Medical Sciences

Iridal vasculature and the vital roles of the iris

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The iris has been increasingly recognized as a key structure in the anterior segment, and probably plays a role in glaucoma and cataract disease processes. The iris is also a tissue remarkably rich in vasculature, and the information of endothelial phenotype provides valuable clues for investigating the iridal circulation and potential function. However, only limited knowledge of the relationship between the iridal vasculature and iris roles in pathogenesis of ocular diseases is available. In order to address this issue, this review aims to link iridal vasculature to the possible roles of the iris in related ocular diseases, from the viewpoint of both the iridal vascular architecture and the iridal endothelium. *Journal of Nature and Science, 1(8):e157, 2015*

Iris | iris microvasculature | endothelium | material exchange | ocular diseases

Introduction

The important role of the iris and iris vasculature has been increasingly recognized in recent decades. The iris is located between the anterior chamber and posterior chamber as a septum, and keeps moving all the time. It is supposed to not only emulate a camera shutter, but also to serve a specific biological function leading to subtle changes in the surrounding micro-environment. The iris vasculature is known to be a major source of oxygen gradients in the aqueous humor and supply nutrients to the avascular tissues in the anterior segment, such as the cornea, lens and trabecular meshwork. However, the impact of the iris vasculature on the anterior segment is still not well defined. This short review aims to illustrate the probable roles of the iris and its vasculature in relevant physiological and pathogenic conditions from both a macro (vascular layer distribution and mechanical change) and micro (endothelial morphometry and material exchange) perspectives.

Before discussing the vital role of the iris and iridal vasculature, we would like to briefly outline the currently revealed characteristics of iridal vasculature. The microvasculature has a specific architecture in a particular tissue to couple with unique structure and function. Additionally, vascular endothelium endowed with multiple functions, including controlling vascular tone, regulating the permeability, trafficking nutrients and so on, responds to as well as reflects the micro-environment of the underlying tissue. Endothelial phenotype heterogeneity has been emphasized to be organ and site-specific, both structurally and functionally. This in turn means that the endothelial appearance also provides valuable information regarding endothelial function [1].

Iridal microvascular architecture

With the help of the intra-luminal micro-perfusion and staining techniques established in our laboratory, which had been successfully applied to study retinal and choroidal vasculature [1-11], we have recently reported layer distributions of porcine iris vasculature through the whole thickness of the iris, average vessel density, and also precise quantitative information of endothelial morphometrics in each order of porcine iris vasculature [12]. Impressively, the iris vascular layers are generally arranged as abundant relatively large arteries and veins sandwiched between a superficial and deep compact capillary plexus in porcine eyes, and radial veins are more stretched than radial arteries (Figure 1). The average vascular density of the middle, superficial, and deep layers were 38.9 $\pm$ 1.93 %, 10.9 $\pm$ 1.61 % and 8.0 $\pm$ 0.79 % respectively. According to the Horton-Strahler's nomenclature, iris vasculature has numerous vessel orders (capillaries, 6 orders of arteries, and 4 orders of veins) with relatively large supply arteries (319.5 ± 25.6 μm) as the 6th order artery (A6) comprising the major arterial half ring. Significant heterogeneity of vascular diameter and endothelial cellular morphology exist in different orders of the iris vasculature (Table 1). These phenotype differences among different orders bear hemodynamic information of iris circulation, a piece of which is the abundant blood supply at the root of iris. Besides, iris blood flow and vascular endothelium are hypothesized to play critical roles in maintaining selective permeability of different size molecules [1,13,14].

Iris volume changes and iridal vasculature

In the past decade, some non-invasive imaging techniques, such as optical coherence tomography and ultrasound biomicroscopy, have given some insights into possible factors in the pathogenesis of angle closure glaucoma, which affects 16 million people worldwide [15]. Among them, many studies conducted within different ethnic groups using these imaging devices have demonstrated that the iris normally lost volume or cross-sectional area with pupil dilation. The irises with angle closure had less volume or area loss per mm pupil enlargement than open angle glaucoma patients [16-18]. Further studies conducted in Chinese subjects with dissimilar dominant mechanisms for angle closure showed dynamic iris change may have a more important role in angle closure where pupil block was the dominant mechanism [19].

Histologically, the anterior surface of the iris is covered with endothelium during embryonic development, which disappears at or soon after birth. Then a dense meshwork of melanocytes and fibroblasts with connected collagen reconstructs the anterior surface of the iris [20-23]. This meshwork of cells will not turn to a continuous barrier overlie the anterior iris surface, but sustains its permeable property that allows the iris stroma communicating freely with anterior chamber aqueous humour. Geometric estimates predict that the iris volume should decrease as the pupil enlarges. The iris which fails to decrease volume appropriately as the pupil dilates would theoretically be more likely to occlude the trabecular meshwork.

