

Axial Length, Retinal Function, and Oxygen Consumption: A Potential Mechanism for a Lower Risk of Diabetic Retinopathy in Longer Eyes

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Submitted: May 15, 2013

Accepted: October 14, 2013

Citation: Man REK, Lamoureux EL, Taouk Y, et al. Axial length, retinal function, and oxygen consumption: a potential mechanism for a lower risk of diabetic retinopathy in longer eyes. *Invest Ophthalmol Vis Sci*. 2013;54:7691-7698. DOI:10.1167/iov.13-12412

PURPOSE. To determine the relationship between axial length (AL), retinal function, and relative oxygen (O₂) consumption to better understand the protective effect of axial elongation on diabetic retinopathy development.

METHODS. Measurements of AL, multifocal electroretinogram (mfERG), and relative O₂ consumption (difference between arteriolar and venular O₂ saturation levels or A-V difference) were performed on 50 healthy individuals. The relationships between AL, mfERG amplitude, and A-V difference were analyzed using linear regression models. Path analysis was performed to determine the direct and indirect effects (via mfERG amplitude) of AL on A-V difference.

RESULTS. mfERG P1 amplitude was positively associated with A-V difference ($\beta = 0.33$; 95% confidence interval [CI]: 0.23–0.42). Increased AL was significantly associated with a decrease in A-V difference ($\beta = -1.08$; 95% CI: -1.52 to -0.65) as well as a decrease in retinal function ($\beta = -3.14$, 95% CI: -4.07 to -2.20). Path analysis models including AL (study factor), retinal function (intermediate variable), and A-V difference (outcome variable) showed that AL had little direct association with A-V difference ($\beta_p = -0.002$), while the indirect effect of AL on A-V difference via changes in retinal function were substantial ($\beta_p = -0.51$).

CONCLUSIONS. In eyes with longer AL, the reduction in A-V difference is explained by the parallel reduction in retinal function. These findings suggest that longer eyes have decreased retinal function and O₂ consumption, and thus are relatively less hypoxic in the presence of diabetes, which may partly explain the reduced risk of DR in these eyes.

Keywords: axial length, retinal function, electroretinogram, oximetry, oxygen consumption, myopia, diabetic retinopathy

Myopia has been observed to have a protective association with the prevalence^{1,2} and progression³ of diabetic retinopathy (DR) in various clinical and population-based studies. However, given the intimate relationship between myopia and its refractive (e.g., corneal curvature) and axial components (e.g., axial length [AL]),^{4,5} the observed protective myopia-DR relationship could have been due to either refractive status or to the influence of these ocular parameters associated with myopia. Recently, we reported findings suggesting that myopia is a surrogate for a longer AL in this protective relationship.⁶

The mechanisms underpinning the protective association between longer AL and a lower risk of DR remain uncertain. One commonly held theory is that as the eye elongates, the retina stretches and thins,^{7,8} resulting in a decreased retinal metabolism. These changes reduce oxygen demand and mitigate the hypoxic condition in the diabetic retina that is

crucial in the development of DR.^{9,10} The hypothesis has been corroborated by studies showing a reduction in retinal function,¹¹⁻¹⁴ and thinning of the retina¹⁵ with increasing AL.

However, up until recently, this theory has remained unproven, as it was extremely difficult to noninvasively measure retinal oxygen (O₂) metabolism in vivo. With the recent advent of modern spectrophotometers,^{15,16} it is now possible to obtain both arteriolar and venular O₂ saturation (SO₂) measurements, and indirectly the relative O₂ consumption of the retina, using the arteriole-venous (A-V) difference in SO₂ as a surrogate marker.

