Original Contributions

Retinal Vascular Autoregulation in Normal Subjects

HISAO TACHIBANA, M.D., FUMIO GOTOH, M.D., AND YOSHIKI ISHIKAWA, M.D.

SUMMARY The retinal arterial diameter and its response to changes in perfusion pressure were measured by means of a fundus camera in 65 normal subjects. A reduction of effective MABP was induced by a postural change from a recumbent to an erect position. A small but significant increase in retinal arterial diameter was observed by reduction of the perfusion pressure in all subjects.

The reduction of retinal arterial reactivity in response to blood pressure changes (\(-\% \text{ change in diameter}/\Delta \text{ effective MABP}\) was significantly correlated with advancing age \((p < 0.01)\). No significant correlations were observed between the retinal arterial reactivity, magnitude of the retinal arterial diameter (range: 60-140 \(\mu\)), and systemic blood pressure (range of MABP: 75-110 mmHg).

These results indicate that the retinal artery has an autoregulatory mechanism which is influenced by aging.

Cerebrovascular autoregulation is defined as constancy of blood flow despite changes in perfusion pressure within the range of 50-160 mmHg.\(^1,2\) The mechanism of autoregulation is mediated by changes in arterial calibre; the vessels dilate as the pressure falls and constrict as the pressure rises. Although cerebrovascular autoregulation is known to be altered in various diseases\(^4,5\) and conditions,\(^6-8\) little is known about the effects of aging on the autoregulation in normal subjects. This lack of basic data is probably related in part to the traumatic and invasive nature of the techniques for estimating autoregulation.

The retinal artery, a branch of the ophthalmic artery deriving from the internal carotid artery, is considered to represent part of the cerebral vessels and is the only vessel seen directly under physiological conditions. Several workers\(^9-18\) have reported that the human retinal circulation responds actively to changes in perfusion pressure, thus demonstrating the presence of an autoregulatory mechanism in the retina. Furthermore, the retinal vessels react to changes in oxygen\(^16-18\) and carbon dioxide tension\(^19,20-24\) as noted in the cerebral vessels.\(^22,23\) These data suggest that the reactivity of the cerebral arteries can be estimated well from the reactivity of the retinal arteries.

The purpose of the present study was to investigate the retinal vascular autoregulation in normal subjects of various ages and to assess the influence of aging on the cerebrovascular autoregulation.

Materials and Methods

Sixty-five normal subjects (40 males, 25 females) with ages ranging from 18 to 73 (mean 36 years) were included in the present study. Thirty-seven were volunteers, while the remaining 28 were out-patients of Keio University Hospital. All were fully active, independent, and non-hospitalized. The out-patients underwent detailed interviews and general physical and neurological examinations. There was no evidence of central nervous system pathology in any of the subjects. Those found to have any of the following abnormalities were excluded: hypertension, diabetes mellitus, diseases of the autonomic nervous system, history of coronary or cerebral vascular disease, and pulmonary abnormalities.

The retinal arterial diameter and its response to changes in blood pressure were measured by means of a special fundus camera (Canon CR2-45 NM) which does not require dilatation of the pupils with a midriatic drug. A reduction in the effective mean arterial blood pressure (effective MABP) at the level of the eyes was induced by a postural change from a recumbent to an erect position. The postural change was performed by using a tilt table. A photograph of each fundus of the subjects was taken in the recumbent position and then in the erect position (fig. 1), and the brachial arterial blood pressure was measured simultaneously using a sphygmomanometer. The procedure was fully explained to the subjects beforehand and the tilting was carried out slowly to prevent apprehension and hyperventilation as well as to avoid rapid changes in effective MABP. A photograph was then taken after an interval of a few minutes, since the cerebrovascular autoregulation takes 30 to 120 seconds to become effective even in normal subjects.\(^6,24,28\)
FIGURE 1a. Apparatus including fundus camera and tilt table — recumbent position.
Figure 1b. Apparatus including fundus camera and tilt table — erect position.
The present findings also demonstrated that the retinal arterial diameter decreased with advancing age (r = -0.34, p < 0.01) (fig. 2-b).

