Increased Blood Pressure Induces a Diameter Response of Retinal Arterioles that Increases with Decreasing Arteriolar Diameter

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Purpose. To study the diameter response of retinal arterioles as a function of the arteriolar diameter.

Methods. Ten healthy young volunteers aged 22 to 33 years were subjected to diameter measurement of four successive segments of a retinal arteriole with a retinal vessel analyzer (RVA). At each of the segments, the diameter response during an increase in the systemic blood pressure (mean arterial pressure [MAP]) induced by isometric exercise was compared to the diameter of the arterioles during rest.

Results. The isometric exercise induced a significant contraction of the studied vessel segments averaging 2.5% ± 0.4% ($P < 0.0001$, $n = 40$). There was a significant negative correlation between the baseline diameter of the studied vessel segments and the diameter response induced by isometric exercise ($P = 0.02$).

Conclusions. The blood pressure–induced diameter response of retinal arterioles increased with decreasing diameter of the vessels. The results indicate that the distal retinal arterioles play a major role in the regulation of retinal blood flow. (*Invest Ophthalmol Vis Sci.* 2007;48:328–331) DOI:10.1167/iovs.06-0360

Disturbances in the regulation of retinal blood flow is a characteristic feature of sight-threatening vascular diseases such as diabetic retinopathy and hypertensive retinopathy. A detailed knowledge of the regulation of retinal blood flow under normal conditions is needed, to understand the pathologic changes in retinal blood flow in these diseases. In most tissues, including the retina, the capillary flow is autoregulated by reflex adjustments of the diameter of arterioles as a response to variations in the blood pressure.[1,2] The magnitude of this diameter response varies along the arteriolar system and is believed to be most pronounced in resistance arterioles with a diameter below 300 μm.[3,4] However, several observations indicate that the diameter response to changes in blood pressure may vary, even within the narrow diameter range observed in resistance vessels of the retina (Rosa RH et al. *IOVS* 2004;45:ARVO E-Abstract 3674),[4,5] and clinical observations indicate that retinal vascular disease may be related to disturbances in tone regulation of either larger or smaller retinal vessels.[6–8] However, the diameter response has not been studied as a function of retinal arteriolar diameter in normal persons.

Consequently, in the present study the diameter response of retinal arterioles after an increase in the arterial blood pressure was studied as a function of the arteriolar diameter in 10 normal persons with a retinal vessel analyzer (RVA; Imedos, Weimar, Germany).

Materials and Methods

Subjects

Ten healthy men were studied. None of the persons had any present or previous history of arterial hypertension, glaucoma, diabetes mellitus, or cardiovascular disease. Written and oral consent was obtained from all persons in accordance with international ethical standards, and the study was approved by the local committee for scientific ethics and adhered to the tenets of the Declaration of Helsinki.

Routine Ophthalmologic Examination

All participants underwent a routine ophthalmic examination including measurement of best corrected visual acuity (VA), slit lamp examination, and pneumotonometry (NT-3000; Nidek, Gamagori, Japan). Finally, fundus examination was performed after induction of mydriasis with phenylephrine 10% and mydriacyl 1% (Alcon, Fort Worth, TX) eye drops.

Diameter Measurements

The left eye from each test person was examined with the RVA by using a procedure previously described in detail.[2] In short, a video sequence of the ocular fundus was recorded and was stored on a videotape. During the examination, the fixation of the test person was adjusted so that that upper temporal arteriole was in the center of the image. With the RVA software, a rhomboid region of interest (ROI) was placed over the segment of the arteriole to be studied, and the contrast borders defining the edges were automatically identified to calculate its diameter along the segment with video speed.

Each examination consisted of two periods. The first (baseline) period was a recording for 3 minutes during rest. During the second (exercise) period the blood pressure was elevated by the person's lifting a 2.5-kg hand weight for 3 minutes with the right arm. The blood pressure was measured on the upper left arm with an oscillometric technique (model M4; Omron Healthcare Ltd., Kyoto, Japan) after the patient had been at rest for at least 2 minutes, after 60 seconds in the baseline period, and after 120 seconds in the exercise period. MAP was calculated from the diastolic (BP_{dia}) and the systolic (BP_{sys}) blood pressure according to the equation: $MAP = 2/3 \cdot (BP_{dia}) + 1/3 \cdot (BP_{sys})$. Previous experiments on normal persons have shown that the intraocular pressure (IOP) does not change significantly during isometric exercise.[2] Thus, the IOP was not recorded during the lifting procedures.