How does the iris change its volume? From the view of iridal vascular distribution, the superficial capillary network is built into a concentrically aligned fishing-net pattern, similar to the architectural features of iris stromal layer which has been described as an arch-lattice ("Bogengitter").

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Table 1: Iris vessel diameter and endothelial cell dimensions according to vessel order

Vessel Order	Vessel Diameter (μm)	Endothelial Length (μm)	Endothelial Width (μm)
C	15.58 ± 1.47(11)	81.35 ± 6.88(11)	10.04 ± 0.87(11)
A1	28.05 ± 2.32(11)	87.36 ± 6.17(11)	9.69 ± 0.93(11)
A2	49.31 ± 4.54(11)	100.59 ± 8.82(11)	9.91 ± 0.91(11)
A3	83.72 ± 5.63(11)	104.72 ± 7.76(11)	10.14 ± 0.95(11)
A4	132.64 ± 12.94(11	109.54 ± 7.53(11)	9.38 ± 0.52(11)
A5	225.40 ± 15.26(11)	110.41 ± 8.28(11)	8.10 ± 0.69(11)
A6	319.48 ± 25.65(11)	113.54 ± 10.04(11)	8.45 ± 0.81(11)
V1	36.95 ± 2.92(11)	49.13 ± 4.82(11)	12.01 ± 0.76(11)
V2	74.47 ± 6.58(11)	49.91 ± 4.52(11)	12.53 ± 1.20(11)
V3	114.69 ± 5.36(11)	52.74 ± 3.33(11)	11.00 ± 1.07(11)
V4	160.85 ± 14.00(11)	58.70 ± 3.13(11)	9.82 ± 0.90(11)

Values are mean ± standard deviation (number of eyes measured). Data fromYang et. al. [12].