In this study, we investigated the following associations: AL and retinal function (as measured using the multifocal electroretinogram [mfERG] response amplitude); retinal function and A-V difference; and direct and indirect (via retinal function) associations of AL with A-V difference. We hypothesize that healthy, nondiabetic eyes with longer AL have

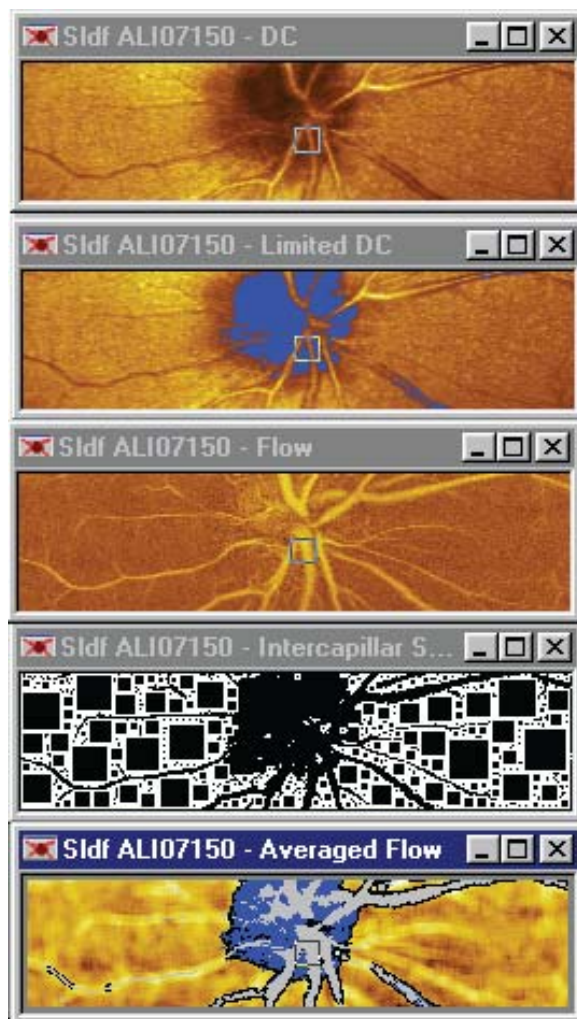


FIGURE 1. Optic nerve centered scan from the HRF processed using the AFFPIA.

decreased A-V difference due to reduced retinal function. If confirmed, our findings will support a reduction of hypoxia with increased AL as an important mechanism in decreasing DR risk in longer eyes.

METHODS

Study Population

Fifty healthy, nonsmoking Caucasian individuals were recruited as subjects for this study. All participants had a best-corrected logarithm of minimum angle of resolution (logMAR) visual acuity (BCVA) of 0.00 (equivalent to 6/6 on the Snellen chart) or better. Subjects were excluded if they had intraocular pressure (IOP) >21 mm Hg, presence of cataract, or other media opacities, or any history or signs of retinal or optic nerve disease. All subjects were over the age of 18 years, and did not have any self-reported history of systemic conditions that might affect blood flow (i.e., diabetes mellitus and hypertension). This was further confirmed by blood pressure measurements (<140/80 mm Hg)¹⁷ and blood chemistry analysis of glycated hemoglobin (HbA_{1c}; <6.5%)¹⁸ and random glucose (<11.1 mmol/L).¹⁹ All subjects were also advised to refrain from consuming caffeinated products and alcohol for at least 12 hours before the study. The study was approved by the

human ethics committee of the Royal Victorian Eye and Ear hospital (#11/1304H) and abided by the tenets of the Declaration of Helsinki.

Blood Chemistry

Nonfasting blood samples were collected for analysis of blood glucose, HbA_{1c}, and lipids (total, HDL, LDL cholesterol; and triglycerides). All blood analyses were performed at Melbourne Pathology, Melbourne, Australia, with individual results electronically delivered through a password-protected program. The laboratory is accredited to the International Standard ISO15189 (Medical Laboratories) and is certified by NATA (National Association of Testing Authorities).

Assessment of Key Covariables

Standardized questionnaires were used to assess basic demographic details (age, sex), history of ocular and systemic conditions, and medication use. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) measurements were taken using an automatic blood pressure monitor (Omron Model IAIB; Omron Healthcare, Inc., Lake Forest, IL). Intraocular pressure (IOP) was assessed using Goldmann applanation tonometry. Key covariables were age, sex, SBP, and DBP. Two-field fundus images of the right eye were also taken using a retinal camera (Canon CR6-45NM; Canon, Inc., Tokyo, Japan). The images were graded at the Centre for Eye Research Australia; and eyes with pigment abnormalities or myopia-related changes other than tessellated fundi or slight crescents at the optic disc were excluded from the study.

