A New Pressure Attenuation Index to Evaluate Retinal Circulation

A Link to Protective Factors in Diabetic Retinopathy

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Background: Low ocular perfusion pressure (two thirds of mean arterial pressure minus intraocular pressure) and myopia have been associated with protection of the retina from clinical diabetic retinopathy. This prompts the question as to whether myopia's protective role could also be a pressure effect, given that pressure could be dissipated in the longer arteriole tree of the myopic eye.

Methods: We combined the Ohm, Poiseuille, and Murray laws to derive the following new formulation: the pressure attenuation along a vessel varies directly with its length and inversely with its diameter. A mean pressure attenuation index was calculated for 22 healthy control subjects, 25 patients with axial myopia, and 6 patients with retinitis pigmentosa using digitized fundus images.

Results: The myopic arteriolar tree would produce a 16% greater pressure attenuation than that of controls ($P = .002$), with a linear relationship between mean pressure attentuation index and axial length ($r = 0.93$). Mean pressure attentuation index of the group with retinitis pigmentosa is increased 67% above that of controls, which is calculated to contribute an additional 10 mm Hg of pressure dissipation along their retinal arteriolar system.

Conclusions: Pressure attenuation in retinal arterioles is directly proportional to the length and inversely proportional to the diameter of the arteriole segment being measured.

Clinical Relevance: A pressure attenuation index may be important in light of the entities known or presumed to protect the retina from diabetic retinopathy. The results support the hypothesis that low-end arteriolar pressure is a common denominator for many protective conditions in diabetic retinopathy.

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SYSTEMIC BLOOD pressure is considered important in the evolution of diabetic retinopathy.[1] In a large, population-based 1994 study, Moss et al[2] demonstrated the even more highly significant association of low ocular perfusion pressure (two thirds of mean arterial pressure minus intraocular pressure) with decreased incidence and progression of diabetic retinopathy. This same study also showed that myopia had a protective effect for progression to proliferative diabetic retinopathy in patients with onset at a younger age (odds ratio, 0.40; 95% confidence interval, 0.18-0.86; P=.02). The recently published report by the United Kingdome Prospective Diabetes Study Group has demonstrated that tight control of systemic blood pressure in type 2 diabetes mellitus resulted in a significant reduction of progression of retinopathy ($P<.001$).[3] In addition, microvascular complications, including retinopathy requiring photocoagulation, vitreous hemorrhage, and renal failure, were significantly decreased in the group with tightly controlled blood pressure ($P = .009$). If we accept that a low ocular perfusion pressure is indeed the cause of a decrease in the incidence and progression of diabetic retinopathy, we hypothesize that the protective effect of myopia for diabetic retinopathy is also a pressure effect, given that blood must travel a longer distance in the arteriolar tree in these larger-than-normal eyes.[4] The Poiseuille law predicts that this increased distance would result in an increased downstream pressure reduction (all other factors being constant)[5] (**Figure 1**). Our goals were to describe those features of the retinal arteriolar tree that could alter intratubal hydrostatic pressure, to quantify the effects that these features would have on the pressure, and to compare them with arterioles in conditions known or presumed to protect the retina from diabetic retinopathy.

PATIENTS AND METHODS

From a model based on the physiological laws governing blood flow in living vessels, we derived an index that incorporates flow alterations induced by vessel caliber changes to permit a comparison of the pressure-attenuating effects of the retinal arteriolar system in different eyes. The Ohm law, which relates pressure differential along a tube to flow and resistance; the Poiseuille formulation[5] of resistance to flow along a tube; and the Murray law,[6] which describes flow in blood vessels, are combined to give a new formulation (**Figure 2**). This states that the pressure differential along a vessel is proportional to its length and inversely proportional to its diameter (Figures 1 and 2). We propose the term pressure attenuation index (PAI) and express it algebraically as PAI = L/D, where L is length and D, diameter.

