Retinal Blood Flow Autoregulation in Response to an Acute Increase in Blood Pressure

Fane Robinson, Charles E. Riva, Juan E. Grunwald, Benno L. Petrig, and Stephen H. Sinclair

The response of the retinal circulation to an acute elevation in systemic blood pressure was studied in three healthy normotensive volunteers using the noninvasive laser Doppler velocimetry (LDV) technique combined with retinal vessel size measurements. Isometric exercise was employed to induce the acute rise in arterial pressure. There was no detectable change in retinal blood flow until the mean brachial artery blood pressure was elevated to an average of 115 mm Hg, which represented an average rise in mean blood pressure of 41% above baseline values. Above this value, blood flow increased along with further increments in blood pressure. The parallel rise between the ophthalmic artery pressure and the brachial artery pressure indicates that the regulation of retinal blood flow observed in the above mentioned pressure range is achieved through an increase in retinal vascular resistance rather than by a mechanism that would act to maintain a constant ocular perfusion pressure. Invest Ophthalmol Vis Sci 27:722-726, 1986

The relationship between perfusion pressure and blood flow has been extensively studied in many organs of the body.1,2 Previous studies of the macular microcirculation in normal volunteers suggested the presence of retinal autoregulation in response to acute changes in perfusion pressure induced by changes in intraocular pressure.3,4 Investigations of the response of the retinal circulation to an acute increase in systemic blood pressure5-7 have thus far been limited to the study of vessel diameter changes. These studies have demonstrated various degrees of vasoconstriction of the retinal vessels suggesting that the retina increases its vascular resistance in an attempt to counteract any potential rise in blood flow which might otherwise result from the elevated perfusion pressure.

The laser Doppler velocimetry technique allows for studies of retinal blood flow regulation to be undertaken in humans. Using this technique together with monochromatic fundus photography we investigated the regulation of retinal blood flow in response to acute systemic hypertension induced by isometric exercise.

Isometric exercise was chosen to induce the acute increase in blood pressure for the following reasons:

Firstly, it permits nonpharmacologic, noninvasive manipulation of the blood pressure, thus eliminating potential drug side-effects including direct effects on the retinal vessels. Secondly, it results in a dramatic increase in mean arterial pressure by producing increases in the diastolic as well as the systolic blood pressure.8-10

Materials and Methods

The study was performed on three healthy subjects aged 23, 30, and 45 yr. All eyes studied (one per subject) had a best refracted visual acuity of 6/6, normal intraocular pressure, and a normal fundus examination. Informed consent was obtained after the nature of the study had been explained fully.

Types of isometric exercise included squatting, leg extension, and handgrip. Subjects were seated for the latter two types of exercise. These forms of isometrics were chosen so as to ensure a wide range of hypertensive responses—from a modest increase in blood pressure with handgrip to an intermediate pressure rise with leg extension and a more marked elevation in pressure with squatting. Systolic and diastolic brachial artery blood pressures (BABP<sub>s</sub> and BABP<sub>d</sub>) were measured by sphygmanometry at rest and every 30 sec for the duration of the exercise. Mean brachial artery blood pressure, BABP<sub>m</sub>, was calculated according to the formula:

$$\text{BABP}_m = \text{BABP}_d + \frac{1}{3} (\text{BABP}_s - \text{BABP}_d). \quad (1)$$

Heart rate and end-tidal pCO<sub>2</sub> were recorded continuously, the former with an earlobe transducer and the latter with a Godart capnograph. Intraocular pressure
was measured by applanation tonometry during the same types of isometric exercise performed on a separate occasion.

Bidirectional laser Doppler velocimetry (BLDV) was utilized to noninvasively measure $V_{\text{max}}$, the maximum center-line velocity of the red blood cells in retinal vessels. $V_{\text{max}}$ was measured from a single main superior or inferior retinal vein in each subject after unilateral pupillary dilatation with one drop of tropicamide 1%. The measurements were performed on veins whose caliber was approximately 150 μm. At each pressure, $V_{\text{max}}$ was determined only after 1.5 min had lapsed (1 min if the previous blood pressure had been within 10 mm Hg of the current recorded pressure) to allow any potential autoregulation to take place. The investigator who calculated $V_{\text{max}}$ was masked with respect to the blood pressure.

The mean and standard deviation for $V_{\text{max}}$ at a given blood pressure was derived from at least ten consecutive LDV measurements at that pressure. In an attempt to obtain a relatively stable blood pressure for each set of measurements of $V_{\text{max}}$, we arbitrarily imposed a limit of 5 mm Hg for the standard deviation of the average BAPBm for the time period in which the recordings were to be analyzed (average $4 \pm 2$ min).