Assessment of Axial Length

Axial length of the right eye of each subject was obtained using an intraocular lens (IOL) master unit (version 3.02.304; Carl Zeiss Meditec AG, Jena, Germany). At least three consecutive measurements were taken to ensure consistency and all readings were within 0.02 mm of each other, with signal-to-noise ratio of at least 2.0.

Imaging for Retinal Capillary Flow

Retinal capillary flow was captured using the Heidelberg retinal flowmeter (HRF). Briefly, the examination was performed in the sitting position at room temperature with diffuse natural light on undilated pupils. An optic disc centered scan was obtained, together with the regions within 1 to 1.5 disc diameters to either side of the optic disc margin. A total area of 2.56×0.64 mm was scanned within 2 seconds at a resolution of 256 points \times 64 lines \times 128 times with the default 780-nm wavelength laser head installed in the HRF camera.

During the data acquisition, the participant was asked to fixate on a mounted artificial light spot placed approximately 1 m in front and slightly temporally of him or her. The scans were taken from both eyes of each person.

Analysis of Capillary Flow

Image analysis was done with the automatic full field perfusion image analyser (AFFPIA) software (version 3.3). Briefly, AFFPIA calculates the Doppler frequency shift of 780-nm laser light from the HRF arising from moving blood cells within each pixel of the entire image and estimates the overall flow in the form of arbitrary units (AU).²⁰ For a valid estimation of retinal blood flow, the software adjusts brightness to mask under- or overexposed pixels and also eliminates noise from artificial movement (saccades), avoids measuring extremely wide retinal



FIGURE 2. A fundus photograph showing the peripapillary annulus where oxygen saturation readings were taken. A false color map showing saturation values has been superimposed on the image. Saturation values are color coded according to the *scale bar*.

vessels and the optic nerve head, and accounts for the heart phases (systole and diastole) by averaging the differences between the two phases. Figure 1 shows an example of an image processed using the AFFPIA software. For analysis purposes, the flow readings from the temporal and nasal regions adjacent to the optic disc were averaged.

Imaging for SO_2 Measurements

Subjects' pupils were dilated with 1% tropicamide and optic disc-centered images (30° field) of the right eye were taken using a fundus camera (FF450; Carl Zeiss Meditec AG). Care was taken to ensure that the images were sufficiently illuminated (as indicated by the "illumination indicator" algorithm provided in the oximetry module of the vessel map system [Imedos UG, Jena, Germany]), the magnification and flash settings were not changed between images, and that the background illumination remained constant.

Assessment of A-V Difference

Retinal vessel oxygenation measurements in both retinal arteries and veins were estimated using the oximetry module of the vessel map system (Imedos UG). In brief, two monochromatic fundus images were obtained using a

double-band pass filter (light transmission at 548 ± 10 nm and 610 ± 10 nm) inserted in the illumination path of a fundus camera (FF450; Carl Zeiss Meditec AG). Only one observer (REKM) was assigned to take the images. The ratio of the optical densities at 610 nm to that at the isosbestic 548-nm wavelength is proportional to the vessel hemoglobin SO_2 ²¹ after compensation for vessel diameter and fundus pigmentation.²²

For each image, a peripapillary annulus (specifically designed by Imedos UG to be adjustable to account for different optic disc sizes as per our request) was used to mark an area in the image for analysis (Fig. 2). Within this area (inner radius of 1 and outer radius of 1.5 disc diameters), the O_2 saturation was measured for all arterioles and venules. Typically, approximately 20 measurements consisting of between 8 to 10 arterioles and 8 to 10 venules above 50 μ m in diameter were averaged. This value was chosen as it was observed that the algorithm had difficulty tracing and measuring the O_2 saturation of vessels smaller than 50 μ m without repeated efforts by the observer to mark the edges of the vessel walls. Values along the vessel that were more than 20% over the mean value were excluded to eliminate the confounding effects of specular reflection (these made up on average 5% of values along a vessel).²² The A-V difference was