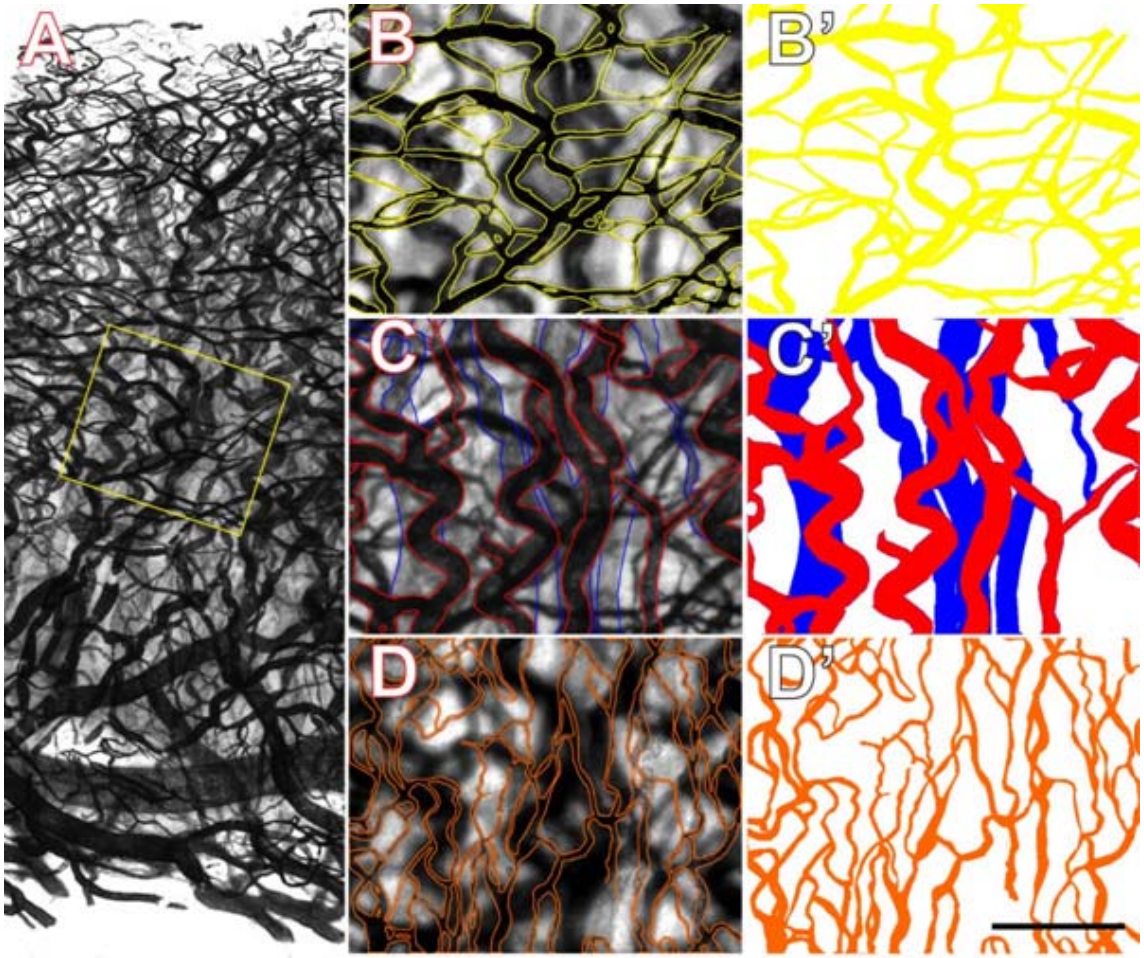

Figure 1. Light microscope images of iris vascular network. Low magnification images were taken from temporal side of iris vasculature illustrating the distribution of the iris vascular network. "A" shows iris vasculature of the middle iris region and "B" to "D" was taken from the outlined region in "A". Three layers of iris vasculature were identified. B, C and D showed the light microscopic image of the superficial capillary, middle vascular and deep capillary layers in this iris respectively, with the corresponding layer in focus and outlined in colour. B', C' and D' show the schematic drawing of the corresponding layers in solid colour. In "B'", red indicates arterioles and blue indicates venules. Scale bar equals 800 μm in A and 400 μm in B-D. Data from Yang et al. [12].

In this manner, when the pupil dilates, this capillary network would be drawn by reducing the space in between, but still keeping the lumen open like a folded arch-lattice, without blocking the blood flow. Additionally, the middle iridal vascular network contains abundant and substantially larger arteries and veins, occupying the main bulk of the iris stroma. Quantitatively, the averaged density of vessels in this middle layer reaches as high as 38.9 ± 4.9% [12]. These large vessels in the mid-stroma exhibit a three-dimensional vascular organization with arteries located generally more superficially than veins, interconnected by capillaries close to the pupil margin. Arteries were generally tortuous, whereas veins were fairly straight. Moreover, it was found that arteries also could communicate with each other through arterial anastomoses. This observation of rich vasculature and its unique arrangements may provide some initial information of the possible role of iris vasculature in iris volume changes. It is postulated that the rich vascular network embedded in the iris stroma, similar to a skeleton structure or scaffold, would help squeeze extracellular fluid out of the stroma with pupil dilation, which may be the effector mediating the iris to change its volume and prevent angle closure.

In the eyes of individuals with dark complexions the anterior border layer is quite dense and heavily pigmented. While in lighter-coloured eyes, such as green, blue and grey colour eyes, the anterior border layer is much looser, large numbers of empty spaces in the stroma grossly open to the iris crypts at the anterior border [24]. This might suggest the communication between iris

stroma and anterior chamber is possibly freer in lighter coloured eyes compared with brown eyes. In that case, when the pupil dilates, the light coloured eyes are more readily able to squeeze fluid out of iris stroma and reduce iris volume, while dark brown eyes are more fluid-retentive. It may explain to a certain degree why some races with dark brown eyes are more inclined to develop angle closure glaucoma because of less iris volume reduction. However, it is still hard to interpret why some ethnic groups with dark coloured iris have a low incidence of angle closure glaucoma.

In brief, changes in iris volume were postulated to be a major pathogenic factor for primary angle closure glaucoma [25-30]. The dynamic processes leading to changes in iris and choroid volume could have a more significant and mechanistic effect to its surrounding structures than a simple anatomical observation [25]. Hence the disturbed mechanisms involved in iris volume change as well as the consequence of troubled iridal volume change could well be an important pathogenic factor in angle closure glaucoma.

Material exchange and iridal microvasculature

A large body of evidence has supported multiple functions of endothelial cells in maintaining micro-environmental homeostasis and integration of blood circulation [1]. The vascular endothelium serves not merely as a barrier separating extravascular matrix from intravascular factors, but as an effective sensor and an active signal transducer for circulating influences. It also does the duty for a key regulator of molecular permeability and material exchange, playing a pivotal role in many physiological processes [31]. Alteration in endothelial function would cause lesion development and later manifest symptoms.

