The response of the light reflex of retinal vessels to reduced blood pressure in hypertensive patients

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Abstract. The response of retinal arteries and veins to 3 months of antihypertensive medication was studied in 10 patients (39-56 years old) with essential hypertension. We used computerized microdensitometry on fundus photographs, a technique allowing for objective and simultaneous measures of the caliber of blood columns and the width and intensity of their central 'light reflex'. A moderate lowering of diastolic and systolic blood pressures (\(P<0.001\)) resulted in a significant reduction in the intensity of reflection from retinal arteries (38.6%; \(P<0.005\)). An increase in the width of the blood column (2.8%; n.s.) and the reflex (8.6%; n.s.) was indicated. Traditionally, changes in light reflectivity has been associated with arteriosclerosis of the vessel wall. The study shows, however, that the vascular reflex is most sensitive to changes in the systemic blood pressure. This signals a need for critical review of interpretation and usefulness of classical grading systems of ophthalmoscopic signs of hypertensive retinopathy.

Key words: blood pressure - retinal vessels - vascular light reflex - arterial hypertension - hypertensive retinopathy - densitometry - fundus photography.

The ophthalmoscopic image of retinal vessels shows the intravascular column of streaming red cells and a 'light reflex', centered along the blood column in middle-sized and large vessels. Both normal arteries and veins have transparent vessel walls. Caliber changes and changes in the characteristics of light reflectivity may be related to the severity of hypertensive disease. Gowers (1876) showed that retinal arteries narrowed in hyperten-

sion, and Gunn (1982, 1989) described ophthalmoscopic changes in 'increased arterial tension' as caliber variations and increased brightness of the central light reflex of arteries. The signs implied a differentiation between vessel constriction caused by increased tonus due to systemic hypertension and 'increased' light reflex due to secondary arteriosclerotic changes in the arterial wall. These observations, along with their clinical interpretations, have been adopted in various classification systems dealing with ophthalmoscopic signs of systemic hypertension (Keith et al. 1939; Wagener et al. 1947; Scheie 1953; Evelyn et al. 1958).

Recent theoretical studies (Brinchmann-Hansen & Heier 1986; Brinchmann-Hansen & Engvold 1986a,b) and clinical experiments (Brinchmann-Hansen et al. 1988; Brinchmann-Hansen & Myhre 1989a,b) suggest, however, that the vessel wall is of minor significance in forming the reflex, compared to the reflective surface of the blood column. In consequence, we believe that changes in hemodynamic conditions of retinal flow and in physical properties of the red cells may change the ophthalmoscopic image of retinal vessels.

By use of a computerized microdensitometric technique on fundus photographs (Brinchmann-Hansen & Engvold 1986; Brinchmann-Hansen et al. 1986) we can determine numerically the width of the blood column and the width and the intensity profile of the light reflex. We show that 3 months of antihypertensive treatment affect the
fundoscopic appearance of retinal vessels, dominated by a significant lowering of the intensity of the light reflex in arteries.

Materials and Methods

Two females and 8 males with essential hypertension and aged 39 to 56 years (mean 49.1) were included in the present study. They were participating in a multicenter double-blind study in which the antihypertensive effect of the peripheral alpha-adrenoceptor antagonist doxazosin was compared to prazosin and placebo (Torvik & Madsbu 1986; 1987). Twelve of the patients accepted for participation in the multicenter study were to be examined by one internist, identical to one of the authors of the present study (CCC). These patients also agreed to take part in the present study. However, one patient did not agree to dilation of the pupil for fundus photography, and another patient was excluded since his intraocular pressure rose after dilation of his pupil.

Among the 10 remaining patients, only one subject received antihypertensive medication (propranolol 80 mg daily), and this medication was withdrawn 4 weeks before the start of the study. All patients were subjected to a 4 week single-blind placebo run-in phase. Participation in the study required that the diastolic blood pressure was between 95 and 114 mmHg, both supine and standing up, immediately before the double-blind treatment (Torvik & Madsbu 1986). The patients were randomly assigned to treatment with doxazosin, prazosin or placebo for 12 weeks, and we had no knowledge of the mode of treatment received by the 10 subjects until after the study was finished.

Identical test protocols were used before and after the 12 weeks of medication. Ophthalmic examination showed no sign of previous or present eye diseases, except for amblyopia caused by esotropia in the left eye in one subject (visual acuity: 20/200). Otherwise, all had visual acuity of 20/20 in both eyes and normal intraocular pressure (≤18 mmHg; applanation in sitting position). The refractive errors were from -1.75 to +1.50 (mean: -0.2) diopters, examined by retinoscopy in cycloplegia.