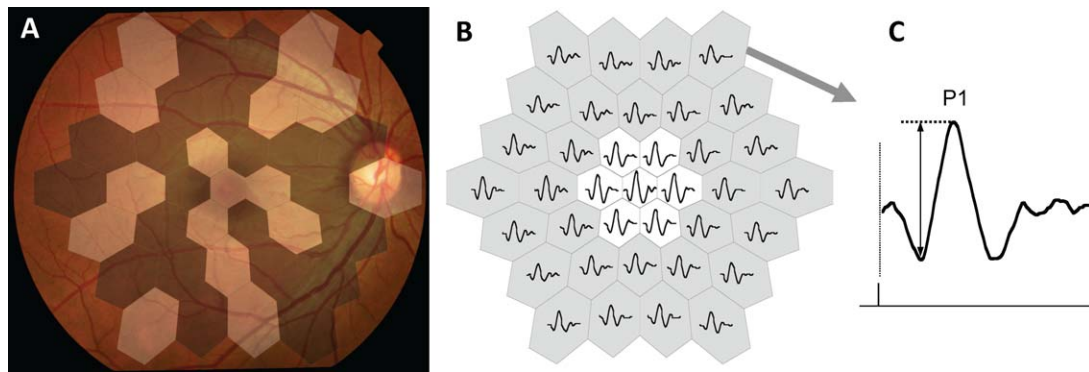


FIGURE 3. (A) The multifocal electroretinogram recording stimulus superimposed over a fundus image. The area of measurement covers approximately 22° of the central retina. (B) A typical trace array response obtained in a healthy subject. The central and peripheral retinal functions are indicated by the white and grey area, respectively. (C) A spatial summation response of the peripheral retinal function. The *double-headed arrow* indicates the measurement of the P1 [first positive peak] amplitude.

calculated as the difference between the arteriolar and venular SO₂ values.

Assessment of Retinal Function

Central retinal function of the right eye was assessed using a visual evoked response imaging system (VERIS Science, version 6.0; Electro-Diagnostic Imaging, Inc., Redwood City, CA) on a dilated pupil. There was at least a 30-minute interval in the time between the last fundus imaging and retinal function measurements, to allow the retina to recover fully and eliminate the potential effect of the preceding camera flash on the mfERG recording. Dawson-Trick-Litzkow fiber electrodes were used for all the recordings. A fixation monitoring system (FMS III) was used to deliver the test stimulus, and refractive error was corrected by adjusting the refractor unit within the FMS. The testing stimulus contained 37 retinally scaled hexagons, which were randomly displayed on the FMS microdisplay using a pseudorandom m-sequence (m = 14) at a rate of 75 Hz. This test stimulus covered the central 22° of the retina from the fovea. The stimulus contrast was approximately 99% with the luminance of a white hexagon of 5.33 cd·s·m⁻² and a background luminance of 200 cd·m⁻². Recorded signals were band-pass filtered between 10 to 100 Hz and amplified 100,000 times (Grass NeuroData Model 12, Quincy, MA). The duration of the recording was approximately 3.5 minutes, which was divided evenly into eight slightly overlapping segments of approximately 28 seconds each, for patients' comfort and to suppress eye movement and blinks. The summed P1 amplitudes of the first-order response of the central (rings 1-2, central 7.5°) and peripheral area (rings 3-4,

7.5-22° of the retina) were obtained and used for the analysis (Fig. 3).

Statistical Analysis

Analyses were performed using statistical software (Intercooled STATA version 12.1 for Windows; StataCorp, College Station, TX). Eye-specific data (AL, A-V difference, mfERG central and peripheral amplitudes) from the right eye of each subject were used in the analysis. Beta coefficients (β), derived from linear regression models, were used to estimate the associations between: AL (mm) and mfERG (central and peripheral amplitudes, nanovolts per degree squared [nV/deg²]); mfERG (central and peripheral amplitudes) and A-V difference (%); AL and A-V difference; and the effect of other key covariables (age [years], sex, SBP, and DBP [mm Hg]) on A-V difference and mfERG (central and peripheral amplitudes). Partial coefficients (β_p), derived from path regression analysis models, were then used to explore the direct and indirect effects (via retinal function) of AL on A-V difference. These partial coefficients are standardized regression coefficients, indicating the steepness or magnitude of a change in the outcome (dependent) variable per unit change in the study (independent) variable in a linear association. They can be compared directly in terms of the magnitude of the association given the same unit of changes. Path analysis²³ is a specialized regression model that aims to provide estimates of the magnitude of hypothesized, unidirectional causal relationship between the study and outcome variables, either directly or indirectly via changes in the intermediate variables.