One piece of evidence for iridal vascular and endothelial cellular roles in material exchange is from the comparison of blood flow between the iris and retina. Alm and Bill [32], using radioactively labelled microspheres, directly demonstrated in cats a much higher blood flow in the iris (97 g/min per 100 g tissue) than many other tissue well known with high blood flow rate (retina: 19 g/min per 100 g tissue; brain: 34 g/min per 100 g tissue). Indirectly, the area of the iris is much smaller than the retina, but the supplying arteries for the porcine iris appeared approximately twice as wide as those for the porcine retina [12,33], which reflects that the blood supply for the iris is remarkably abundant. It also reflects the draining needs of a large blood flow volume that the less tortuous iridal venous vessels present in the iris with relatively large diameter. Additionally, the long spindle phenotype of endothelial cells in these numerous larger arteries are also indicative of a high blood velocity based on the relationship between shear stress and endothelial cellular shape. Taken together, these all pointed to the conclusion that massive blood flow exists in the porcine iris. Furthermore, as reported previously, there are some characteristics of vascular distribution in the porcine iris: (1) the high iridal vascular density; (2) the microvascular beds located on both sides of the iris stroma and at the pupil edge, (3) capillary plexus fed by two to three orders of arteriolar branches rising within short distances from large arteries running in the mid-stroma. Combining the high inflow rate with the microvascular network arrangement, we could anticipate that sufficient resources were provided for material exchange between the blood stream and the iris interstitial space, predominantly for the delivery of oxygen and exchange of fluid and other nutrients. The relatively large diameter of capillaries (15.58 ± 1.47 μm) in the iris compared with common ones in other tissues also supports our speculation.

As mentioned previously, there appears no obvious diffusion barrier between the iris and the anterior chamber, thus it is reasonable to assume that open communications exist between the interstitial spaces of the iris and the aqueous humor. Moreover, the stroma of the iris is a sponge-like tissue formed from an interwoven, collagenous framework in a matrix of hyaluronidase-sensitive substance [34]. In that case, the iris microvasculature (in particular the superficial microvascular network consisting of capillary meshworks concentrically aligned) and its endothelium hold the control mechanism for maintaining homeostasis in the anterior segment.

Contribution of iridal vasculature to oxygen gradients

To date, both clinical and experimental studies have demonstrated steep oxygen gradients are present physiologically in the anterior chamber. It has been well known that changes in oxygen gradients and higher oxygen tensions are chief pathogenic factors for cataract and glaucoma [35-37]. The lens normally exposes to a relatively low level of oxygen [35,36]. Increased intraocular oxygen and the consequent rise in reactive oxygen species (ROS) [36,38] have been demonstrated as a risk factor for nuclear cataracts [35,36,39]. It has also been claimed that elevated oxidation may be the hallmark of age-related nuclear cataracts [38]. Vitrectomy and cataract surgery were revealed recently to be able to raise the oxygen delivered to the outflow pathway and escalate oxidative stress [39-41], which probably presents a key pathogenic step in primary open-angle glaucoma by promoting trabecular meshwork degeneration, giving rise to an intraocular pressure (IOP) increase, therefore priming the glaucoma pathogenic cascade [42,43].

It has been found that intraocular oxygen is mostly derived from the retinal and iris vasculature and by diffusion across the cornea [37]. The amount of iris vasculature is patently more abundant than the iridal tissues own needs. In regard to further function of the elaborate distribution of iridal vasculature other than iris metabolic demands, evidence has been provided by measuring the oxygen tension at different location along the iris anterior surface in the anterior chamber of rabbit and monkey eyes [44]. It was shown that the oxygen level in front of the pupil is substantially lower than in front of the anterior iris surface. What's more convincing is that after partial or total iridectomy, the oxygen level in front of the partial iridectomy was as low as in the centre of pupil. Inhalation of pure oxygen raised the oxygen level in front of the remaining iris, but not in the iridectomy region. This suggests some oxygen supply to the corneal endothelium and the anterior chamber is delivered by the iris vasculature. Even though the microvasculature in the iris is non-fenestrated, there would be no barrier for oxygen penetration, just as in the blood-brain-barrier.