The model we have derived reasonably assumes a comparable whole-blood viscosity[7] in the different microvasculatures of the groups being studied and a constant ocular perfusion pressure. The Ohm and Poiseuille laws are well-described and have been experimentally validated in numerous vascular systems, including blood vessels of the caliber that exist in the retina (10-150 µm).[8] In addition, it is reasonable to assume that pressure losses in the microvasculature are related exclusively to viscous or frictional forces and that kinetic energy effects (as per the Bernoulli theorem) are trivial.[5,8] The Murray law is less well-known but also has been shown to be valid in many vascular systems,[8] including healthy retina and retina in patients with diabetes, optic atrophy, and retinitis pigmentosa (RP).[9-12]

To compare the pressure-dissipating effect induced by retinal arteriolar systems in different eyes, we considered the eye to be a sphere of measurable diameter (axial length), lined by an arteriolar tree whose vessels will induce a hydrostaticpressure drop, depending on their length and caliber. Given that blood must travel through the arteriolar tree from the origin of the central retinal artery at the optic nerve to the retinal periphery, it is evident that a comparison of any 2 eyes should be performed on an angular basis (**Figure 3**). In fact, the telecentric fundus camera performs this function and captures an image that is of constant angular size, regardless of lens or corneal optical powers.[13-16] The linear magnification of this captured image is directly and only proportional to the axial length of the eye.[13-15] Our formulation of PAI is such that the magnification of the length and diameter of the vessels of interest cancel, thus permitting direct measurements from our photographs. It is in this manner that we are able to compare the PAIs of different subjects directly from fundus photographs.

Finally, we calculated the absolute pressure attenuation that would occur in the retinal arteriolar system to verify that the downstream effect a given PAI would have in absolute pressure units (millimeters of mercury) is real and substantial. The present state of knowledge does not permit direct pressure measurements in small vessels in vivo. Thus, we used the Poiseuille formulation[8] $\Delta P = 8\eta LQ/\pi r^4$ with arteriolar length (L) and diameter (D) ($D = 2 \times$ radius [r]) measurements from fluorescein angiograms, normal flow (Q) calculations from laser Doppler velocimetry[9] or color Doppler ultrasonography[17] in normal retinal vessels, and an estimate of whole-blood viscosity (η)[7] to arrive at an estimation of pressure drop (ΔP) in the arteriolar system of subjects with nonretinal vascular diseases (**Figure 4** and **Figure 5**).

The sample groups studied were recruited from our colleagues, friends, and patients (**Table**). All subjects were in good health and receiving no vasoactive medications. The study was approved by the institutional ethics committee, and informed consent was obtained from all subjects. A

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RESULTS

The demographic data are given in the Table. All statistical analyses consisted of a 1-way analysis of variance with the appropriate post hoc test (Scheffé), unless otherwise indicated. The groups are comparable in all respects, except for axial length ($P<.001$; patients with myopia vs controls and patients with RP) and refractive error range. Further analysis revealed no difference in vessel caliber measurements between groups receiving and not receiving phenylephrine. The total number of arterioles measured at the disc margin and the number at 8.5° were not statistically different from those of controls in either of our groups. Thus, all groups shared comparable arteriolar tree arborization parameters. Furthermore, no difference was noted in the mean vessel length from any 1 quadrant to another in any of the groups.

Figure 6 illustrates the mean PAI in controls, patients with axial myopia, and patients with RP. A 16% increase in the mean PAI is noted in the myopia group compared with the control group ($P = .002$; 2-tailed Student t test). A much larger (67% compared with controls) increase in mean PAI is clearly evident in the RP group. Raw data analysis of the axial myopia and control groups reveals a linear relationship (correlation coefficient, $r = 0.65$) between mean PAI and axial length (**Figure 7**). Data point averaging with axial length increments of 0.7 mm results in a graph with 8 points and a regression coefficient of 0.93 (**Figure 8**).

The calculation of the absolute pressure attenuation along the retinal arteriolar system of the 5 subjects with angiograms assumes a whole-blood viscosity of 0.03 poise (a reasonable estimate, given the sizes of blood vessels studied)[7] and a flow of 10 µL/min in an arteriole 110 µm in diameter (which is in agreement with the more conservative estimated flow rates in the literature).[9,17] By the Murray law, $Q = kr^3$; thus $k = 1001.8$ second^{-1} (Figures 4 and 5), where Q indicates blood flow; k, constant; and r, vessel radius. Blood viscosity, although slightly lower in the patients with RP due to the reduced vessel calibers in RP (68 mm in patients with RP vs 110 mm in controls), will alter minimally the value of k in this absolute pressure calculation.[7] No significant difference was noted in vessel dimensions among these 5 subjects ($P = .67$) or between their photographs obtained before and after injection ($P = .18$). The analysis demonstrates that the calculated pressure drop along the retinal arteriolar system from the disc to a vessel of 30 to 40 µm will be in the order of 15 mm Hg in controls (range, 13-20 mm Hg).