RESULTS

Data from 50 subjects were included in the analysis. The median age (interquartile range [IQR]) was 26 (8) years and 22 (44%) were male. The mean \pm standard deviation (SD) for AL was 24.76 \pm 1.51 mm, A-V difference was 33.83% \pm 3.36%, and the mfERG central and peripheral amplitudes were 39.78 \pm 6.69 nV/deg² and 15.34 \pm 2.52 nV/deg², respectively. Table 1 summarizes the demographic and clinical parameters of the sample.

Association Between Retinal Function and A-V Difference

Linear regression analyses showed that an increased retinal function was associated with greater A-V difference (per unit

TABLE 1. Demographic and Clinical Parameters of Participants Recruited for the Study

Parameters	Mean, SD/ Median, IQR	Range of Values
Age, y	26, 8	18-58
AL, mm	24.76, 1.51	21.61-28.35
Capillary blood flow, AU	247.66, 39.50	126.22-345.92
mfERG central amplitude, nV/deg ²	39.78, 6.69	22.40-53.20
mfERG peripheral amplitude, nV/deg ²	15.34, 2.52	8.80-21.00
A-V difference, %	33.83, 3.36	24.13-42.47
SBP, mm Hg	113.29, 12.42	84-138
DBP, mm Hg	76.10, 8.86	56.5-97.5

AU, arbitrary unit. n = 50.

TABLE 2. Univariate Associations Between Age, Sex, AL, mfERG Amplitudes, SBP, DBP, and A-V Difference

Parameters	Regression Coefficient, mfERG	95% CI	P Value
Outcome: A-V difference			
Age, y	0.03	−0.04 to 0.10	0.38
Female sex	−1.12	−2.58 to 0.35	0.13
AL, mm	−1.09	−1.50 to −0.67	<0.001
Capillary blood flow, AU	−0.0006	−0.02 to 0.02	0.96
mfERG central amplitude, nV/deg ²			
	0.33	0.19 to 0.46	<0.001
mfERG peripheral amplitude, nV/deg ²			
	0.87	0.53 to 1.22	<0.001
SBP/10 mm Hg	−0.001	−0.49 to 0.49	1.00
DBP/10 mm Hg	−0.03	−0.71 to 0.66	0.94

n = 50.

increased mfERG central amplitude: regression coefficient [β] = 0.33, $P < 0.001$, per unit increased mfERG peripheral amplitude: $\beta = 0.87$, $P < 0.001$, Table 2).

Association Between AL and Retinal Function

Longer AL was significantly associated with decreased mfERG central and peripheral amplitudes (per mm increase in AL, changes in mfERG central amplitude: $\beta = -3.14$, $P < 0.001$; and mfERG peripheral amplitude: $\beta = -1.18$, $P < 0.001$, Table 3).

Associations Between AL and A-V Difference

Linear regression models showed that longer AL was associated with a decrease in A-V difference (per mm increase in AL, $\beta = -1.09$, $P < 0.001$, Table 2).

Effects of Age, Sex, SBP, and DBP on A-V Difference and Retinal Function

In univariate regression models with A-V difference as the outcome, there were no significant associations between age, sex, SBP, and DBP (Table 2) in this sample. Similarly, with the mfERG central and peripheral amplitudes as the outcomes, there were no significant associations with age, sex, SBP, or DBP (Table 3).

Relationship Between AL, Retinal Function, and A-V Difference

Path analysis was used to determine the direct and indirect associations between AL, retinal function, and oxygen consumption. As none of the key covariables (age, sex, SBP, DBP) were significantly associated with AL ($P > 0.05$, data not shown), retinal function, or A-V difference, these variables were not included in path analysis models.

In the first path analysis model with AL as the exposure factor, mfERG central amplitude as the intermediate variable and A-V difference as the outcome, we found that AL had little direct influence on the A-V difference ($\beta_p = -0.002$, pathway 1, Fig. 4), whereas the indirect effects on A-V difference via changes in central amplitude were greater ($\beta_p = -0.51$, pathway 2).