As the predominant source of oxygen for the anterior segment, the iris microvasculature most likely plays a crucial role in maintaining oxygen homeostasis in the anterior chamber. Hence any interference or abnormality of the iris vasculature could disturb anterior chamber oxygen gradients which may lead to pathological consequences. Take for instance, although iridotomy has been demonstrated to be a relatively safe procedure and widely used since its introduction into clinical practice in 1981, there is still the potential long-term risk of corneal decompensation, for which a corneal transplantation may be indicated [45-47]. The longest interval between laser iridotomy and corneal decompensation reported was 8 years [45]. The causative mechanism is unknown. Although ophthalmologists have proposed a long list of risk factors such as direct focal injury, thermal damage, and transient rise in intraocular pressure are less likely to cause such a delayed pathology. If taking the iridal physiological functions to corneal endothelium into consideration, including providing the major oxygen supply and partial metabolic needs, the long-term risk of corneal decompensation after iridotomy seems explainable. Furthermore, as another avascular tissue in the anterior chamber, the trabecular meshwork is directly exposed to aqueous humour and is responsible for most of its outflow, it is unknown whether or not iridotomy, the treatment of angle-closure glaucoma, paradoxically has any unexpected side effect to the trabecular meshwork as the sequelae of disturbing oxygen gradients in the anterior chamber. Experiments conducted on animals could provide us some evidence on this point in the future.

Contribution of iridal vasculature to protein concentration

Differential protein concentration has been confirmed to be present in the aqueous humour and ciliary process stroma. Protein

concentration in the aqueous humour (50 mg/dl) is less than 1% of that in plasma (8 g/dl) [48] whereas that in the ciliary process stroma is 74% of that in plasma [49]. This is possibly an outcome of different permeability to proteins in the iridal and ciliary vasculature. It has been shown that iridal vasculature is non-fenestrated and serves as part of the blood-aqueous humour barrier. It has also been proven that intravascular horse radish peroxidase appearing in the iridal stroma had leaked from ciliary body instead of from the iridal vasculature [44]. However, transport in the reverse direction from the stroma back into the blood stream could occur both on iridal and ciliary muscle vasculature [50], with only anionic but not cationic molecules found to be transported back via plasmalemmal vesicles of endothelial cells in iridal vasculature [45]. This further suggests the heterogenic property of the endothelial permeability in the iridal and ciliary vasculatures, and vascular endothelium may play critical roles in retaining selective permeability to molecules of different sizes [13, 14]. Vasculature in the iris and ciliary body likely offers different roles to keep a certain concentration gradient of each molecule in the aqueous humour. Previous studies have proposed the pathway that plasma constituents might permeate from ciliary vasculature, and then diffuse into the iridial stroma through the ciliary body interstitial spaces, and finally into the anterior chamber [51,52]. Some molecules can also be selectively transported through the iris endothelium [52]. However, the process of fluid and molecules exchange between blood vessels, stroma and aqueous humor has not been delineated. Therefore the roles of the iris microvasculature, particularly its endothelium, need to be explored further.

Summary

The roles of the iris and iridal microvasculature have been increasingly recognised in the pathogenesis of glaucoma and cataracts. Not only the mechanical change of the iris volume takes part in this process, but iridal micro-vasculature related oxygen delivery and nutrition exchange also contribute to the homeostasis in the anterior chamber. Morphological characteristics of porcine iris microvasculature and its endothelium have been provided recently. It is postulated that the mid-stroma vascular layer may be the effector in mediating the iris volume change, and that the superficial and deep capillary meshworks are possibly the site of dynamic fluid and nutrient exchange. Exact mechanisms may also involve the unique structure of the iris surface, sponge-like iris stroma, fluid exchange mechanisms between the iris microvasculature and interstitial spaces, as well as vascular activities. Detailed information on topography of the iris microvasculature and morphometrics of the iris endothelial cells, combined with unique structural features of the iris, may help us to further understand the physiological and pathogenic roles of the iris in relevant ocular diseases.

Future direction

In spite of what has been described above, there is still a shortage of knowledge as to how the vasculature mediates iris volume change and the detailed mechanisms of endothelium selectively transporting molecules. Additionally, endothelial cells have a very slow turnover rate so that inevitably endothelial senescence would occur. Consequently, endothelial functions are altered in the aging blood vessel, causing an increase in the severity of age related vascular pathology. This process in the iris vasculature may also contribute as a factor to the pathogenesis of ocular diseases including glaucoma and cataracts, where morbidity rises with aging. Further studies need to be conducted to investigate the precise roles of iridal vasculature and its endothelium in both normal and disease conditions, including the detailed mechanisms of molecular and environmental factors involved, so as to improve our approach to new diagnostic and therapeutic techniques for related ocular diseases.

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[1] D. Y. Yu, P. K. Yu, S. J. Cringle, M. H. Kang, and E. N. Su, "Functional and morphological characteristics of the retinal and choroidal vasculature," *Prog Retin Eye Res*, vol. 40C, pp. 53-93, May2014.

[2] P. K. Yu, C. Balaratnasingam, W. H. Morgan, S. J. Cringle, I. L. McAllister, and D. Y. Yu, "The structural relationship between the microvasculature, neurons, and glia in the human retina," *Invest Ophthalmol Vis Sci*, vol. 51, no. 1, pp. 447-458, Jan.2010.

