Autoregulation of retinal circulation in response to decrease of perfusion pressure

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Autoregulation of the retinal circulation in response to an acute elevation of intraocular pressure was investigated in 17 subjects (23 eyes) with no ocular abnormalities, by means of the blue field entoptic phenomenon. This phenomenon allows a person to observe leukocytes flowing in his own macular capillaries. Subjects were instructed to compare the speed of their leukocytes in one eye with that in the other eye. All subjects perceived equal speed in both eyes. During their observation of the leukocytes, the intraocular pressure (IOP) was rapidly raised in one eye to a level at which autoregulation was not sufficient to maintain normal blood flow. At that level of IOP, subjects described the leukocytes moving slower in this eye than in the fellow eye. The IOP was then decreased in steps of 2 to 3 mm Hg until the subjects reported observing equal leukocyte speeds in both eyes. The IOP at which this occurred, IOP$_{\text{max}}$, represents the highest IOP (lowest mean perfusion pressure P$_{\text{min}}$) at which the retina is able to maintain normal blood speed, and presumably normal blood flow, by autoregulation. In our normal subjects, the average IOP$_{\text{max}}$ was 29.6 ± 2.0 mm Hg, corresponding to an average P$_{\text{min}}$ of 27 ± 6 mm Hg and demonstrating that a decrease of 36% or less in perfusion pressure is adequately compensated by retinal vascular autoregulation.

Key words: blood flow, autoregulation, intraocular pressure, perfusion pressure, retinal circulation, blue field entoptic phenomenon, leukocytes

The retina displays a tendency to maintain constant blood flow in spite of variations of perfusion pressure (mean blood pressure in the ophthalmic artery minus intraocular pressure). This property, termed autoregulation, is intrinsic to nearly all tissues.

Studies performed in cats and monkeys with the use of the microsphere technique suggest that blood flow through the retina is autoregulated within a wide range of perfusion pressures. Information on the extent of this range in the human retina, however, is still lacking.

A noninvasive technique that provides quantitative information on retinal blood flow autoregulation in man was described by Riva and Loebl. By utilizing the blue field entoptic phenomenon, which allows a subject to perceive leukocytes moving in his own macular retinal capillaries, the method showed that the retinal autoregulatory response to a sudden decrease of perfusion pressure is completed within approximately 2 min. Furthermore, autoregulation appears to be effective only within a limited range of perfu-
sion pressures because acute elevations of intraocular pressure (IOP) above 36 mm Hg reduced blood flow below normal values in spite of the autoregulatory response. However, the method did not permit determination of the range of the regulatory mechanism.

Using the blue field entoptic phenomenon, we have attempted to obtain quantitative information on the maximum intraocular pressure (IOP\text{max}) and the corresponding minimum mean perfusion pressure (\(P_{\text{min}}\)) at which autoregulation is maximally efficient.

Subjects and methods

Experiments were performed in 17 healthy volunteers (23 eyes) whose eye examinations were normal and who did not have histories of systemic hypertension. Ages of the subjects ranged from 22 to 41 years (mean 32 ± 7). IOP, recorded with a Model 30R Digilab Pneumatonometer, ranged from 12 to 21 mm Hg (mean 15 ± 2). Brachial systolic and diastolic blood pressure, measured by sphygmomanometry, was between 105/60 and 165/90 mm Hg (mean 114/73).

Observation of leukocytes. Subjects were seated in a darkened room before two blue field entoptoscopes (Medical Instrument Research Associates, BFE-100), one in front of each eye (Fig. 1), and were instructed to look alternately into each instrument. With these instruments, the retina can be illuminated diffusely and uniformly over a region of 12 degrees around the macula at a wavelength of 430 nm. This type of illumination provides optimal entoptic observation of the macular retinal leukocytes. To equalize the luminance in each eye, the voltage to one entoptoscope could be varied. Retinal irradiance was always well below potentially dangerous levels.