In the second path analysis model with AL as the exposure factor, A-V difference as the outcome, and using mfERG peripheral amplitude as the intermediate variable (Fig. 5), AL

TABLE 3. Univariate Associations Between Age, Sex, AL, SBP, DBP, and mfERG Amplitudes

Parameters	Regression Coefficient, mfERG	95% CI	P Value
Outcome: mfERG central amplitude			
Age, y	0.16	−0.01 to 0.38	0.16
Female sex	−3.24	−7.14 to 0.66	0.10
AL, mm	−3.14	−3.98 to −2.29	<0.001
Capillary blood flow, AU	0.01	−0.04 to 0.07	0.68
SBP/10 mm Hg	0.68	−0.78 to 2.14	0.35
DBP/10 mm Hg	0.76	−1.72 to 3.23	0.54
Outcome: mfERG peripheral amplitude			
Age, y	0.75	−0.06 to 0.16	0.10
Female sex	−0.88	−2.36 to 0.60	0.24
AL, mm	−1.18	−1.48 to −0.89	<0.001
Capillary blood flow, AU	0.006	−0.02 to 0.03	0.61
SBP/10 mm Hg	0.39	−0.16 to 0.94	0.16
DBP/10 mm Hg	0.52	−0.29 to 1.33	0.20

n = 50.

again had little direct effect on A-V difference ($\beta_p = 0.02$, pathway 1), whereas the indirect effects of AL on A-V difference via changes in peripheral amplitude were greater ($\beta_p = -0.54$, pathway 2).

DISCUSSION

In this study, we investigated the relationships between AL, retinal function, and relative O₂ consumption (using A-V difference as a surrogate marker). We showed that retinal function decreases in eyes with longer AL, and the decrease in retinal function is associated with a reduction in A-V difference. We have further demonstrated, using path analysis models, that the decrease in A-V difference in eyes with longer AL is indirectly associated with the decrease in retinal function in these eyes. These findings are consistent with the hypothesis that a longer AL leads to a decrease in retinal metabolic demands, which then results in a reduction of hypoxia in diabetic eyes. This decrease in hypoxia is believed to be partially responsible for the protective association between a longer AL and lower risk of DR.

There is substantial evidence in the literature suggesting retinal neuronal dysfunction and degeneration with axial elongation. For example, Wosley and colleagues demonstrated delayed mfERG amplitude and implicit timings, as well as retinal thinning, in the peripheral retina of eyes with axial myopia.¹³ These results are believed to reflect decreased retinal photoreceptor density,²⁴ morphological changes in the photoreceptor outer segment,^{25,26} as well as photoreceptor dysfunction²⁷ due to mechanical stretching of the retina during elongation of the ocular axis. The role of retinal neurodegeneration in the reduction of retinal function in elongated eyes has been further corroborated by Luu and associates,¹² who found a reduction in mfERG amplitude in adult eyes with axial myopia, but not in children with the same myopic status. The results suggest that the reduction in retinal function in longer eyes is not due to optical or electrical aberrations resulting from the increased distance between the retina and the recording electrode, but is related to degenerative retinal changes over time, given that these changes are more apparent in adults than children. In this study, we found strong

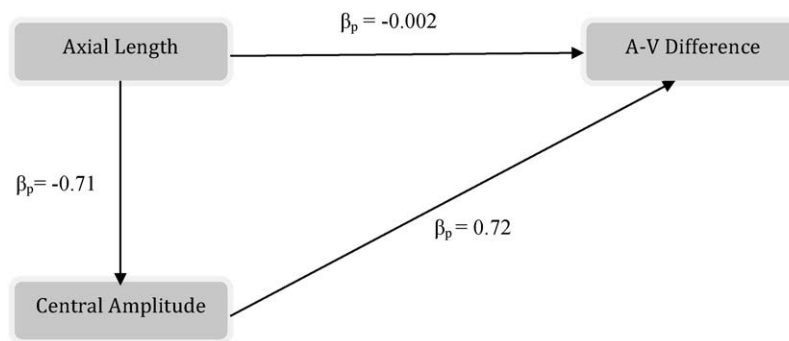


FIGURE 4. Path regression analysis for AL (study variable), mfERG central amplitude (intermediate variable), and A-V difference (outcome variable). Pathway 1 is the direct association between A-V difference and AL: $\beta_p = 0.002$; Error/residual of pathway: 0.71 Pathway 2 is the indirect association between A-V difference and AL via central amplitude as the intermediate variable: $\beta_p = (-0.71 \times 0.72) = -0.51$, Error/residual of pathway: 0.69.

associations between AL and both the mfERG central and peripheral amplitudes, which is in line with previous findings.