[3] P. K. Yu, C. Balaratnasingam, S. J. Cringle, I. L. McAllister, J. Provis, and D. Y. Yu, "Microstructure and network organization of the microvasculature in the human macula," *Invest Ophthalmol Vis Sci*, vol. 51, no. 12, pp. 6735-6743, Dec.2010.

[4] P. K. Yu, P. E. Tan, W. H. Morgan, S. J. Cringle, I. L. McAllister, and D. Y. Yu, "Age-related changes in venous endothelial phenotype at human retinal artery-vein crossing points," *Invest Ophthalmol Vis Sci*, vol. 53, no. 3, pp. 1108-1116, 2012.

[5] P. K. Yu, P. E. Tan, S. J. Cringle, I. L. McAllister, and D. Y. Yu, "Phenotypic heterogeneity in the endothelium of the human vortex vein system," *Exp Eye Res*, vol. 115C, pp. 144-152, July2013.

[6] G. Chan, C. Balaratnasingam, P. K. Yu, W. H. Morgan, I. L. McAllister, S. J. Cringle, and D. Y. Yu, "Quantitative changes in perifoveal capillary networks in patients with vascular comorbidities," *Invest Ophthalmol Vis Sci*, vol. 54, no. 8, pp. 5175-5185, Aug.2013.

[7] P. E. Tan, P. K. Yu, C. Balaratnasingam, S. J. Cringle, W. H. Morgan, I. L. McAllister, and D. Y. Yu, "Quantitative confocal imaging of the retinal microvasculature in the human retina," *Invest Ophthalmol. Vis. Sci.*, vol. 53, no. 9, pp. 5728-5736, Sept.2012.

[8] P. E. Tan, P. K. Yu, S. J. Cringle, W. H. Morgan, and D. Y. Yu, "Regional heterogeneity of endothelial cells in the porcine vortex vein system," *Microvasc. Res*, vol. 89, pp. 70-79, Sept.2013.

[9] P. J. Adam, P. L. Weissberg, N. R. B. Cary, and C. M. Shanahan, "Polyubiquitin is a new phenotypic marker of contractile vascular smooth muscle cells," *Cardiovascular Research*, vol. 33, pp. 416-421, 1997.

[10] M. H. Kang, C. Balaratnasingam, P. Yu, W. H. Morgan, I. L. McAllister, S. J. Cringle, and D. Y. Yu, "Morphometric characteristics of central retinal artery and vein endothelium in the normal human optic nerve head," *Invest Ophthalmol Vis Sci*, vol. 52, pp. 1359-1367, 2011.

[11] M. H. Kang, C. Balaratnasingam, P. K. Yu, W. H. Morgan, I. L. McAllister, S. J. Cringle, and D. Y. Yu, "Alterations to vascular endothelium in the optic nerve head in patients with vascular comorbidities," *Exp Eye Res*, vol. 111, pp. 50-60, June2013.

[12] H. Yang, P. K. Yu, S. J. Cringle, X. Sun, and D. Y. Yu, "Quantitative study of the microvasculature and its endothelial cells in the porcine iris," *Exp Eye Res*, vol. 132C, pp. 249-258, Feb.2015.

[13] D. Abraham and M. Dashwood, "Endothelin--role in vascular disease," *Rheumatology. (Oxford)*, vol. 47 Suppl 5, p. v23-v24, Oct.2008.

[14] W. C. Aird, "Endothelial cell heterogeneity," *Cold Spring Harb Perspect Med*, vol. 2, no. 1:a006429, pp. 1-13, Jan.2012.

[15] B. Wang, L. M. Sakata, D. S. Friedman, Y. H. Chan, M. He, R. Lavanya, T. Y. Wong, and T. Aung, "Quantitative iris parameters and association with narrow angles," *Ophthalmology*, vol. 117, no. 1, pp. 11-17, Jan.2010.

[16] F. Aptel and P. Denis, "Optical coherence tomography quantitative analysis of iris volume changes after pharmacologic mydriasis," *Ophthalmology*, vol. 117, no. 1, pp. 3-10, Jan.2010.

[17] H. A. Quigley, D. M. Silver, D. S. Friedman, M. He, R. J. Plyler, C. G. Eberhart, H. D. Jampel, and P. Ramulu, "Iris cross-sectional area decreases with pupil dilation and its dynamic behavior is a risk factor in angle closure," *J Glaucoma*, vol. 18, no. 3, pp. 173-179, Mar.2009.