The diameter, $D$, of the vein at the site of LDV recordings as well as that of a single large retinal artery was measured using photographic negatives taken through an interference filter centered at 570 nm. The photographic negatives were projected onto a screen and the diameter of the vessels was measured with a caliper by a single observer who was masked with respect to the LDV results and the blood pressure. Total magnification of the fundus was 167X. $D$ was obtained from an average of three measurements. The average coefficient of variation of $D$ was 2% for veins and 1.3% for arteries. Since the experimental set-up did not permit simultaneous LDV recordings and fundus photography, an identical isometric experiment was performed on each subject to obtain fundus photographs. For each subject, vessel size measurements were performed on photographs taken at baseline blood pressure as well as an average of four higher blood pressure levels. Although these pressures did not correspond exactly to those in the LDV sessions, they did span the range of pressures recorded in those experiments.

Changes in the volumetric blood flow rate in veins, $Q$, were determined according to the relationship:

$$Q \propto D^2 \cdot V_{\text{max}}$$  \hspace{1cm} (2)

For each subject, the sensitivity of the method, $S$ (ie, the smallest detectable significant percentage change in $V_{\text{max}}$ from its baseline value), was calculated using the formula:

$$S = \frac{|\bar{V}_{m2} - \bar{V}_{m1}|}{\bar{V}_{m1}}$$

$$= \frac{t_{df,0.05}}{\bar{V}_{m1} \cdot \sqrt{N}} \cdot \sqrt{S_{V_{m2}}^2 + S_{V_{m2}}^2} \cdot 100(\%)$$  \hspace{1cm} (3)

$\bar{V}_{m1}$ and $S_{V_{m1}}$ are the mean and standard deviation of the $V_{\text{max}}$ values measured at rest; $\bar{V}_{m2}$ and $S_{V_{m2}}$ are those at any given elevated blood pressures. $N$, the number of measurements in each group of blood pressures, was 9, 5; and 9 for each of the three subjects respectively. The quantity $t_{df,0.05}$ is the tabulated t-value for a significance level of $P = 0.05$ in a two-tailed Student’s t-test with df degrees of freedom:

$$df = (N - 1) + \frac{2(N - 1)}{S_{V_{m2}}^2 + S_{V_{m2}}^2}$$  \hspace{1cm} (4)

Equation (3) is derived from

$$t = \frac{|\bar{x}_2 - \bar{x}_1|}{\sqrt{S_1^2 + S_2^2}} \geq t_{df,0.05}$$  \hspace{1cm} (5)

where $t$ represents the estimated test variable for the comparison of two non-paired sample populations of equal size $N$ with means $\bar{x}_1$, $\bar{x}_2$ and standard deviations $S_1$, $S_2$.

In our calculations using (3) and (4), $\bar{V}_{m1}$, and $S_{V_{m1}}$ were obtained from those $N$ data points taken at the lowest blood pressures. The second standard deviation, $S_{V_{m2}}$, stems from those $N$ values measured at the next to lowest blood pressures with the subject still at rest. This analysis assumes that the standard deviation of the data points at more elevated pressures is comparable to $S_{V_{m2}}$.

Using compression ophthalmodynamometry we investigated the relationship between the mean ophthalmic artery pressure and the mean brachial artery pressure during isometric exercise in each of the same three subjects. This series of experiments was performed with one investigator observing the central retinal artery with an indirect ophthalmoscope while a second investigator recorded the ophthalmic artery pressure with a Bailliert ophthalmodynamometer. A third observer concurrently measured the brachial artery blood pressure by sphygmomanometry. Each of the three investigators was masked with respect to the recorded measurements of the other two investigators. Ophthalmic artery diastolic pressure (OABPd) was taken as the pressure equivalent to that dynamometer force (vide infra) which resulted in the first observed brief collapse of the central retinal artery on the optic disc. The external force was then raised to a level which caused total collapse of the central retinal artery. On gradual release of the plunger, the pressure equivalent
to the force at which systolic pulsation was first observed was designated as the ophthalmic artery systolic pressure (OABP<sub>s</sub>). The mean ophthalmic artery pressure, OABP<sub>m</sub>, was calculated according to the formula:

\[
\text{OABP}_m = \text{OABP}_d + \frac{1}{3}(\text{OABP}_s - \text{OABP}_d).
\]  

On a separate occasion, ophthalmodynamometer force (grams) was calibrated against applanated intraocular pressure (mm Hg) in all three eyes for a range of forces from 50 grams through 110 grams. A significant correlation was found between the ophthalmodynamometric measurements and the intraocular pressure measurements in all three subjects (r = 0.99, 0.99 and 0.98 respectively; \( P < 0.05 \) in all three subjects). The regression equations thereby obtained were used to convert the ophthalmodynamometric force readings from the isometric experiments into intraocular pressure equivalents which in turn closely correspond to the prevailing ophthalmic arterial pressures.

**Results**

Figure 1 shows \( V_{\text{max}} \) as a function of the mean brachial artery blood pressure for each of the three subjects.