Our study also establishes that the reduced retinal function in longer eyes is paralleled by a decrease in A-V difference. Given that the A-V difference is an implicit measure of O_2 consumption,²⁸ and O_2 consumption reflects the level of demand in healthy eyes,²⁹ our results support the hypothesis that in longer eyes, O_2 demand is reduced due to a loss of functional neurons in these eyes.

In eyes of healthy persons, the outer retina, including the photoreceptor layer, is supplied by the choroid.³⁰ It has been proposed that the protective relationship between myopia and DR may be partially due to degenerative changes, as a result of axial elongation, in the photoreceptor layer, leading to a decrease in O_2 consumption in the outer retina. This results in relatively greater availability of O_2 from the choroid to the inner retina. Consequently, the inner retina requires less O_2 from the retinal circulation, indicated by a decrease in the A-V difference on the retinal oximeter.

However, recent studies have shown a decrease in choroidal thickness³¹ and choroidal blood flow with increasing myopia.^{7,32,33} It is unclear whether these changes precede, or are a result of, the degenerative outer retinal changes in axial myopia. Even if these changes result in a decrease in outer retinal O_2 supply, it is uncertain whether the decrease in supply mirrors the rate of the choroidal changes. There may still be excess in O_2 available if the decrease in O_2 supply is slower than that of the preceding choroidal changes. As we did not measure the changes in choroidal flow prospectively, this is beyond the scope of the current study and more investigations are therefore warranted.

It has also been suggested that retinal blood flow is directly correlated with the amount of arteriolar and venular SO_2 .³⁴ Since retinal blood flow has been found to decrease with axial elongation,^{7,8,32} the decrease in A-V difference could partially be due to this reduction in retinal blood flow. In our study, we measured retinal capillary flow and found that it was not associated with AL ($P > 0.05$, unpublished data), the A-V difference in SO_2 ($P > 0.05$), or the central or peripheral mfERG amplitude responses ($P > 0.05$). Our results are consistent with findings of the only other study reporting the relationship between RCF with AL.³² As we did not assess retinal blood flow, we are unable to comment on its relationship with AL, as well as its potential effects on mfERG response or the A-V difference, even though both retinal blood flow and RCF are most likely correlated. A possible reason for the nonassociation between RCF and AL was that subjects with degenerative myopic retinal pathologies were excluded from both our study and the study by Benavente-Pérez and associates³²; hence autoregulation of retinal blood flow is unlikely to be disrupted in these subjects. In contrast, studies reporting a positive association between decreased retinal arteriolar and venular blood flow with increasing AL included subjects with pathologic myopic changes such as posterior staphylomas and peripheral retinal degeneration.^{7,8}

We used path regression analysis to explore the direct and indirect (via retinal function) effects of AL on the A-V difference, in order to corroborate the above hypothesis. We showed that a longer AL had a very weak direct influence on the A-V difference; instead, its effect on decreasing the A-V difference was mainly via the reduction in retinal function. It is important to note that a limitation of this analysis is that it only