After 10 min rest in sitting position, the blood pressure was measured auscultatory. Ten minutes later a second blood pressure was undertaken, immediately followed by fundus photography. The mean of the 2 measurements was used. Electrocardiography was performed continuously and displayed on an oscilloscope while the patient was seated in front of the fundus camera. The oscilloscope was connected to a device which set off the xenon-flash of the fundus camera in such way that the R-wave of the electrocardiogram triggered the exposure. This procedure was designed to standardize the exposure in the diastolic phase and thereby reduce the effect of pulsative variation in retinal vessel diameters.

The right eye of each subject was chosen for fundus photography and was performed in cycloplegia (cyclopentolati chlorid 1% and metaoxedrini chlorid 10%). We used a Zeiss fundus camera with 30 degrees field of illumination. An interference filter with maximum transmission peak at 535 nm was inserted in the light path, and 35-mm Kodak Plux-X Panchromatic films were used. We centered each photograph at one half the distance between the fovea centralis and the temporal edge of the optic disc.

A computerized scanning microdensitometer was used directly on the negatives to analyse the caliber of retinal vessels and the intensity profiles of their central light reflex. This technique has previously been described in detail (Brinchmann-Hansen & Engvold 1986c; Brinchmann-Hansen et al. 1986) and only a short summary is presented here. By photographing a 48 step density wedge on film, and by developing the grey scale with each experimental film, we transform film density into a linear intensity scale. Identification marks across selected sites on the vessels are cut directly in the emulsion of the film denoting the starting point of the scanning. The transmission coefficient of the negatives are sampled and digitized at 2 μm intervals. The scanning aperture is 5 μm wide (in the scanning direction) and the length used are 250 μm. A typical scan profile across a retinal vessel is illustrated in Fig. 1. The intensity difference between the background retina and the blood column is denoted I₀. If the background level is different on the two sides, an averaged value is automatically used. The width of the retinal vessel (=width of the blood column), W₀, is always measured, by the computer, at half the intensity of I₀. The width of the light reflex, Wᵣ, is measured at half maximum intensity of the peak intensity of the reflex, Iᵣ. We also study the width of the reflex
relative to the width of the blood column, $W/W_o$.

We preferably selected vessels having a straight course in the retina and chose one large and 2 middle-sized arteries and veins in each subject. The widths are measured as microns ($\mu m$), representing the size on the retina, while the intensities of the reflex are expressed as arbitrary units. Variations in the magnification of the fundus camera, caused by refractive errors, are individually corrected for (Bengtsson & Krakau 1977; Brinchmann-Hansen et al. 1986).

Intensity measurements from fundus photographs are sensitive to focus errors (Brinchmann-Hansen et al. 1986) and an essential effect of defocusing is a decrease in the 'steepness' (or widening of the 'leg') of the scan profile of the blood column (Heier & Brinchmann-Hansen 1989) (Fig. 1). We compared averaged values of steepness from 'right' and 'left' side of every profile before and after anti-hypertensive medication.

The Wilcoxon signed rank test for paired data is used for comparing changes before and after treatment.

We use the mean value of the percentage change at each vessel site in each patient ($n = 10$), and the level of significance is 5%.

Results

Table 1 presents the mean ($\pm sd$) blood pressure value, the diameter of retinal vessels, and the intensity and width of the light reflex before and after 12 weeks of medication, for all 10 participants. Three subjects had used doxazosin, and 3 had used prazosin. Systolic pressure was reduced from average $164.8 \pm 10.3$ mmHg to $153.8 \pm 8.6$ mmHg, and diastolic pressure changed from $105.4 \pm 8.0$ mmHg to $97.8 \pm 10.1$ mmHg in this group ($n = 6$). Four subjects had received placebo medication and the average systolic and diastolic pressure reduction was from $166.5 \pm 14.2$ mmHg to $153.4 \pm 13.0$ mmHg and from $111.8 \pm 4.0$ mmHg to $105.5 \pm 2.7$ mmHg, respectively. Since the aim of the study was the vascular effect of reduced blood pressure on retinal vessels and since the blood pressure fell in all subjects, the 10 subjects were grouped together, as shown in Table 1. Average systolic pressure fell from $165.5 \pm 11.5$ mmHg to $153.7 \pm 10.1$ mmHg ($P < 0.001$), and diastolic pressure was reduced from $108.0 \pm 7.0$ mmHg to $100.9 \pm 8.4$ mmHg ($P < 0.001$).

The vessel sizes ($W_o$) measured in the present study ranged from $83.6 \mu m$ to $140.9 \mu m$ in arteries and from $108.0 \mu m$ to $191.4 \mu m$ in veins. After 12...
Table 1.
Reduced blood pressure and its effect on caliber of retinal vessels and intensity and width of their light reflexes
(n = 10 patients; mean ± sd).