[18] S. B. Ganeshrao, B. Mani, S. Ulganathan, B. Shantha, and L. Vijaya, "Change in iris parameters with physiological mydriasis," *Optom. Vis. Sci.*, vol. 89, no. 4, pp. 483-488, Apr.2012.

[19] Y. Zhang, S. Z. Li, L. Li, M. G. He, R. Thomas, and N. L. Wang, "Quantitative analysis of iris changes following mydriasis in subjects with different mechanisms of angle closure," *Invest Ophthalmol. Vis. Sci.*, vol. 56, no. 1, pp. 563-570, Jan.2015.
[20] M. J. Hogan, J. A. Alvarado, and J. E. Weddell, *Histology of the Human Eye: An Atlas and Textbook*. Philadelphia: W.B. Saunders Company, 1971.
[21] A. J. TOUSIMIS and B. S. Fine, "Ultrastructure of the iris: the intercellular stromal components," *Arch Ophthalmol*, vol. 62, pp. 974-976, Dec.1959.
[22] F. Vrabec, "[The anterior superficial endothelium of the human iris]," *Ophthalmologica*, vol. 123, no. 1, pp. 20-30, Jan.1952.
[23] T. F. Freddo, "Ultrastructure of the iris," *Microsc. Res Tech.*, vol. 33, no. 5, pp. 369-389, Apr.1996.
[24] P. C. Kronfeld, "The gross anatomy and embryology of the eye," in *Vegetative Physiology and Biochemistry*. H. Davson, Ed. New York and London: Academic Press Inc., 1962, pp. 1-62.
[25] H. A. Quigley, "Angle-closure glaucoma-simpler answers to complex mechanisms: LXVI Edward Jackson Memorial Lecture," *Am J Ophthalmol*, vol. 148, no. 5, pp. 657-669, Nov.2009.
[26] H. Mak, G. Xu, and C. K. Leung, "Imaging the iris with swept-source optical coherence tomography: relationship between iris volume and primary angle closure," *Ophthalmology*, vol. 120, no. 12, pp. 2517-2524, Dec.2013.
[27] F. E. Seager, J. L. Jefferys, and H. A. Quigley, "Comparison of dynamic changes in anterior ocular structures examined with anterior segment optical coherence tomography in a cohort of various origins," *Invest Ophthalmol Vis Sci*, vol. 55, no. 3, pp. 1672-1683, Mar.2014.
[28] F. Aptel, C. Chiquet, S. Beccat, and P. Denis, "Biometric evaluation of anterior chamber changes after physiologic pupil dilation using Pentacam and anterior segment optical coherence tomography," *Invest Ophthalmol Vis Sci*, vol. 53, no. 7, pp. 4005-4010, June2012.
[29] M. Baskaran, S. W. Ho, T. A. Tun, A. C. How, S. A. Perera, D. S. Friedman, and T. Aung, "Assessment of circumferential angle-closure by the iris-trabecular contact index with swept-source optical coherence tomography," *Ophthalmology*, vol. 120, no. 11, pp. 2226-2231, Nov.2013.
[30] C. W. Oyster, "The Human Eye, Structure and Function," *Ophthal. Physiol. Opt.*, vol. 20, no. 4, pp. 349-350, 2000.
[31] J. E. Deanfield, J. P. Halcox, and T. J. Rabelink, "Endothelial function and dysfunction: testing and clinical relevance," *Circulation*, vol. 115, no. 10, pp. 1285-1295, Mar.2007.
[32] A. Alm and A. Bill, "The oxygen supply to the retina, I.Effects of changes in intraocular and arteriolar blood pressures, and in arterial PO_2 and PCO_2 on the oxygen tension in the vitreous body of the cat," *Acta Physiol Scand*, vol. 84, pp. 261-274, 1972.
[33] E. N. Su, D.-Y. Yu, and S. J. Cringle, "Histamine induces opposing vasoactive effects at different levels of the ocular vasculature," *Curr Eye Res*, vol. 30, pp. 205-212, 2005.
[34] W. Tasman and E. A. Jaeger, "Duane's Clinical Ophthalmology on CD-ROM," Philadelphia, PA: Lippincott Williams & Wilkins, 2005.
[35] N. M. Holekamp, Y. B. Shui, and D. C. Beebe, "Vitrectomy surgery increases oxygen exposure to the lens: a possible mechanism for nuclear cataract formation," *Am J Ophthalmol*, vol. 139, no. 2, pp. 302-310, Feb.2005.