Data Analysis

Vascular Segments. In each volunteer, four segments on the upper temporal arteriole were analyzed, each segment having a length of between one-fifth and one-half disc diameter (DD). The first segment (S1) was located within 1 DD of the margin of the disc, and the ROI for diameter measurements was placed over the vessel during the exami-

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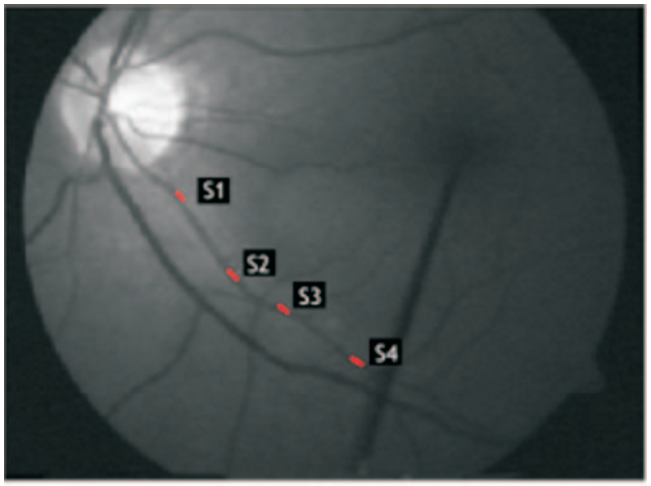

FIGURE 1. Fundus image from one of the examined subjects showing the location of segments S1–S4 along which the diameter was determined.

nation. The other three segments (S2–S4) were placed over the vessel during reanalyses of the video recording of the examination. These segments were placed successively along the examined vessel so that the peripheral limitation of S4 was between two and three DD from the disc margin and included vessels with a diameter down to 50 μm (Fig. 1). If a branching point occurred, the next segment was measured downstream of the largest trunk.

Vascular Diameters. The vascular diameters were measured after the blood pressure had stabilized after each change in the experimental conditions.[1] Thus, mean diameters obtained between 120 and 150 seconds in the lifting periods ($diam_{120-150}$) were calculated as percentages of the means of all vascular diameters along the segment measured during the last 90 seconds of the baseline period. The diameter response was related to the MAP and to the baseline diameter of the vessel. Furthermore, to test whether an initial vasodilatation occurred at the beginning of the lifting period, the mean diameter was calculated from the first 20 seconds of the lifting period for all segments ($diam_{0-20}$) and related to baseline diameter of the vessels as the percentage of change from baseline.

Propagation Rate. The increase in the systemic blood pressure induced by the lifting of hand weights and the resultant diameter response of retinal arterioles develop gradually. Consequently, the onset of the response was defined by fitting the diameter trace from each examination to the Hill equation: $d = d_{min} + (d_{max} - d_{min})/1 + (t/TC_{50})^n$, where d is diameter, t is time, d_{max} is the baseline diameter before the lift, d_{min} is the arteriolar diameter after it has become stable in the lifting period, TC_{50} is the time point where 50% of the maximum contraction of the arteriole has been reached, and n is the Hill slope. TC_{50} was calculated for each of the four vascular segments from the 10 persons examined. Ten of these 40 traces were unsuitable for the fitting procedure due to an insufficient diameter response.

Statistical Methods

Two-way analysis of variance showed no significant difference between the variance contributions from the intra- or the interindividual variation (F test, $P = 0.63$, df 3, 9). Consequently, all measurements from all individuals were pooled for the statistical analysis.

The change in the arteriolar diameter between the baseline and the weight-lifting period was tested using the paired t-test. The relations between the diameter response and respectively MAP and the baseline diameter were tested by linear regression analysis. The change in diameter between the beginning of the lifting period and baseline was tested with a paired t-test. The temporal relations between the TC_{50} from vessel segments 1 and 4 were tested with linear regression analysis.

RESULTS

The baseline IOP, the MAP, and the change in MAP induced by isometric exercise was 15.2 ± 0.7, 92.9 ± 2.8, and 21.8 ± 1.7 mm Hg, respectively. The baseline diameters and diameter changes during isometric exercise for the four arteriolar segments are shown in Table 1.

The isometric exercise induced a significant contraction of the studied vessel segments of averagely 2.5% ± 0.4% ($P < 0.0001$, $n = 40$). There was no significant correlation between the diameter response and the change in MAP, although a trend was found toward an increased diameter response with higher increase in MAP ($P = 0.06$; Fig. 2).

There was a significant negative correlation between the baseline diameter of the studied vessel segments and the diameter response induced by isometric exercise ($R^2 = 0.13$, $P = 0.02$; Fig. 3).