<table>
<thead>
<tr>
<th>Blood pressure (BP)</th>
<th>Before treatment</th>
<th>After treatment</th>
<th>Change (%)</th>
<th>Sign. level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP (mmHg)</td>
<td>165.5 ± 11.5</td>
<td>153.7 ± 10.1</td>
<td>-7.1</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>108.0 ± 7.0</td>
<td>100.9 ± 8.4</td>
<td>-6.5</td>
<td>P &lt; 0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Retinal arteries*</th>
<th>Diameter, (W_o) (µm)</th>
<th>103.6 ± 29.4</th>
<th>106.5 ± 28.1</th>
<th>2.8</th>
<th>n.s.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retinal veins*</td>
<td>Intensity, (I_R) (arb. unit)</td>
<td>842.1 ± 631.8</td>
<td>516.9 ± 399.7</td>
<td>-38.6</td>
<td>P &lt; 0.005</td>
</tr>
<tr>
<td>Width, (W_R) (µm)</td>
<td>21.3 ± 4.1</td>
<td>23.8 ± 7.0</td>
<td>8.6</td>
<td>n.s.</td>
<td></td>
</tr>
<tr>
<td>Width, (W_R/W_o) (ratio)</td>
<td>0.21 ± 0.03</td>
<td>0.21 ± 0.06</td>
<td>0.1</td>
<td>n.s.</td>
<td></td>
</tr>
</tbody>
</table>

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<thead>
<tr>
<th>Retinal veins*</th>
<th>Diameter, (W_o) (µm)</th>
<th>146.0 ± 38.1</th>
<th>145.8 ± 38.8</th>
<th>-0.8</th>
<th>n.s.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retinal veins*</td>
<td>Intensity, (I_R) (arb. unit)</td>
<td>522.8 ± 221.5</td>
<td>396.1 ± 232.3</td>
<td>-24.2</td>
<td>n.s.</td>
</tr>
<tr>
<td>Width, (W_R) (µm)</td>
<td>27.5 ± 7.2</td>
<td>27.7 ± 8.8</td>
<td>0.7</td>
<td>n.s.</td>
<td></td>
</tr>
<tr>
<td>Width, (W_R/W_o) (ratio)</td>
<td>0.19 ± 0.04</td>
<td>0.19 ± 0.03</td>
<td>-0.4</td>
<td>n.s.</td>
<td></td>
</tr>
</tbody>
</table>

*Mean of 3 arteries and 3 veins in each subject.

weeks of medication, no significant diameter changes had occurred in retinal vessels, although a small dilation was indicated in arteries (2.8%).

The average intensity of the reflex (\(I_R\)) was reduced, 38.6% in arteries (\(P < 0.001\)) and 24.2% in veins (n.s.) compared to the pre-medication level.

No statistical significant changes in the width of the reflex (\(W_R\) or \(W_R/W_o\)) were observed, although an increase in \(W_R\) in arteries was indicated (8.6%).

No significant changes in average 'steepness' of the edges of blood columns (Fig. 1) were found in either arteries (−2.9%; n.s.) or veins (2.2%; n.s.). This observation gives confidence to the result of the densitometry across retinal vessels: a stable focusing performance of the fundus photography is documented.

Discussion

Intensity of the light reflex (\(I_R\))

The study shows that moderate reduction of blood pressure in hypertensive patients reduces the intensity of the light reflex from retinal vessels, in particular in arteries. Although an objective measuring technique has not been available in the past, previous studies have observed a relation between the light reflex and the blood pressure level.

Bardsley (1917) observed increased intensity of the light reflex from arteries when the blood pressure was acutely raised by injections of adrenaline. Keyes & Goldblatt (1937) reported increased intensity of arterial reflection in experimental hypertension in monkeys after surgical intervention.

So far, it seems as the level of blood pressure, per se, is an important factor determining the intensity of reflection. We found a similar lowering of \(I_R\) in patients receiving placebo as in patient receiving antihypertensive therapy. Recently we have shown that reduced blood pressure in normotensive subjects, caused by high altitude exposure, also reduced the intensity of the reflex in arteries (Brinchmann-Hansen & Myhre 1989a). In that study and in the present study a similar reduction in \(I_R\) is also indicated in veins, although a sufficient level of statistical significance was not obtained due to smaller reduction in intensity and wider scatter of results. However, in a group of young (18-23 years old) normotensive (systolic blood pressure <145 mmHg) men the intensity of reflection in veins was significantly lower in those with blood pressures below 125 mmHg than in those above 125 mmHg (Brinchmann-Hansen et al. 1987).