[36] I. A. Barbazetto, J. Liang, S. Chang, L. Zheng, A. Spector, and J. P. Dillon, "Oxygen tension in the rabbit lens and vitreous before and after vitrectomy," *Exp. Eye Res*, vol. 78, no. 5, pp. 917-924, May2004.
[37] Y. B. Shui, J. J. Fu, C. Garcia, L. K. Dattilo, R. Rajagopal, S. McMillan, G. Mak, N. M. Holekamp, A. Lewis, and D. C. Beebe, "Oxygen distribution in the rabbit eye and oxygen consumption by the lens," *Invest Ophthalmol Vis Sci*, vol. 47, no. 4, pp. 1571-1580, Apr.2006.
[38] R. J. Truscott, "Age-related nuclear cataract-oxidation is the key," *Exp Eye Res*, vol. 80, no. 5, pp. 709-725, May2005.
[39] C. J. Siegfried, Y. B. Shui, N. M. Holekamp, F. Bai, and D. C. Beebe, "Oxygen distribution in the human eye: relevance to the etiology of open-angle glaucoma after vitrectomy," *Invest Ophthalmol. Vis. Sci.*, vol. 51, no. 11, pp. 5731-5738, Nov.2010.
[40] S. Chang, "LXII Edward Jackson lecture: open angle glaucoma after vitrectomy," *Am J Ophthalmol*, vol. 141, no. 6, pp. 1033-1043, June2006.
[41] F. O. Luk, A. K. Kwok, T. Y. Lai, and D. S. Lam, "Presence of crystalline lens as a protective factor for the late development of open angle glaucoma after vitrectomy," *Retina*, vol. 29, no. 2, pp. 218-224, Feb.2009.
[42] A. Izzotti, S. C. Sacca, M. Longobardi, and C. Cartiglia, "Sensitivity of ocular anterior chamber tissues to oxidative damage and its relevance to the pathogenesis of glaucoma," *Invest Ophthalmol Vis Sci*, vol. 50, no. 11, pp. 5251-5258, Nov.2009.
[43] S. C. Sacca, A. Pascotto, P. Camicione, P. Capris, and A. Izzotti, "Oxidative DNA damage in the human trabecular meshwork: clinical correlation in patients with primary open-angle glaucoma," *Arch Ophthalmol*, vol. 123, no. 4, pp. 458-463, Apr.2005.
[44] J. Hoper, R. Funk, Z. Zagorski, and J. W. Rohen, "Oxygen delivery to the anterior chamber of the eye - a novel function of the anterior iris surface," *Curr Eye Res*, vol. 8, no. 7, pp. 649-659, 1989.
[45] P. X. Wang, V. T. Koh, and S. C. Loon, "Laser iridotomy and the corneal endothelium: a systemic review," *Acta Ophthalmol*, Feb.2014.
[46] J. H. Youm, J. H. Heo, H. M. Kim, and J. S. Song, "Effects of argon laser iridotomy on the corneal endothelium of pigmented rabbit eyes," *Korean J Ophthalmol*, vol. 28, no. 1, pp. 76-82, Feb.2014.
[47] D. Szumny and A. Szelag, "The influence of new beta-adrenolytics nebivolol and carvedilol on intraocular pressure and iris blood flow in rabbits," *Graefes Arch Clin Exp Ophthalmol*, vol. 252, no. 6, pp. 917-923, June2014.
[48] E. L. Smith, R. A. Hill, I. R. Lehman, R. J. Lefkowitz, P. Handler, and A. White, *Principles of Biochemistry:Mammalian Biochemistry*, 7th ed. Singapore: McGraw-Hill Book Company, 1985.
[49] A. Bill, "A method to determine osmotically effective albumin and gammaglobulin concentrations in tissue fluids, its application to the uvea and a note on the effects of capillary "leaks" on tissue fluid dynamics," *Acta Physiol Scand.*, vol. 73, no. 4, pp. 511-522, Aug.1968.
[50] S. H. Sherman, K. Green, and A. M. Laties, "The fate of anterior chamber flurescein in the monkey eye. 1. The anterior chamber outflow pathways," *Exp Eye Res*, vol. 27, no. 2, pp. 159-173, Aug.1978.
[51] T. F. Freddo, S. P. Bartels, M. F. Barsotti, and R. D. Kamm, "The source of proteins in the aqueous humor of the normal rabbit," *Invest Ophthalmol Vis Sci*, vol. 31, no. 1, pp. 125-137, Jan.1990.
[52] G. Raviola and J. M. Butler, "Morphological evidence for the transfer of anionic macromolecules from the interior of the eye to the blood stream," *Curr Eye Res*, vol. 4, no. 4, pp. 503-516, Apr.1985.