The average resting mean brachial artery blood pressures were 79 ± 2 mm Hg, 81 ± 1 mm Hg and 84 ± 2 mm Hg and the pressures at which \( V_{\text{max}} \) first increased significantly (\( P < 0.05 \), Student’s t-test) were 115 ± 5 mm Hg, 115 ± 4 mm Hg, and 114 ± 3 mm Hg respectively, which represented an average mean blood pressure rise of 41 ± 5% above baseline values. The values at which \( V_{\text{max}} \) increased significantly using this method of analysis are in close agreement (ie, within approximately 2 mm Hg) with values obtained using a method of sliding averages whereby an arbitrary baseline \( V_{\text{max}} \) sample size was chosen (in our three subjects \( N = 7 \)) and a Student’s t-test was performed with that group and the seven \( V_{\text{max}} \) data points which corresponded to the 7 next-to-lowest mean blood pressure values (ie, points 8–14). This was then repeated for the group of \( V_{\text{max}} \) data points corresponding to the blood pressure values 9 through 15, 10 through 16, and so on until the first significant result was obtained (\( P < 0.05 \)).

The average sensitivity of the LDV technique to detect the first significant change in \( V_{\text{max}} \) at \( P = 0.05 \) for these three subjects was calculated to be approximately 9%.

The average percentage change in venous diameter from resting levels for the three subjects was −0.3% (range −1.9 to +1.9%) and that for the arteries was −0.2% (range −1.4 to +1.1%). Neither of these changes was significant in any of the three subjects. According to equation (2), retinal volumetric blood flow rate is a function of vessel diameter and \( V_{\text{max}} \), and since we found no significant changes in venous diameter, retinal blood flow becomes directly proportional to \( V_{\text{max}} \). Thus we present our data for \( V_{\text{max}} \) as being representative of retinal blood flow.

There was a significant increase in heart rate with exercise, from 66 ± 4 beats per minute at rest to 96 ± 14 beats per minute at the peak of exercise (\( P < 0.001 \), Student’s t-test). Neither the end-tidal pCO<sub>2</sub> nor the intraocular pressure changed significantly during isometric exercise.

Figure 2 displays the relationship between the mean ophthalmic artery pressure and the mean brachial artery pressure during isometric exercise, showing that the ophthalmic artery pressure rose in parallel with the brachial artery pressure (\( y = -8.77 + 0.61 \cdot x; r = 0.92; P < 0.001 \)).

**Discussion**

In this study, the first significant increase in \( V_{\text{max}} \) was observed at an average mean brachial artery blood pressure of 115 mm Hg. Any change in \( V_{\text{max}} \) that may have occurred below this pressure must have been smaller than 9% (sensitivity). Since the change in venous diameter was extremely small, this sensitivity is in a first approximation also representative of that for retinal blood flow measurements.

It can be seen from Figure 2 that the mean ophthalmic artery pressure rose in parallel with the mean brachial artery pressure, implying that the regulation of blood flow in this experiment occurred within the retina rather than at a site proximal to the globe. Since there was no significant change in the diameter of either the large retinal veins or arteries, it seems reasonable to conclude that the changes in vascular resistance occurred in the smaller retinal vessels whose diameters could not be measured by the above mentioned photographic technique.

There was a highly significant increase in heart rate with all three subjects during isometric exercise. This is to be expected since the increase in heart rate is primarily responsible for the resultant elevation in blood pressure.\(^{16}\) The two other major determinants of systemic blood pressure viz stroke volume and systemic vascular resistance, remain essentially unchanged.\(^{17}\) We found that neither the intraocular pressure nor the end-tidal pCO<sub>2</sub> changed significantly with exercise, which confirms previous observations,\(^{10}\) and enables us to rule out the possibility that the blood flow response to acute hypertension was related to changes in either of these two parameters.

Autoregulation in its restricted sense is usually defined as the intrinsic tendency of an organ to maintain constant blood flow despite changes in perfusion pres-
Fig. 1. $V_{\text{max}}$, the maximum or center-line velocity of red blood cells in the retinal veins, as a function of the mean brachial artery blood pressure for each of the three subjects. The graphs in the left hand column display the individual data points. Each of these points represents the mean value of ten more observations (average 19 ± 4). The average coefficient of variation was 17% (range 9–29%). The corresponding graphs in the right hand column contain the composite data. In the latter series of graphs, error bars represent ±1 S.E.M. ($N = 9$ for each point in the top composite graph; $N = 5$ for each point in the middle graph and $N = 9$ for each point in the bottom graph.)

In this sense, and within the limits of our technique’s sensitivity, it appears that the normal human retina is capable of efficiently autoregulating its blood flow in the setting of acute systemic hypertension until the mean brachial artery pressure reaches approximately 115 mm Hg, which in our three subjects represented an average rise in mean systemic blood pressure of approximately 40% above resting levels. Our results also indicate that some degree of blood flow regulation is still present at pressures higher than...
the abovementioned level, since blood flows even at these pressures are lower than would be predicted for a passive vascular bed where a given elevation in pressure would be accompanied by a proportional rise in flow.

**Key words:** retinal blood flow, laser Doppler velocimetry, vessel diameter, autoregulation, isometric exercise, acute systemic hypertension, ophthalmodynamometry

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**References**