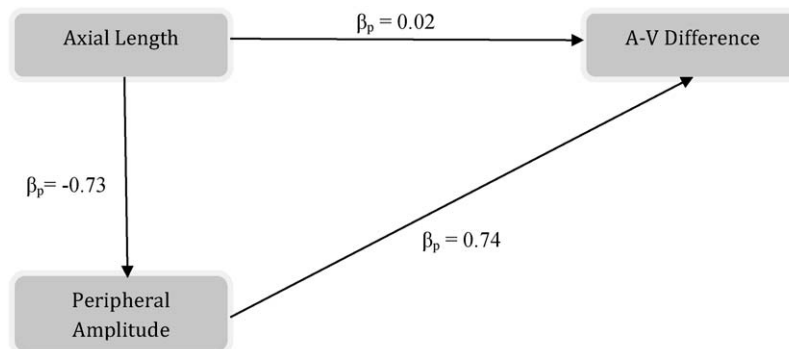


FIGURE 5. Path regression analysis for AL (study variable), mfERG peripheral amplitude (intermediate variable), and A-V difference (outcome variable). Pathway 1 is the direct association between A-V difference and AL: $\beta_p = -0.02$; Error/residual of pathway: 0.69. Pathway 2 is the indirect association between A-V difference and AL via peripheral amplitude as the intermediate variable: $\beta_p = (-0.73 \times 0.74) = -0.54$; Error/residual of pathway: 0.69.

allows for examination of hypothesized unidirectional effects. Specifically, potential feedback loops among the variables are not considered. However, given that Luu and associates have demonstrated that the decrease in retinal function occurs only after initial globe elongation¹² and that laser studies have established that the increase in oxygen tension occurs after destruction of the outer retina layers, we believe that we have adequately justified the unidirectionality of this hypothesis.

The above findings are important in supporting the hypothetical mechanism for the protective association between myopia and DR.^{1,2} We recently documented that myopia was a surrogate for a longer AL in this protective myopia-DR relationship.⁶ It has been suggested that the decrease in metabolic demand as the eye elongates results in a decrease in hypoxia in the diabetic retina, which might be one of the mechanisms responsible. Our findings provide further support for a link between AL, retinal function, and O₂ consumption, which is an essential step for the proposed hypothetical mechanism.

Retinal hypoxia in diabetes, due to pathogenic changes in the retinal microcirculation (e.g., capillary nonperfusion and shunting³⁵), has been established as a major factor contributing to the development of DR.^{9,10} Hypoxia induces upregulation of VEGF production,³⁶ a powerful angiogenic signaling protein³⁷ that has also been shown to increase vessel permeability.³⁷ Both angiogenesis and increased vessel permeability play key roles in the pathogenesis of DR.³⁸ Degenerative changes in the outer retina and greater availability of O₂ from the choroid may help mitigate the effects of hypoxia in diabetes, leading to a potential decrease in VEGF production. This was first speculated by Jonas et al.,³⁹ who observed a reduction of VEGF concentration in the aqueous associated with increasing AL. This speculation has been further supported by evidence from later VEGF studies conducted by Sawada and colleagues.^{40,41} However, prior to our study, no data exist for the relationship between AL, retinal function and O₂ consumption. Our results are therefore the first to document the relationship between a longer AL, reduced retinal function and decreased O₂ consumption (using A-V difference in SO₂ as a surrogate marker) in eyes of healthy persons. These findings are consistent with the hypotheses regarding a reduced metabolic demand in eyes with increasing AL, and may help explain the protective association between longer AL and DR via a reduction in the hypoxic state of the diabetic retina.

Strengths of this study include subjects with a wide range of AL, as well as a detailed and comprehensive clinical protocol. Limitations of our study should also be noted including its cross-sectional nature. Furthermore, this study was conducted in healthy persons; whether this relationship between AL, retinal function, and A-V difference translates to diabetic eyes remains to be determined.

In conclusion, we have demonstrated that eyes with longer AL have lower A-V difference in SO₂. The reduction in A-V difference is in parallel with a reduction in retinal function. These findings are consistent with the hypothesis that a reduced O₂ consumption in eyes with longer AL may help to reduce the risk of DR, possibly via mitigation of hypoxia in the diabetic retina. Further studies to investigate the above relationship in diabetic eyes are warranted.

Acknowledgments

Supported by Australian Research Council linkage Grant No. LP0884108 and by the National Health and Medical Research Council Centre for Clinical Research Excellence Grant No. 52992 – Translational Clinical Research in Major Eye Diseases. The Centre for Eye Research Australia receives Operational Infrastructure

Support from the Victorian Government. The authors alone are responsible for the content and writing of the paper.

Disclosure: **R.E.K. Man**, None; **E.L. Lamoureux**, None; **Y. Taouk**, None; **J. Xie**, None; **M.B. Sasongko**, None; **W.J. Best**, None; **J.E. Noonan**, None; **R. Kawasaki**, None; **J.J. Wang**, None; **C.D. Luu**, None

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