screening eye examination was performed on all subjects to document their status, and an A-scan was performed to determine the axial length. Controls were considered to have refractive errors from +0.75 to –0.75 diopters (spherical equivalent), with astigmatism of less than 1.00 diopters. Subjects with myopia (chosen for their longer arteriolar tree length) were accepted if their refractive error exceeded –4.00 D (spherical equivalent), as this correlates with a predominant axial component.[4] Patients with RP were selected as the other test group, as they are known to have a narrowed arteriolar diameter, and they too are reputed to be protected from diabetic retinopathy.[18] Given that our formulation of pressure attenuation includes length and diameter as variables, we chose the patients with RP to have normal axial lengths to isolate arteriolar diameter as the only variable in our comparison with controls. Again, astigmatism of greater than 1.00 diopter was used as an exclusion criterion in these groups. (Although astigmatism does not affect image magnification, it does produce image blurring).[14] Randomly, the subjects then had 1 pupil dilated using 1% tropicamide or with a combination of 1% tropicamide and 2.5% phenylephrine hydrochloride.

Red-free retinal images (35°) were captured with a digital camera (Kodak Megaplus camera, Model 1.4; Eastman Kodak Co, San Diego, Calif) mounted on a telecentric fundus camera (Topcon TRC-50x; Topcon Corporation of America, Oradell, NJ). These digitized images of 1024 × 1024 pixel size were then resized using commercially available computer software (Adobe Photoshop 3.0; Adobe Systems Incorporated, Mountain View, Calif) to 4000 × 4000 pixels. This computer averaging technique lessens the pixelation and permits better vessel edge definition for diameter measurements. No other image modification was performed. Given that the central retinal artery arborizes at the disc with a dominant vessel per quadrant, the diameter of this largest arteriole in each retinal quadrant is then measured (in pixels) on each photograph as near to the disc as possible in a segment of uniform caliber. The vessel diameter is determined by matching its diameter to the diameter of a measurable cylinder of 120 pixels in length, which is superimposed on the vessel. This provides a reproducible value for vessel diameter with an interobserver variance of 3%, which is comparable to other vessel measuring techniques.[9] Each of our images represents a 35° fundus view. The total length in pixels of the largest retinal arteriole in each quadrant is measured from the origin of the arteriole at the disc to a point 8.5° peripherally using computer software (Adobe Photoshop), with an interobserver variance of less than 1%. This 8.5° is an arbitrary angle that also represents 1000 pixels on our resized photographs. The calculation of the PAI for the arteriole in each quadrant is performed according to our formula $PAI = L/D$. The value so obtained for each retinal quadrant is then averaged to obtain the mean PAI for each subject.

The calculation of the absolute pressure attenuation in the retinal arteriolar system was performed on the superotemporal arteriole from the origin of the central retinal artery to the reproducible limit of resolution of the vessels (30-40 μm) in their course toward the fovea (Figures 4 and 5). We used fluorescein angiograms of 5 patients with emmetropia who had undergone previous testing for central serous choroidopathy (n = 3), potential toxic effects of hydroxychloroquine sulfate (n = 1), and macular degeneration (n = 1), since angiograms permit a better resolution of the diameter of smaller arterioles than the red-free images. The pressure dissipation was calculated for each nonbranching arteriolar segment using length and diameter measurements (Figures 4 and 5). These values (ΔP_1-ΔP_5) were then summed to obtain the total pressure dissipation along the superotemporal arteriole.