The correlations between the retinal arterial reactivity, magnitude of the retinal arterial diameter, and MABP were also evaluated. No significant correlation was observed between the retinal arterial reactivity and MABP. Likewise, there was no significant correlation between the retinal arterial reactivity and MABP in the range of 75–110 mmHg.

The relationship between the retinal arterial reactivity and findings of the optic fundi by ophthalmoscopic examination was investigated. As shown in table 3, there was no significant correlation between the retinal arterial reactivity and the clinical grading of the arteriosclerotic and hypertensive changes assessed according to Scheie's classification.

### Discussion

In the present study, the effects of a reduction in perfusion pressure on the retinal arterial diameter were investigated by effecting a postural change from a recumbent to an erect position. The perfusion pressure to the eye can be reduced in two ways. One is by reducing the blood pressure and the other is by increasing the intraocular pressure. An increase in intraocular pressure cannot be induced without discomfort and anxiety. We therefore chose the former method, by which the retinal vascular autoregulation can be evaluated more physiologically and non-invasively.

The retinal perfusion pressure is calculated as the effective MABP minus the mean retinal venous blood pressure. However, it is believed that the retinal venous blood pressure, which remains above the intraocular pressure, is less affected by changes of body position. We therefore considered the changes in effective MABP to represent alterations of the retinal perfusion pressure.

Some investigators have neglected the magnitude of the changes in perfusion pressure when evaluating their data with respect to autoregulation. However, we believe that it should be taken into account since the magnitude of the changes in perfusion pressure differs in each subject. In the present study concerning autoregulation, the data were evaluated quantitatively by use of the RVIs and % change in diameter.

The results obtained clearly showed a small but significant retinal arterial vasodilatation by reduction of the perfusion pressure in all the subjects studied. The data indicated that the retinal artery has an autoregulatory mechanism as seen in the cerebral arteries.

The present findings also demonstrated that the retinal arterial reactivity was expressed as the average percent increase in the retinal arterial diameter (% change in diameter) induced by the postural change. However, there was a difference in the reduction of perfusion pressure in each subject. For this reason, the retinal arterial reactivity was also shown quantitatively by the Retinal Vasomotor Index (RVI) (% change in diameter /change in effective MABP (mmHg)). The effective MABP was calculated by subtracting the hydrostatic pressure between the heart and the eye from the mean brachial arterial blood pressure of the patient.

All results were expressed as means ± standard deviation and were analyzed statistically using Student's t test.

### Results

The effective MABP fell from 91.0 ± 9.2 mmHg to 68.6 ± 8.9 mmHg by the postural change. There were no subjects whose retinal perfusion pressure fell below 50–60 mmHg in the erect position. As a result of the reduction in perfusion pressure, a small but significant increase in retinal arterial diameter was observed in all cases. The retinal arterial diameter increased from 103 ± 14 μ to 109 ± 15 μ in the right eye, and from 105 ± 14 μ to 111 ± 14 μ in the left eye. The mean percent increase in retinal arterial diameter was 6.2 ± 2.7% and the mean value of RVI was 0.28 ± 0.13 %/mmHg. When a comparison was made between the right and left eyes (table 1), no difference was observed for the % change in diameter or the RVI values.

A comparison between males and females is presented in table 2. The % change in diameter and RVI value in females were on average slightly higher than those in males, but the difference was not significant.

A significant reduction in % increase of retinal arterial diameter was found with advancing age (r = -0.27, p < 0.05) (fig. 2-a). The RVI showed a more significant reduction with advancing age (r = -0.34, p < 0.01) (fig. 2-b).

### Table 1. Comparison of Retinal Arterial Reactivity between Right and Left Eyes

<table>
<thead>
<tr>
<th>Retinal arterial reactivity</th>
<th>% change in diameter</th>
<th>RVI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right eye</td>
<td>6.2 ± 3.4</td>
<td>0.28 ± 0.17</td>
</tr>
<tr>
<td>Left eye</td>
<td>6.2 ± 3.0</td>
<td>0.28 ± 0.14</td>
</tr>
</tbody>
</table>

Values are means ± sd.