Autoregulation experiment. The autoregulation experiment requires initially that subjects perceive the same number of leukocytes in each eye as well as see them move with approximately equal speed in each eye. Accordingly, the subjects were first asked to compare the flow pattern, distribution, number, speed, and pulsatility of the leukocytes between both eyes. A drop of 0.5\% proparacaine hydrochloride (Alcaine; Alcon Laboratories, Inc., Fort Worth, Texas) was then applied to each eye, and the IOP was recorded from each eye. The tonometric scale reading was corrected as indicated by Langham and To'mey. After measurement of the systemic pressure, a Digilab Langham pressure cup was placed with slight suction on the temporal sclera of one eye. Changing the negative pressure applied to the cup varied the IOP. While continually monitored, the IOP was increased to approximately 40 mm Hg. The subjects were then asked to observe the motion of the leukocytes in each eye alternately and to compare their speed. Subjects who clearly identified the diastolic and systolic components of the pulsatile speed were asked to compare each separately. The others were encouraged to compare the speed of the leukocytes between successive "jerks" (diastolic speed). After 5 min of elevated IOP, the IOP was decreased in steps of 2 to 3 mm every 2 min until the speed was judged to be the same in both eyes. The IOP was then recorded and documented as IOP\text{max}. In 11 eyes, the IOP was raised again, and the procedure was repeated to verify the endpoint. When both endpoints were different, the mean of the two values was taken as IOP\text{max}. After the measurement of IOP\text{max}, the IOP was decreased slowly (2 to 3 mm every 2 min) to approximately 20 mm Hg. During the slow decrease, subjects continued to compare the speed of the leukocytes. The cup was then removed, and the systemic blood pressure was remeasured.

In three subjects, the experiment was repeated three times in the same eye on separate days in order to determine the reproducibility of IOP\text{max}. We also determined the minimum change in IOP for which a subject could perceive a difference in leukocyte speeds between eyes. This was deter-
mined at pressures above \( I_{OP_{\text{max}}} \) in order to eliminate the effects of autoregulation. At no time were the subjects aware of the direction or degree of pressure change.

Mean brachial artery pressure was calculated according to the formula \( P_b = 0.33 (P_s + 2P_d) \), where \( P_s \) and \( P_d \) are the systolic and diastolic arterial pressures. The mean perfusion pressure (\( P \)) was calculated with the relation \( P = \frac{\sqrt{2}}{a} V_b - I_{OP} = 0.22 (P_s + 2P_d) - I_{OP} \). The factor \( \frac{\sqrt{2}}{a} \) accounts for the difference in pressure between the brachial artery and the ophthalmic artery.9

**Results**

All subjects observed uniform distribution and approximately equal numbers of leukocytes in each eye. In both eyes all the leukocytes appeared to move at the same speed, in phase with the heart cycle, with a quick jerk during systole and slower but uniform speed during diastole. The corpuscles moved in single file along curved paths without reversal in direction.

After the initial increase in \( I_{OP} \), all subjects observed a decrease in the speed of the leukocytes. The flow pattern, however, did not change. The leukocytes were always seen to be uniformly distributed throughout the field of observation. They kept moving in single file and without reversal of direction. The seven subjects who were able to separate the systolic and diastolic phases reported that both speeds were slower than the corresponding speeds in the fellow eye. Slower motion was still perceived, but to a lesser degree, after 5 min. For all subjects the \( I_{OP} \) had to be decreased in order for the same diastolic speed to be observed in both eyes.

In the subjects who were able to compare systolic and diastolic speeds separately, \( I_{OP_{\text{max}}} \) was documented as the \( I_{OP} \) for which the diastolic speed was equal in both eyes. When the \( I_{OP} \) was decreased below \( I_{OP_{\text{max}}} \), 11 subjects first reported a transient increase of the speed of the leukocytes that then was followed after a variable period of time by a return of the speed to normal. The other six subjects did not report this transient increase. When the cup was removed, the average \( I_{OP} \) was 8 mm Hg and all subjects saw faster speed in the tested eye.