No significant change from baseline diameter was found at the beginning of the lifting period (mean 0.28%; 95% CI, −0.29 to 0.86; $n = 40$, $P = 0.32$).

The TC_{50} of the diameter response showed no significant linear correlation ($P = 0.29$, $n = 30$). The mean TC_{50}s for the four segments are given in Table 1.

DISCUSSION

The dynamic variations in the blood flow differ along the vascular system due to differences in the perfusion pressure and the vascular resistance. The resistance in the arterioles depends on the caliber and elastic properties of the vascular walls. The larger arteries serve as wind kettles to minimize the pulse pressure, increase the efficiency of the heart pump, and provide a more continuous blood flow to the peripheral vascular bed. The smaller arteries and arterioles autoregulate the amount and distribution of blood through the capillary beds by adjusting the tone of vascular smooth muscle cells with a resultant change in the vascular diameter. Several types of autoregulation exist. Pressure autoregulation is changes in the diameter of retinal arterioles with the purpose of keeping the blood perfusion at a balanced level when the blood pressure changes.[9] In vitro studies of vascular beds outside the eye indicate that the diameter response may vary among arterioles of different sizes. However, hitherto, no studies have been performed to show whether this variation also exists in retinal arterioles in vivo.

In the present study isometric exercise was used to induce an increase in systemic blood pressure. Our analysis of the

TABLE 1. Baseline Measurements of Arteriolar Parameters for Each of the Four Segments

	S1	S2	S3	S4
Baseline diameter (AU)	132.1 ± 7.1	131.1 ± 8.8	112.6 ± 6.1	104.8 ± 6.4
Diameter change$_{0-20}$ (%)	−0.1 ± 0.2	−0.5 ± 0.5	−0.6 ± 0.4	0.2 ± 0.7
Diameter change$_{120-150}$ (%)	−2.0 ± 0.6	−1.4 ± 0.6	−3.3 ± 0.9	−3.5 ± 0.6
TC_{50} (sec)	68.9 ± 13.5	48.4 ± 14.4	59.2 ± 9.6	44.8 ± 12.9

AU, arbitrary unit.

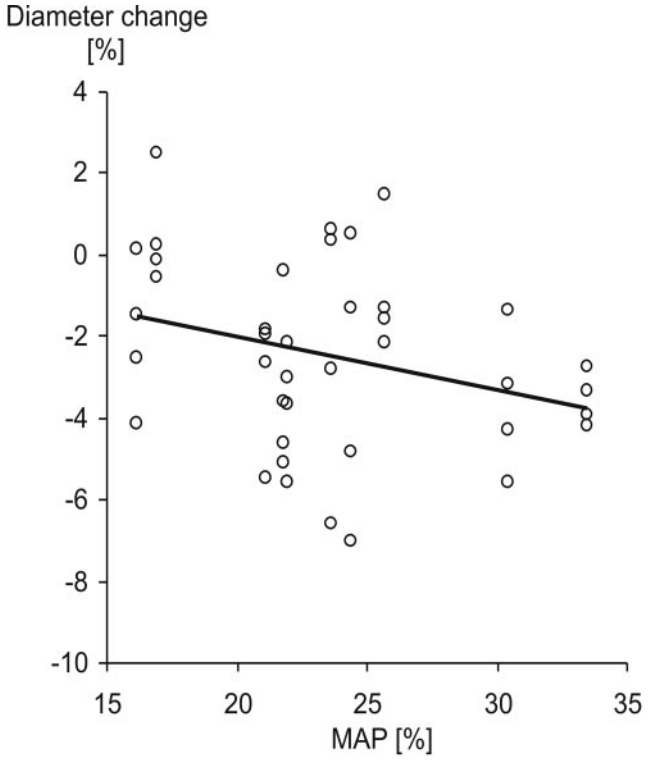

FIGURE 2. The correlation between the diameter response and the change in MAP for all measurements.

initial diameter change in the lifting period failed to show a significant change. If a prompt increase in blood pressure occurs, it would be expected to induce an initial vasodilatation followed by a subsequent contraction. However the blood pressure increase during isometric exercise may be suspected to occur gradually over the lifting period and is a possible explanation of why no significant vasodilatation was seen at the beginning of the lifting period.

In the present study, a significant increase in the diameter response was observed in temporal retinal arterioles when the baseline diameter decreased from approximately 200 μm at the margin of the optic disc to approximately 100 μm at the final branching levels before the terminal arteriole feed vessels. This finding may be because the distal segments are located closer to the terminal arteriole feed vessels, and it is possible that the diameter response may be even higher for smaller arterioles, since in vitro studies have shown that arterioles with a diameter of ~25 μm have a significantly greater potential for showing a diameter response than do larger vessels.[4] However, the diameter of these precapillary vessels was below the detection limit of the RVA and therefore could not be examined in the present study.

