessary to introduce a step disturbance (stimulus) in ocular perfusion pressure and to record the responses of ocular blood flow continuously before and after this step disturbance.

The thigh cuff technique for the study of the dynamic behavior of cerebral autoregulation was introduced by Aaslid et al., after observations in animals and humans that the cerebral blood flow response to sudden changes in arterial blood pressure (ABP) shows a characteristic latency. We have adapted this mechanical noninvasive technique to induce an ocular and cerebral perfusion pressure step disturbance without drugs or changes in the concentration of vasoactive substances in the blood. Our study was designed to minimize interventions and to study the normal physiologic response to acute reductions in ABP. We deem it important to adapt such a simple autoregulatory test for the eye, because pronounced differences in regulation of blood flow and oxygenation in the eye and brain have been described.

We studied dynamic autoregulation using an ultrasound Doppler technique in the middle cerebral artery (MCA) and ophthalmic artery (OA). The autoregulatory test used in this study may also be applicable in patients with ocular vascular diseases, including diabetic retinopathy, glaucoma, and age-related macular degeneration.

METHODS

Subjects

The present study conformed to the provisions of the Declaration of Helsinki and the Good Clinical Practice (GCP) guidelines. After ap-
proval of the study protocol by the Ethics Committee of the Vienna University School of Medicine and after written informed consent was obtained, 18 healthy, nonsmoking male subjects were enrolled. All subjects were drug free for at least 3 weeks before inclusion and passed a pre-study screening 1 week before the first study day that included medical history and 12-lead electrocardiogram. Subjects were excluded if any abnormality was found during the screening, unless the investigators considered an abnormality to be clinically irrelevant. In addition, subjects with any evidence of eye disease that might interfere with the purpose of the present trial were excluded.

Experimental Design
Ultrasound parameters and ABP were recorded in each subject before, during, and after a step decrease in blood pressure. Continuous ABP recordings were made with a finger plethysmograph (Finapres BP Monitor, model 2300; Ohmeda, Tokyo, Japan) with the subject’s hand maintained at the same level as the heart. The finger plethysmograph provides a reliable assessment of rapid changes in ABP. A thigh cuff technique was used to induce the decrease in ABP. Large bilateral thigh cuffs were wrapped around both thighs and inflated, and a thigh cuff pressure of approximately 20 mm Hg above peak systolic arterial pressure was applied. The occlusion was maintained for 5 minutes, and a decline in ABP was induced by rapid deflation of bilateral thigh cuffs.

Flow velocities and ABP were continuously recorded in each subject before (1 minutes), during, and after (1 minutes) a step decrease in blood pressure. The test procedure was repeated two times (for MCA and for OA) in each subject. An interval of >5 minutes was allowed between each cuff release and the next inflation to permit ABP and flow velocities to return to baselines. The recording for each subject was performed in a single session of approximately 30 minutes, during which the volunteer remained supine.

Study Methods
Blood Pressure and Pulse Rate. Continuous noninvasive finger ABP was measured with a blood pressure monitoring system (Finapres BP Monitor system; Ohmeda, Tokyo, Japan). At each pulse cycle, systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured. The Finapres system is based on the volume clamp method. The finger cuff was applied to the midphalanx of the middle finger of the right hand and held at heart level with the arm across the chest supported by a sling to avoid hydrostatic errors. In the Finapres device, a built-in expert system is in operation to establish and adjust a correct volume clamp set point. Pulse rate was derived from the intervals between pressure pulses.

Color Doppler Imaging of the OA and MCA. The color Doppler imaging (CDI) examinations were performed with an ultrasound device (VingMed Ultrasound AS, General Electric, Mountain View, CA). Peak systolic flow velocity and minimal diastolic flow velocity of the OA were assessed with a 3.25-MHz color Doppler flow velocimeter (Acuson, Mountain View, CA). Peak systolic flow velocity in the OA (cm/s) 52.1

End diastolic flow velocity in the MCA (cm/s) 25.0

Pulse rate (bpm) 72.0

Diastolic blood pressure (mm Hg) 77.0

Systolic blood pressure (mm Hg) 130.0

Age (y) 24.0 ± 0.6

Systolic blood pressure (mm Hg) 130.0 ± 3.8

Diastolic blood pressure (mm Hg) 77.0 ± 2.2

Mean arterial pressure (mm Hg) 90.0 ± 3.6

Pulse rate (bpm) 72.0 ± 3.1

Peak systolic flow velocity in the MCA (cm/s) 63.2 ± 2.8

End diastolic flow velocity in the MCA (cm/s) 25.0 ± 1.0

Peak systolic flow velocity in the OA (cm/s) 52.1 ± 4.1

End diastolic flow velocity in the OA (cm/s) 7.7 ± 0.7

Data are expressed as the mean ± SEM.