### Table 2. Comparison of Retinal Arterial Reactivity between Males and Females

<table>
<thead>
<tr>
<th>No. of cases</th>
<th>Age (yr)</th>
<th>% change in diameter</th>
<th>RVI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>40</td>
<td>37 ± 13</td>
<td>6.0 ± 2.6</td>
</tr>
<tr>
<td>Females</td>
<td>25</td>
<td>35 ± 15</td>
<td>6.6 ± 2.8</td>
</tr>
</tbody>
</table>

significant reduction with advancing age (r = -0.34, p < 0.01) (fig. 2-b).

The correlations between the retinal arterial reactivity, magnitude of the retinal arterial diameter, and MABP were also evaluated. No significant correlation was observed between the retinal arterial reactivity and magnitude of the diameter in the range of 60–140 μ. Likewise, there was no significant correlation between the retinal arterial reactivity and MABP in the range of 75–110 mmHg.

The relationship between the retinal arterial reactivity and findings of the optic fundi by ophthalmoscopic examination was investigated. As shown in table 3, there was no significant correlation between the retinal arterial reactivity and the clinical grading of the arteriosclerotic and hypertensive changes assessed according to Scheie's classification.
retinal arterial reactivity decreases with advancing age in normal subjects. This may be attributable in part to organic changes occurring in the retinal vessels of normal elderly persons even in the absence of symptoms or risk factors of cerebral arteriosclerosis. However, the present results do not necessarily support this assumption, since no significant relationship was observed between the grading of the arteriosclerotic and hypertensive changes according to Scheie's classification and the retinal arterial reactivity. Sieker et al. reported that the retinal arterial reactivity to oxygen was gradually reduced with advancing age in normal subjects, and persons with hypertension or diabetes mellitus showed impairment of the constrictor response of the retinal arteries. Furthermore, they observed a rough relationship between clinical grading of the arteriosclerotic changes by ophthalmoscopic examination and the impairment of the retinal arterial reactivity. The discrepancy between their data and ours suggests the possibility that the

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**Figure 2a.** Gradual reduction of retinal arterial reactivity with advancing age in 65 normal subjects. Correlation between % change in retinal arterial diameter and age. The correlation is significant. The regression of the reactivity with respect to age is given by $Y = -0.053X + 8.1$.

**Figure 2b.** Gradual reduction of retinal arterial reactivity with advancing age in 65 normal subjects. Correlation between RVI and age. The correlation is highly significant. The regression of the reactivity with respect to age is given by $Y = -0.0032X + 0.40$. 
mechanism of retinal vascular autoregulation may be somewhat different from that of chemical control of the retinal vessels.

The mechanism of autoregulation of the retinal blood flow is still unclear, although several hypotheses have been proposed.\(^{10, 13, 84, 85}\) Regardless of the actual mechanism, the results of the present study suggest that the cerebrovascular autoregulatory response might show a similar reduction with advancing age. In fact, Hoffmann et al.\(^{86}\) have reported that aging in the experimental animals exerted an influence on the ability of the cerebrovascular system to autoregulate. Previous reports on cerebrovascular dysautoregulation in patients with stroke and other neurological diseases, however, have not considered the influence of age, probably because there are no available data concerning the influence of aging on the human cerebrovascular autoregulation. The present study thus justifies further research on aging of the cerebrovascular autoregulation in man.