COMMENT

The significant association of low ocular perfusion pressure and myopia with decreased clinical diabetic retinopathy prompted the question as to whether the protective role of myopia could also be a pressure phenomenon. We therefore developed a measure of the pressure effects of the retinal arterioles in different eyes. Our physiological index shows that the arteriolar vessel geometry (length and diameter) is the important determinant of hydrostatic pressure attenuation in a given retinal arteriolar system. In addition, because of the Murray law, we are able to infer downstream vessel caliber and hence pressure attenuation through the arteriolar system from the largest arteriole measured. For example, a 20% decrease from control in the mother vessel should also be associated with a similar decrease in each of the daughter vessels. Thus, the mean PAI across the arteriolar tree would be 1/(1 – 0.2) or 1.25 times the value of the control. Furthermore, the similar arteriolar arborization pattern among the study groups permits interindividual comparisons of photographically derived PAIs. The results also clearly demonstrate the linear relationship between the mean PAI and increasing axial length, as a result of the corresponding longer arteriolar tree. The extremely narrow arterioles in the patients with RP result in the largest mean PAIs.

A PAI can be measured directly from a fundus photograph. The fundus camera generates an image that is of constant angular size (35° in our study) but is also fixed in size when displayed. This means that there exists a certain linear magnification associated with each image and, as previously stated, this magnification is proportional to the axial length of the globe. We have found (data not shown) that the arteriolar length, as measured on the red-free images, is constant for the 8.5° used. This confirms that there is no change in tortuosity of the arteriolar vessels between the images. As previously noted, in all groups, the number of arterioles at the disc and at 8.5° do not differ significantly. From this, we infer that in these groups, fundus photographs of arterioles will differ only in their diameter. Thus, the fundus camera performs its function such that a mean PAI could be measured directly from each image as an average 1/D of 4 quadrants, and interindividual comparisons can be made on this basis. In other words, the size of the retinal arteriole as measured on a fundus photograph taken with a telecentric fundus camera is inversely proportional to its pressure-attenuating capability or to the pressure-attenuating capacity of its downstream arteriolar system.

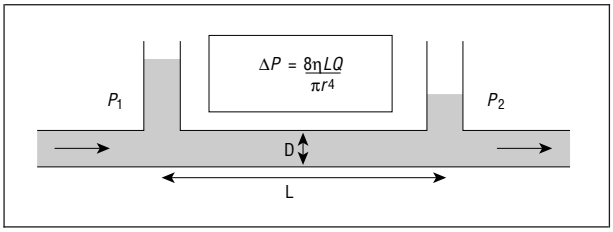

Figure 1. *Pressure attenuation (ΔP) along a tube. ΔP = $P_1 - P_2$, where P_1 and P_2 are manometer readings of pressure along model tube, with fluid flowing from left to right. The Poiseuille formulation for ΔP is provided. η indicates viscosity of the fluid; L, vessel length; D, vessel diameter; Q, flow; and r, radius of the tube (D/2).*

$\Delta P \propto Q \times R$	Ohm Law
$Q \propto r^3$	Murray Law
$R \propto L/r^4$	Poiseuille Formulation for Resistance
$\Delta P \propto r^3 \times L/r^4$	Substitution of Lines 2 and 3 into Line 1
$\Delta P \propto L/r$	Simplification of Line 4
$PAI = L/D$	PAI Formula

Figure 2. *Derivation of the pressure attenuation index (PAI). The Ohm law relates to a pressure differential to flow and resistance. The Murray law states that flow in a given arteriolar system varies with the third power of the radius. The Poiseuille formulation relates resistance to length and radius. ΔP indicates pressure differential; α, proportional to; Q, flow; R, resistance; r, vessel radius; L, vessel length; and D, vessel diameter.*

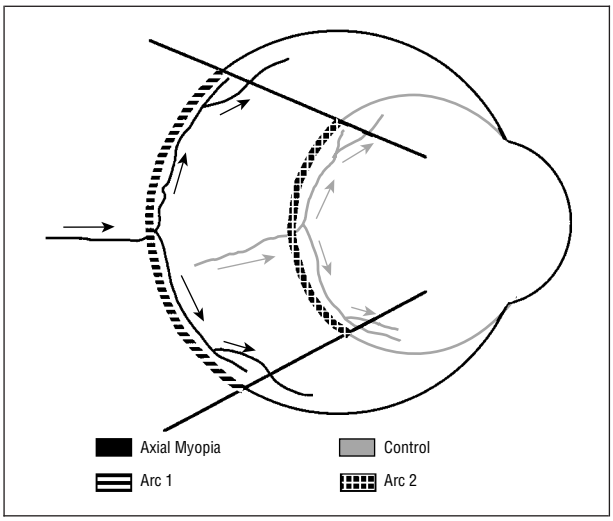

Figure 3. *Angular comparison of blood flow along the arteriolar tree in eyes of different axial lengths (side view of 2 eyes in overlay). An increase in axial length (eye with axial myopia) above that of control subject (eye with emmetropia) results in an increased arc length (arc 1 vs arc 2) or surface area over which blood must flow. Arrows indicate the direction of blood flow in each eye.*