TABLE 1. Baseline Values of the Study Population

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>24.0 ± 0.6</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>130.0 ± 3.8</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
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</tr>
<tr>
<td>Pulse rate (bpm)</td>
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<td>Peak systolic flow velocity in the MCA (cm/s)</td>
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<td>End diastolic flow velocity in the MCA (cm/s)</td>
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</tr>
<tr>
<td>Peak systolic flow velocity in the OA (cm/s)</td>
<td>52.1 ± 4.1</td>
</tr>
<tr>
<td>End diastolic flow velocity in the OA (cm/s)</td>
<td>7.7 ± 0.7</td>
</tr>
</tbody>
</table>

RESULTS
Demographics of the studied subjects at baseline are summarized in Table 1. The procedure was well tolerated by all subjects, and no adverse events were observed. Data analysis in the MCA was based on the results of 17 subjects only, because in one subject the MCA was not measurable through the temporal cranial window.

A clear blood pressure decrease was seen in all experiments. The changes in blood pressure and flow velocities after the cuff release are summarized in Table 2. The mean ABP decrease in response to the thigh cuff release during the MCA experiments was −11 mm Hg (10%) for SBP(MCA) and −6 mm Hg (9%) for DBP(MCA) and during the OA experiments −16 mm Hg (14%) for SBP(OA) and −11 mm Hg (15%) for DBP(OA). The corresponding sample average decrease in blood flow velocity was 7.0 cm/s (11%) for PSV(MCA) and 4.0 cm/s (15%) for DBP(MCA). In the OA the reduction in flow velocities immediately after thigh cuff release was 5.0 cm/s (10%) for PSV(OA) and 1.1 cm/s (14%) for EDV(OA).

Figure 1 shows the time course of the blood pressure, flow velocities, and IRs before and after cuff deflation in both arteries. During all experiments, it took approximately 7 to 10 pulse cycles for systemic blood pressure to return to baseline. Both, PSV(MCA) and EDV(MCA) returned to baseline earlier than systemic blood pressure. Approximately six to seven pulse cycles after the cuff release, there was a small overshoot in both PSV(MCA) and EDV(MCA). Thereafter flow velocities in the MCA returned to baseline. Accordingly, IRs in the MCA showed a decrease, with a maximum of five to six pulse cycles after the blood pressure decrease, reflecting peripheral vasodilatation (P < 0.001, post hoc analysis).

In the OA, flow velocities returned to baseline later than did the systemic blood pressure. Approximately 20 pulse
cycles after the cuff release PSV(OA) and EDV(OA) reached baseline again. Accordingly, IRs in the OA showed an increase, reflecting peripheral vasoconstriction, which reached its maximum approximately 10 to 15 pulse cycles after the blood pressure decrease ($P = 0.002$; post hoc analysis).

**Table 2. Changes in Blood Pressure and Flow Velocity after Thigh Cuff Release**

<table>
<thead>
<tr>
<th>Latency (Number of Heart Cycles before Return to Baseline)</th>
<th>Change after Cuff Release %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Middle cerebral artery experiments</strong></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>−11 ± 3</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>−9 ± 4</td>
</tr>
<tr>
<td>Peak systolic flow velocity in the MCA</td>
<td>−11 ± 3</td>
</tr>
<tr>
<td>End diastolic flow velocity in the MCA</td>
<td>−15 ± 4</td>
</tr>
<tr>
<td><strong>Ophthalmic artery experiments</strong></td>
<td></td>
</tr>
<tr>
<td>Systolic arterial pressure (mmHg)</td>
<td>−14 ± 4</td>
</tr>
<tr>
<td>Diastolic arterial pressure (mmHg)</td>
<td>−15 ± 4</td>
</tr>
<tr>
<td>Peak systolic flow velocity in the OA</td>
<td>−10 ± 4</td>
</tr>
<tr>
<td>End diastolic flow velocity in the OA</td>
<td>−14 ± 4</td>
</tr>
</tbody>
</table>

Data are expressed as the mean ± SEM.