**References**


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**Table 3. Relationship between Retinal Arterial Reactivity and the Clinical Grading of Arteriosclerotic and Hypertensive Changes According to Scheie's Classification**

<table>
<thead>
<tr>
<th>Clinical grading</th>
<th>No. of cases</th>
<th>% change in diameter</th>
<th>RV1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertensive changes</td>
<td>H(_0)</td>
<td>51</td>
<td>6.1 ± 2.8</td>
</tr>
<tr>
<td></td>
<td>H(_1)</td>
<td>12</td>
<td>6.8 ± 2.3</td>
</tr>
<tr>
<td></td>
<td>H(_2)</td>
<td>2</td>
<td>6.2 ± 2.8</td>
</tr>
<tr>
<td>Arteriosclerotic changes</td>
<td>S(_0)</td>
<td>52</td>
<td>6.5 ± 2.1</td>
</tr>
<tr>
<td></td>
<td>S(_1)</td>
<td>10</td>
<td>6.6 ± 3.9</td>
</tr>
</tbody>
</table>

*Values are means.

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The relationship between retinal arterial reactivity and the clinical grading of arteriosclerotic and hypertensive changes according to Scheie's classification is presented in Table 3. The table shows the percentage change in diameter and the retinal vascular index (RV1) for different clinical grades. The data suggest that arteriosclerotic changes are associated with a higher percentage change in diameter compared to hypertensive changes, indicating a more significant effect on retinal blood flow.
rCBF in Patients with Carotid Occlusion

Resting and Hypercapnic Flow Related to Collateral Pattern

Bo Norrving, M.D., Bengt Nilsson, M.D., and Jarl Risberg Ph.D.

SUMMARY  rCBF was measured by 133Xenon inhalation technique in 39 patients with unilateral carotid artery occlusion in a subacute-chronic stage. Resting flow values (ISI) varied between 23.7 and 52.4 ml/100 g/min. An almost constant finding was interhemispheric asymmetry, the degree of which was correlated with the severity of the initial symptoms. An ischemic focus was an insignificant finding. The CO$_2$ response was normal in patients with angiographic signs of circle of Willis collateral flow and without significant contralateral carotid stenosis, whereas it was impaired in patients with a retrograde ophthalamic flow or collateral flow via the circle of Willis and contralateral carotid stenosis $\geq$ 50%. It is concluded that the CO$_2$ response is a useful rCBF variable and may be applied for analysis of collateral flow capacity in patients with carotid artery occlusion considered for bypass surgery.

CAROTID OCCLUSION is the single most common arterial lesion considered for extra-intracranial bypass operation.$^1$ Although this procedure is performed in numerous patients, its definitive therapeutic value remains unproven. In most centers, bypass surgery is confined to patients with TIA or only mild stroke at the time of the occlusion, and is attempted to reduce the incidence of future stroke.

Recent studies suggest that the long term prognosis in carotid occlusion is favorable, with a stroke rate on the occluded side of only 1–2% per year.$^2, 3$ This would limit the value of bypass surgery as a general prophylactic measure in carotid occlusion. Because a bypass operation is a hemodynamically directed procedure, the identification of a subset of patients with impaired capacity of the collateral circulation would be of importance.

In this report we examine the usefulness of rCBF (regional cerebral blood flow) studies in evaluating hemodynamic features in carotid occlusion. rCBF was measured with the 133Xenon-inhalation technique during rest and induced hypercapnia and results were correlated with clinical symptoms and collateral flow pattern.

Patients and Methods

Thirty-nine patients with unilateral carotid occlusion were examined with rCBF by 133Xenon inhalation. The patients were collected in the following manner. Twenty-six patients were evaluated for bypass operation after angiographic identification of the occlusion at this or at an admitting hospital. The interval between the onset of the symptoms and the rCBF study was one to six months in these patients. From a recent study on the long-term prognosis in carotid occlusion,$^8$ a further 13 patients with previous TIA or minor stroke were randomly selected for rCBF examination, performed one to nine years after the diagnosis of occlusion was established. The ratio male/female was 31/8 and the mean age of the patients was 60 years (range 34–77 years).

Angiograms were examined for the presence of lesions in extracranial arteries other than the occluded carotid as well as intracranially, and for the source of collateral supply to the occluded hemisphere. All patients underwent selective common carotid angiography on the occluded side. The contralateral carotid artery was studied with selective angiography in 33 patients and with aortic arch angiography in 6 patients. The vertebral arteries, examined in 30 patients, were...
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