A calculation of the absolute pressure attenuation in the emmetropic retinal arteriolar system of 5 subjects shows the hydrostatic pressure drop occurring along the retinal arteriolar system from the disc to a vessel of 30 to 40 µm will be on the order of 15 mm Hg in controls. This pressure change is comparable to measured pressure attenuations occurring in other vascular systems for vessels of this caliber.[8] Our mean PAI indicates that in the eye with RP, a 67% greater pressure dissipation will occur because of the extreme arteriole narrowing. As such, a 10–mm Hg increase in pressure attenuation above that

$\Delta P = 8\eta LQ/\pi r^4$	Poiseuille Formulation
$Q = kr^3$	Murray Law
$\Delta P = 8\eta L(kr^3)/\pi r^4$	Substitution of Line 2 Into Line 1 for Q
$\Delta P = 16\eta L(kr^3)/D\pi r^3$	Factor Out L/D (=PAI)
$\Delta P = PAI \times (16\eta k/\pi)$	Simplification of Line 4
$\Delta P = PAI \times (16 \times 0.03 \times 1001.752)/(\pi \times 1333)$	Substitution of Values
$\Delta P = PAI \times 0.115$ mm Hg	Calculated Pressure Attenuation

Figure 4. *Calculation of pressure attenuation in the arteriolar tree. ΔP indicates pressure differential; Q, flow; η, viscosity (0.03 dyne multiplied by seconds per square centimeter); r, vessel radius; L, vessel length; D, vessel diameter; PAI, pressure attenuation index (L/D); and k, constant (1001.752 second^{-1}). Pressure measurements can be converted into millimeters of mercury by dividing by 1333.*

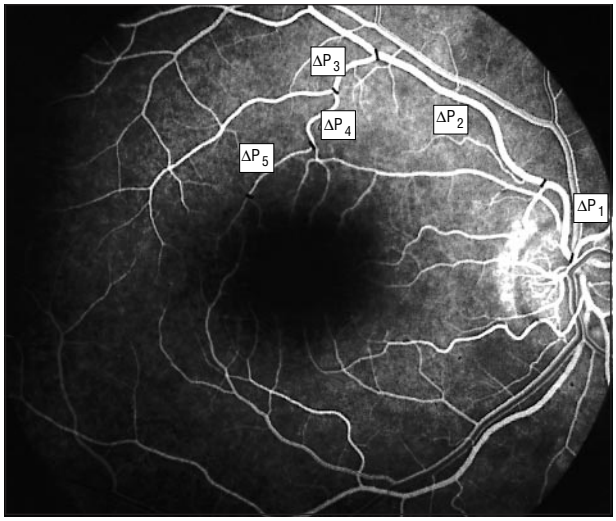

Figure 5. *Angiographic image used in the calculation of the absolute pressure attenuation in the retinal arteriolar tree. ΔP_1 to ΔP_5 indicates pressure differential along the arteriolar segment. The total pressure attenuation is the sum of ΔP_1 to ΔP_5. Pressure differential for each segment is calculated as described in Figure 4.*

of controls has occurred in patients with RP in the retinal arteriole tree down to 40-µm vessel size. Thus a real and significant pressure drop would occur across the retinal arteriolar tree of patients with RP because of their arteriolar narrowing.