Obviously light reflectivity from both arteries and veins are sensitive to dynamic changes in blood pressure. This signals that the traditional classifications of early hypertensive retinopathy (Keith et al. 1939; Gans 1944; Wagener et al. 1947; Scheie 1953; Evelyn et al. 1958), which all include a static association between the light reflex and arte-
riosclerosis, need a critical review. Although diffused light from arteriosclerosis of vessel walls may add some light to the reflection from the blood column (Salus 1958; Brinchmann-Hansen & Heier 1986), this diffused reflection is incompatible with the specular image of the light reflex being present in both arteries and veins (Brinchmann-Hansen & Sandvik 1986a,b). Accumulating evidence from previous studies (Svardsudd et al. 1978; Brinchmann-Hansen et al. 1987; Hayreh 1989; Dimitt et al. 1989) and the present study strongly suggest that the use of classification systems may lead to a loss of information. Ophthalmoscopic signs of hypertension have specific significance and clinical usefulness is dependent upon individual description of the various lesions.

Since a high correlation exists between brachial blood pressure and ophthalmic artery pressure (Robinson et al. 1986), 12 weeks of antihypertensive regimens have probably reduced the arterial pressure to the retinas. Due to the many different refractive surfaces overlaying the anterior surface of the retinal blood column, microscopic studies on red cell level is not possible in the living human eye. A theoretical approach is thus necessary in order to propose an explanation of the observed characteristics of the reflex. Light reflection occurs only across surfaces of abrupt steps in refractive indices, and \( I_R \) is strongly related to both the indices of red cells (\( n_r \)) and the surrounding plasma (\( n_p \)) (Brinchmann-Hansen & Engvold 1986b). Hemodynamic variations of the streaming column of red cells may also account for changes in reflectivity (Brinchmann-Hansen & Heier 1986; Brinchmann-Hansen & Engvold 1986b), as in the case of the present study and in other studies (Bardsley 1917; Keyes & Goldblatt 1937; Brinchmann-Hansen et al. 1988; Brinchmann-Hansen & Myhre 1989a,b). The intensity of reflection is sensitive to small changes in \( n_r \) or \( n_p \) (Brinchmann-Hansen 1986b), and reduced pressure followed by a change in osmotic equilibrium between red cells and plasma could change the indices of refraction. When \( n_r \) approaches \( n_p \) or vica versa, the intensity will be reduced.

**Width of the reflex (\( W_R \))**

Concomitant with the reduction in blood pressure a small increase in the width of the arterial light reflex (\( W_R \)) was indicated. No change was found, however, in \( W_R \) relative to the size of the blood column (\( W_R/W_O \)) neither in arteries nor veins. This underlines the difference in response pattern between width and intensity, since the intensity of the reflex (\( I_R \)) was significantly reduced. While \( I_R \) is a function of surface reflectivity (indices of refraction) (Brinchmann-Hansen & Engvold 1986b), \( W_R \) is basically determined by the caliber of the blood column (\( W_O \)) and by the 'texture' ('roughness') of the reflecting surface (Brinchmann-Hansen & Engvold 1986a). Although it is an approximate measure, this roughness of optical surface can be characterized using the ratio \( W_R/W_O \) (Brinchmann-Hansen & Engvold 1986a). We do not know, however, how sensitive the width parameter \( W_R/W_O \) is in detecting flow changes in human retinal vessels. With this important reservation in mind, the result of the present study indicates that no significant velocity changes occurred in neither middle-sized and large arteries nor veins.

A few experimental studies, using ophthalmoscopy, have reported relations between high systemic blood pressure and increased intensity and width of the reflex (Bardsley 1917; Keyes & Goldblatt 1937). It is, however, not possible to obtain an objective measurement of either the width or the intensity of the reflex by ophthalmoscopy. The central intensity gradually fades away toward the peripheral part of the blood column, creating the problem of deciding where the width of the reflex should be taken. In consequence studies of the past have often used non-specific terms in describing observed fundus changes in hypertension. The arterial light reflex has been found 'exaggerated' (Keith et al. 1939), 'increased' (McDonough et al. 1964; Kagan et al. 1966; O'Sullivan et al. 1968), and 'abnormal' (Bechgaard 1950).

Studies, which have solely evaluated the width of the reflex, found, however, that it did not correlate to the level of systemic blood pressure (Van Buchem et al. 1964; Aurell & Tibblin 1965; Svardsudd et al. 1978). The present study and previous reports (Brinchmann-Hansen et al. 1987; Brinchmann-Hansen & Myhre 1989a) are in accordance with these observations: the width of the reflex seems not related to the systemic blood pressure level.

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