**Figure 1.** Time course of the outcome variables in the MCA (left) and the OA (right) before and after thigh cuff release. Data are expressed as the mean ± SEM ($n = 18$). The first vertical line in each graph represents the time point when the cuff was released. The second vertical line denotes the time point at which baseline was reached again. There was no statistical difference from baseline.
There were statistically significant differences between the time courses of IRs(MCA) and IRs(OA) \( (P < 0.001 \) two-way ANOVA) and IRd(MCA) and IRd(OA) \( (P < 0.001) \).

**DISCUSSION**

The purpose of this study was to investigate the dynamic regulatory behavior in the MCA and OA during an acute decrease of perfusion pressure in healthy humans. Our data suggest a difference in the autoregulatory response pattern between the OA and MCA. Initially, PSV and EDV decreased in response to the step decrease in blood pressure, as expected. Thereafter, flow velocities in the MCA returned to baseline earlier than systemic blood pressure. Accordingly, IRs showed a decrease reflecting peripheral vasodilatation with a maximum approximately 5 seconds after cuff release. By contrast, flow velocities in the OA returned to baseline later than systemic blood pressure. Hence, IRs showed an increase reflecting peripheral vasoconstriction, which occurred later, however, than the response in the MCA.

Obviously, it is of critical importance for the conclusions drawn from the present study that the diameter of the MCA and the OA remain constant during the experiments, because otherwise flow velocities would no longer be proportional to blood flow. This is supported at least by two arguments. On the one hand, there is evidence that the main site of autoregulatory action in the brain in response to a decrease in blood pressure is located in small arterioles in the brain parenchyma, whereas larger vessels react very little. This argument also applies in the OA, where most of the change in vascular resistance occurs distally. On the other hand, it has been shown for the MCA that during experiments with the thigh-cuff method the power of the ultrasound signal does not show any changes, strongly arguing against changes in MCA vessel diameter. To the best of our knowledge no such data are available for the OA.

The results of the present study suggest that different autoregulatory mechanisms are active in the vascular beds peripheral to the MCA and OA. It has been hypothesized that vasodilation peripheral to the MCA is caused by a metabolic feedback system with a high open loop gain. Alternatively, the early vasodilatation may result from a myogenic response. Accordingly, peripheral vasodilatation in small cerebral arteries occurs as a result of the decrease in transmural pressure, due to the step decrease in blood pressure.

In the OA other mechanisms may be responsible for the observed results. The early vasodilatation in the vascular beds peripheral to the measurement site appeared to be absent. The small vasoconstriction observed approximately 15 seconds after the blood pressure decrease may have several reasons. On the one hand, it may represent a sympathetically driven vasoconstriction, most probably through the \( \alpha_2 \) receptor. This hypothesis is supported by the fact that a baroreflex mechanism is responsible for blood pressure restoration after the decrease in blood pressure. On the other hand, it could be that \( CO_2 \)-rich and hypoxic blood from the legs returning to the circulation influenced the results obtained in the present study. The transport time from the legs to the brain is approximately 15 seconds, which would fit well with the time constant obtained in the present study. It appears, however, that hypercapnic and hypoxic blood would induce vasodilatation at the level of the brain or the eye. Moreover, such an effect should be detectable in the MCA as well as in the OA.

The thigh cuff technique may be a simple approach to the assessment of autoregulation in patients with ocular vascular disease. In the brain, this technique has been successfully applied to the study of the influence of different anesthetics on cerebral autoregulation. In addition, results in patients with carotid artery stenosis, head injury, systemic hypertension, or ischemic stroke have been published. A recent study indicates that dynamic autoregulation in the MCA is impaired in patients with primary open-angle or normal-tension glaucoma. In this study dynamic autoregulation was assessed by inducing oscillations in mean arterial pressure after deep breathing at 0.1 Hz. The thigh cuff technique comparing the autoregulatory behavior of the MCA and OA may therefore represent an interesting approach to the study of the association between systemic and ocular vascular dysregulation, both assumed to be present in glaucoma.

In conclusion, the present study showed that the thigh cuff technique can be applied to study the autoregulatory behavior in vascular beds distal to the MCA and the OA. Pronounced differences in the flow velocity response of these arteries were observed, suggesting the possibility of substantial differences in the autoregulatory mechanisms of these vascular beds. Further studies are needed, to elucidate these differences and to show the applicability in patients with ocular vascular disease.

**References**