The physiological laws used in the derivation of the PAI have been validated in the diabetic retinal circulation.[11] Our index predicts that the longer and/or thinner the retinal arterioles, the better will be their pressure-attenuating effect. One of our original goals was to examine and compare the pressure effects of ocular conditions that protect in diabetic retinopathy. The following excerpt from the study by Miller and D'Amico[19] summarizes these conditions:

> Early investigators observed that certain ocular conditions seemed to prevent severe diabetic retinopathy. Eyes with chorioretinal scarring, optic atrophy, retinitis pigmentosa, and high myopia were protected from severe proliferative retinopathy. Beetham,[20] studying patients at the Joslin clinic, described spontaneous resolution of PDR [proliferative diabetic retinopathy] in approximately 10% of patients. The fundus picture in these patients consisted of lacy reticulated proliferative tissue; attenuated arterioles; and obliterated vessels appearing as white lines. The fundus picture resembled that of the ocular conditions described earlier as

Demographics

Parameters	Healthy Control Subjects	Subjects With Myopia	Subjects With Retinitis Pigmentosa
	Subjects		
No. of subjects	22	25	6
Mean age, y	34.7	35.1	38.8
Age range, y	21-50	23-51	25-57
Sex, No.			
Male	10	13	2
Female	12	12	4
	Eyes		
No. of eyes*			
Right	11	13	4
Left	11	12	2
Mean intraocular pressure, mm Hg†	14.9 ± 1.6‡	15.0 ± 2.0	15.7 ± 1.6
Mean refraction range§	+0.75 to −0.75	−4.25 to −18.50	−2.50 to +1.25
Axial length, mm			
Mean	22.9 ± 0.45‡	26.0 ± 1.38	22.8 ± 0.98
Range	22.2 to 23.7	24.0 to 31.2	21.1 to 23.8
	Blood Vessels		
No. of arteries at disc margin	8.0 ± 1.33‡	7.8 ± 1.19	7.3 ± 1.37
No. of arteries at 8.5°	11.9 ± 2.29‡	10.9 ± 2.08	11.3 ± 2.58
Arborization index‖	1.52 ± 0.34‡	1.42 ± 0.26	1.57 ± 0.40

*One eye was studied per subject.
†Intraocular pressure of studied eye only.
‡Indicates ±1 SD.
§Measured as spherical equivalent.
‖Calculated by dividing number of arteries at 8.5° by number of arteries at disc margin.

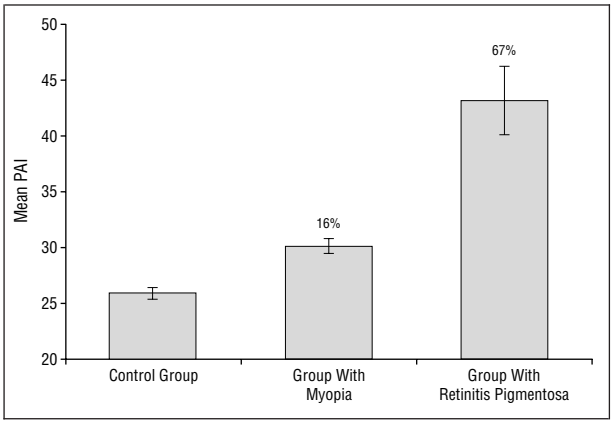

Figure 6. *Pressure attenuation index (PAI) variation with axial myopia and retinitis pigmentosa. Percentages represent difference from control group. The error bars indicate SEM.*

well as the fundus picture that develops after successful hypophysectomy for PDR. It was recognized that this appearance could be achieved with photocoagulation.

This clinical observation was considered important supportive evidence to proceed with the retinal photocoagulation trials of the Diabetic Retinopathy Study. All of the ocular conditions protective of diabetic retinopathy present with attenuated or long retinal arterioles. The critical role that these attenuated or long retinal arterioles would have in dissipating pressure is apparent from our index.

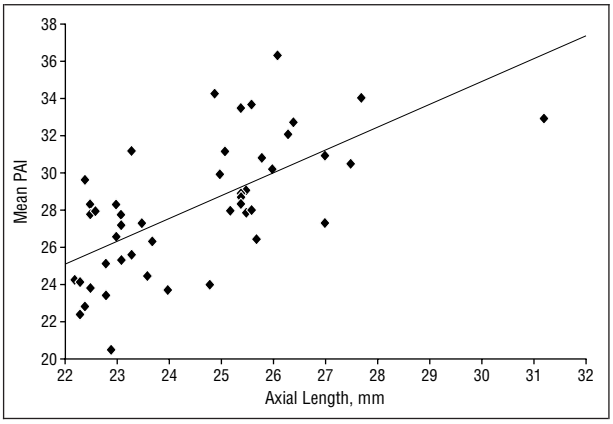

Figure 7. *Linear relationship between axial length and the mean pressure attenuation index (PAI), derived from raw data of control and myopic groups (n = 47). F(x) = (1.23 × x) − 1.97 (regression coefficient,* R *= 0.650).*