Average \( I_{OP_{\text{max}}} \) was 29.6 ± 2.0 mm Hg. Average mean perfusion pressure at normal \( I_{OP} \) was 42 ± 6 mm Hg, and average mean perfusion pressure at \( I_{OP_{\text{max}}} (\text{\( P_{\text{min}} \)}) \) was 27 ± 6 mm Hg. Therefore a decrease of perfusion pressure of 36% or more caused continued observation of slower leukocyte speed, whereas a decrease of less than 36% resulted only in a temporary reduction of the speed of the leukocytes.

The minimum change in \( I_{OP} \) that was needed to elicit the perception of a difference in leukocyte speed between both eyes (speed discrimination threshold) in the three subjects tested was found to be 2 to 3 mm Hg. Furthermore, values of \( I_{OP_{\text{max}}} \) obtained on three different occasions from the same eye did not differ by more than 2.5 mm Hg in each of three subjects tested.

The experiment required approximately 8 to 12 min, after which almost all subjects noted blurred vision for 2 to 3 hrs caused by astigmatic and drying changes of the cornea. In most subjects, perception of the leukocytes remained normal for the duration of the experiment. Some subjects reported a decrease in the sharpness and contrast of the leukocytes after about 8 to 10 min of elevated \( I_{OP} \). One subject developed a subconjunctival hemorrhage. In nearly all subjects, the mean brachial artery pressure at the beginning of the experiment was within 4 mm Hg of that at the end.

**Discussion**

The retinal capillaries in which the entopically perceived leukocytes move have not as yet been identified. Most probably these are capillaries with a diameter between 7 to 10 \( \mu \text{m} \) as suggested by the fact that the motion of these leukocytes corresponds closely to the description given by Schmid-Schönbein et al.10 of the motion of white blood cells in capillaries of that size: motion in single file; no passing of any two cells; free and smooth motion without adhesion to the wall. Furthermore, the mean speed calculated for the leukocytes in macular capillaries (0.8 \( \text{mm/sec} \))11 is similar to that of white blood cells observed in 7 to 10 \( \mu \text{m} \) capillaries.10
The pattern of leukocyte motion and the distribution of the leukocytes throughout the field of observation were observed to be the same at elevated IOP as at normal. Increase in the IOP appeared to affect only the speed of the leukocytes.

Our study and the results of previous work indicates that a step elevation of IOP 20 to 30 mm Hg above normal markedly reduces the speed of leukocytes. An autoregulatory response is induced which is not sufficient, however, to restore leukocyte speed to normal. For the speed to return to values that are judged equal to the speed of the leukocytes in the fellow eye, the IOP must be decreased to at least 30 mm Hg on the average, a value that corresponds to a 36% decrease of the mean perfusion pressure at normal IOP.

The technique employed in this study provides values of IOP\textsubscript{max} somewhat higher than the actual ones because IOP\textsubscript{max} is obtained by decreasing the IOP until the subjects observe equal leukocyte speed in both eyes. Considering a speed discrimination threshold equivalent to 2 to 3 mm Hg in IOP, as obtained from measurements in three subjects, the speed of the leukocytes may appear equal in both eyes when the IOP reaches a value 2 to 3 mm Hg above the actual IOP\textsubscript{max}.

IOP\textsubscript{max}, as determined from the changes in speed of leukocytes, appears to provide a valid estimate of the upper level of IOP for which the retina can return blood flow to normal by autoregulation. In capillaries with a diameter between 7 to 10 μm, the speed of the leukocytes is equal (within a few percent) to the mean speed of the bulk flow, and is proportional to the speed of red cells. Therefore one can expect that at IOP\textsubscript{max} the return of leukocytes speed to normal represents the return of blood speed to normal. This would correspond to a return of blood flow to normal if it can be assumed that capillary diameter remains constant during the experiment. The constancy of capillary diameter is supported by the work of Friedman et al., who found no evidence of vasomotion of the retinal capillaries; by that of Baez et al., who showed that capillary diameter remains constant within a wide range of perfusion pressure; and by theoretical considerations on the structural rigidity of blood capillaries.

The literature contains no data on the range of autoregulation of the human retina to which our findings can be compared. However, the range of autoregulation obtained in this study, extending from normal perfusion pressure to approximately 64% of it, compares well with that of the cerebral circulation in human subjects.

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REFERENCES