The findings extend the ordinary conceptual understanding of pressure autoregulation as a resistance point with no extension along the vessel. Thus, the findings suggest that a change in the blood pressure in the central retinal artery is transmitted to successively smaller retinal arterioles so that the burden of regulating the resistance of the vessel is not loaded on a small vascular segment but is distributed along the whole length of the vessel. Thus, a change in the blood pressure is transmitted directly to all parts of the arteriole, and the contraction occurring along the whole length of the vessel can be explained as the sum of the local diameter responses in all the vascular segments. This implies that currently used simple models of the relation between resistance and flow in the retinal vessels are insufficient for describing the complex interaction of successive segments along the arteriole. It can be expected that the modeling of vascular flow will grow in parallel with the emergence of new techniques for measuring retinal blood flow in localized areas.

The physiological background for the increase in the diameter response in smaller retinal arterioles is not clear, but several explanations may be considered. First, the increased contractility in smaller retinal vessels could be due to a relatively more dense distribution of vascular smooth muscle cells in these vessels. Second, the contraction of smaller retinal vessels may be facilitated by less stiffness of the arteriolar wall. Third, a more optimal length–tension relation of the smooth muscle cells in smaller arterioles may increase the active force developed by the muscle contraction in these vessels. A further

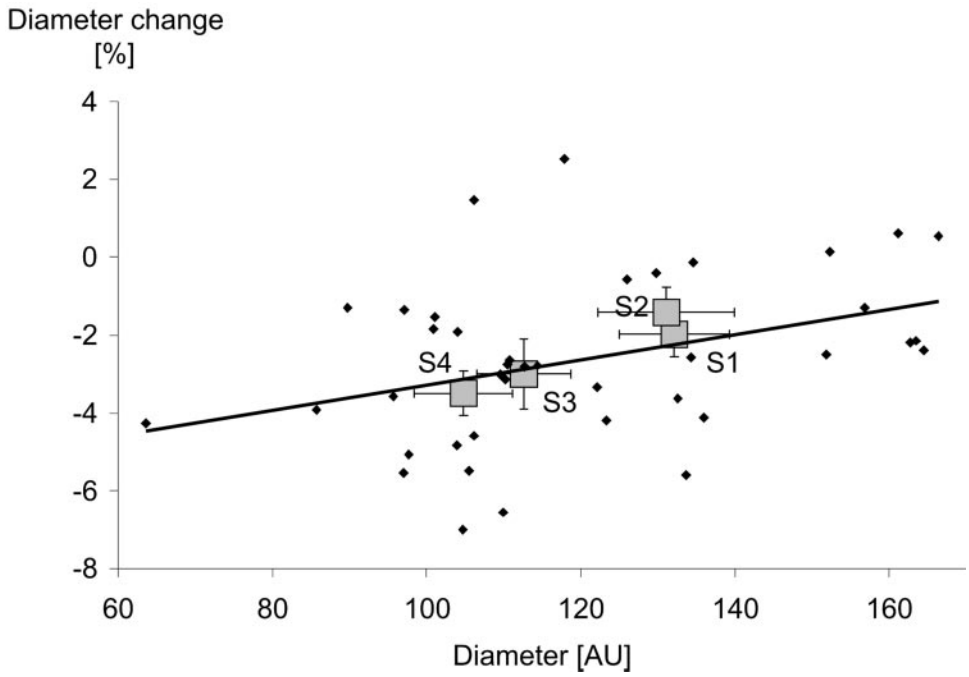

FIGURE 3. The correlation between the diameter response and the baseline diameter for all measurements (*diamonds*). The *gray boxes* with error bars indicate the mean diameter response and SEM and for each of the four groups of segments. AU, arbitrary unit (corresponding approximately to micrometers).

elucidation of the structural and functional background for the difference in diameter response among retinal arterioles of different size requires histologic and biomechanical investigations of isolated human small retinal arterioles.

In conclusion, the study has shown that the blood pressure–induced diameter response of retinal arterioles increases with decreasing diameter of the vessels, but with no significant difference between the onset of the response at different locations along the vessel. This enables the whole length of the vessel to participate in the pressure autoregulatory response. Our results indicate that the distal retinal arterioles are important sites for the regulation of retinal blood flow and possible sites of pathologic function in retinal vascular diseases where autoregulation is challenged or disturbed, such as arterial hypertension and diabetic retinopathy.

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