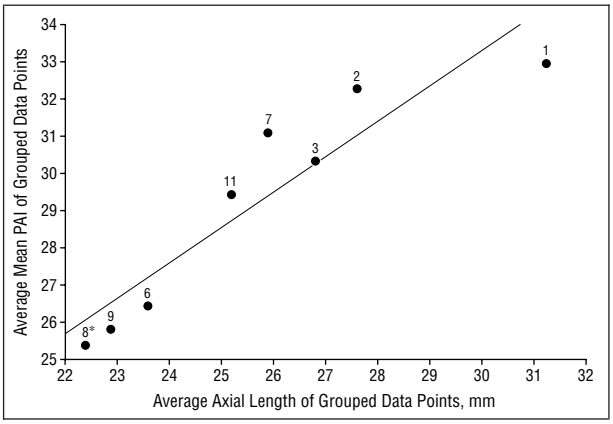

Figure 8. *Data point averaging of raw data from Figure 7. Using axial length increments of 0.7 mm, the raw data points are subdivided into groups (black dots) in which the average of the mean pressure attenuation index (PAI) for each group is plotted as a function of the average of the axial length of each group. F(x) = (0.955 × x) + 4.68 (regression coefficient,* R *= 0.927). Asterisk indicates value corresponds to the number of raw data points included in each group.*

Experimental evidence from other vascular systems shows that perfusion pressure is linearly related to small-vessel pressure down to small-vessel size (30-40 mm).[8] Thus, a low systemic pressure, or low ocular perfusion pressure, will result in a low-end arteriolar pressure. Thereafter, local control mechanisms effect the necessary adjustments to maintain homeostatic flow and pressure to the capillaries. However, the diabetic vascular system is known for its abnormal autoregulatory capacity.[21] An inability of the retinal vessels to dissipate the upstream pressure head could lead to an abnormally high intratubal pressure of the capillary bed. Clinical diabetic retinopathy manifests itself at the capillary level with leakage, hemorrhage, and capillary dropout.[22] An unattenuated perfusion pressure, in addition to the well-known anatomical abnormalities described in the capillaries of patients with diabetes,[23] could result in leakage (Starling law[5]) and an increased risk for rupture (Laplace law[5]), given that pressure plays such a critical role in both these laws. If pressure attenuation can be achieved upstream of the smaller vessels by any means, whether by lowering systemic pressure or by hydrostatic pressure at-

tenuation in retinal arterioles, then the smaller vessels would have fewer requirements to decrease the pressure head to a tolerable level in the capillary bed. Low-end arteriole pressure appears to be the common denominator that protects against diabetic retinopathy and that is shared by low ocular perfusion pressure and the ocular conditions associated with thin and/or long retinal arterioles.[24]

We believe that mean PAI may serve as a risk indicator of the development and progression of diabetic retinopathy. In addition, mean PAI may also provide a quantifiable measure of the efficacy of therapeutic interventions in diabetic retinopathy, be they surgical or pharmaceutical. The PAI permits a physiological approach and appears to link the protective factors in diabetic retinal microangiopathy to their pressure effects. Although the absolute pressure change estimates would be slightly different in patients with diabetes because of their blood viscosity alterations[25] and the different proportionality constant to calculate flow,[26] the principles are the same: pressure will be better dissipated in arterioles if they are increased in length or decreased in caliber above that of normal-sized arterioles. We believe this results in a more unified understanding of the pathogenesis of diabetic retinopathy and hence a rationale for future therapies, not only in the eye but in the vascular system at large. The usefulness of this index in the evaluation of other retinal vascular and systemic vascular diseases remains to be investigated.

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Notes From Our Ophthalmic Heritage

A look at the past . . .

Conical Cornea

Soon after the immortal invention of Helmholtz, I found the ophthalmoscope very useful in detecting slight degrees of conical cornea. For this purpose the concave mirror only is to be used without a convex lens. On turning the mirror so as to throw light at different angles, the side of the cone opposite to the light is dark.

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