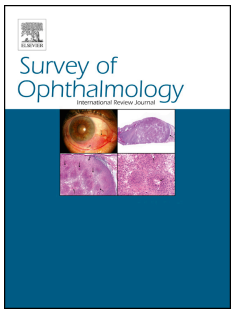
Accepted Manuscript



Assessment of flow dynamics in retinal and choroidal microcirculation

Xin Wei, MD, Praveen Kumar Balne, PhD, Kenith E. Meissner, PhD, Veluchamy A. Barathi, Leopold Schmetterer, PhD, Rupesh Agrawal, MD

PII: S0039-6257(17)30232-1

DOI: 10.1016/j.survophthal.2018.03.003

Reference: SOP 6787

To appear in: *Survey of Ophthalmology*

Received Date: 31 August 2017

Revised Date: 19 March 2018

Accepted Date: 19 March 2018

Please cite this article as: Wei X, Balne PK, Meissner KE, Barathi VA, Schmetterer L, Agrawal R, Assessment of flow dynamics in retinal and choroidal microcirculation, *Survey of Ophthalmology* (2018), doi: 10.1016/j.survophthal.2018.03.003.

Xin Wei, MD[1], Praveen Kumar Balne, PhD[2], Kenith E. Meissner, PhD[3], Veluchamy A Barathi[2], Leopold Schmetterer, PhD[2,4,5,6], Rupesh Agrawal, MD[1,2,4*]

Affiliations

[1] National Healthcare Group Eye Institute, Tan Tock Seng Hospital, Singapore.

[2] Singapore Eye Research Institute, Singapore.

[3]Department of Physics, Swansea University, UK.

[4]Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore.

[5]Department of Clinical Pharmacology, Medical University of Vienna, Vienna.

[6]Center for Medical Physics and Biomedical Engineering, Medical University of Vienna, Vienna.

E-mail addresses

Xin Wei (weixin89@gmail.com)

Praveen Kumar Balne (praveen.kumar.balne@seri.com.sg)

Kenith E. Meissner (k.meissner@swansea.ac.uk)

Veluchamy A Barathi (amutha.b.veluchamy@seri.com.sg)

Leopold Schmetterer (leopold.schmetterer@seri.com.sg)

Rupesh Agrawal (rupesh_agrawal@ttsh.com.sg)

*** Corresponding author**

Dr Rupesh Agrawal

National Healthcare Group Eye Institute,

Tan Tock Seng Hospital,

Singapore 308433

Email: rupesh_agrawal@ttsh.com.sg

Conflicts of interest: None

vision loss in patients with various ocular disorders such as diabetic retinopathy, glaucoma, and age-related macular degeneration. Assessment of retinal and choroidal blood flow is also a window to evaluate systemic diseases that affect microvasculature. Quantification and qualification of the blood flow in the retina and choroid help us understand pathophysiology, stratify disease risk, and monitor disease progression in these disorders. Multiple methods are employed by researchers for assessment of blood flow, but a gold standard is lacking. We review commonly used methods, both invasive and non-invasive, for evaluation of blood flow including intravital microscopy, laser Doppler velocimetry, laser Doppler flowmetry, laser interferometry, confocal scanning laser Doppler flowmetry, laser speckle flowgraphy, Doppler optical coherence tomography, blue-field entoptic simulation, retinal vessel calibre assessment, optical coherence tomography angiography, retinal function imaging, color Doppler imaging, and scanning laser ophthalmoscope angiogram. As technology evolves, better evaluation of blood flow in various ocular and systemic diseases will likely bring new perspectives into clinical practice and translate to better diagnosis and treatment.

Key words

Retinal blood flow; choroidal blood flow; optic nerve head blood flow; diabetic retinopathy; glaucoma; age-related macular degeneration.

rich blood supply to bring in nutrients and remove waste. In order to meet the demand of retinal metabolism, there is a dual blood supply : choroidal circulation for the outer part of the retina and choroidal tissues as well as retinal circulation for the inner portion of the retina. The retinal vasculature has a barrier function, similar to the cerebral and renal vasculature, and has the characteristic vascular hierarchy of an end-arterial system. The arterioles supply blood to a superficial capillary network in the nerve fiber layer and to the deeper capillary plexus at the level of the inner nuclear layer. In contrast, choroidal vasculature has a lobular fenestrated capillary system replenishing nutrients to the outer retina, including the photoreceptors. Photoreceptors, being metabolically active, need high blood flow in order to ensure adequate support.[259] A great deal of investigation and research has been conducted and is currently on-going to investigate flow dynamics of retinal and choroidal circulation.[185,209]

Investigating blood flow in retinal and choroidal circulation is imperative for understanding pathophysiology of potentially blinding ocular diseases like diabetic retinopathy (DR), age-related macular degeneration (AMD), glaucoma, vascular occlusion, and ocular inflammatory diseases. Conventional fluorescein and indocyanine green angiograms are based on fluorescence arising from the plasma protein bound dye molecule, but do not provide information on red blood cell (RBC) flow or oxygenation status.[109,57] In retinal and choroidal circulation it is, however, the RBCs that carry oxygen to the tissue and reflect the metabolically efficient circulation.[109,57] Importantly plasma flow and RBC flow do not necessarily equal each other, and their relative relation depends on local hematocrit. Also it needs to be

and vessel irregularities.

Numerous techniques have been researched and employed to quantify blood flow in retinal circulation. The techniques used for examining flow dynamics in retinal and choroidal circulation include intravital microscopy, laser Doppler velocimetry, laser Doppler flowmetry, confocal scanning laser Doppler flowmetry, laser speckle flowgraphy, Doppler optical coherence tomography, blue-field entoptic simulation, retinal vessel calibre assessment, retinal function imager, color Doppler imaging and scanning laser ophthalmoscope fluorescein and indocyanine green angiography.

We will present the advantages and limitations of a number of commonly used techniques used in clinically and research setting. Whereas several recent review articles have focused on regulation of retinal blood flow,[121,156,161,185-187,214,251] there are no recent review papers focusing on the measurement techniques .[209,83]

2. Intravital microscopy

Intravital video microscopy allows direct visualisation of flow dynamics in retinal vessels and computational analysis from these video acquired images.[84] The technique is straightforward and as such has few limitations. Most of the intravital microscopy techniques used fluorescent labelled RBCs as velocity markers and were able to quantify the amount of blood flow in the retinal and possibly choroidal circulation. At the moment the technique is, however, only available for use in experimental animals.

2.1. Using fluorescein labelled microspheres

marker, they have computed the blood flow in mice retinal circulation using video analysis of live retinal vascular imaging. Even though authors tried to correlate the velocity of fluorescein labelled microspheres with that of RBCs, there was a significant difference related to the different properties of RBCs and microspheres in circulation. This may be related to local haematocrit and the difference in vessel size dependent viscosity. Most of the intravital microscopy studies were not based on physiologic conditions and used single or discrete live cell imaging and tracking. Due to the lack of physiologic hematocrit, the blood flow rate calculated in the retinal and choroidal circulation may not provide valid data both in normal and abnormal animal models. Harris and coworkers used micrometer scale on software analysis to convert pixels to µm and did acknowledge several critical assumptions for their technique. These included minimal optical magnification error resulting from the refractive nature of the eye, relatively low optical resolution, dextran filling the entire vascular lumen, vessels area being circular cylindrical, and sampling of velocities represent the mean. Using microspheres, Khoobehi and coworkers obtained a velocity of 1.64 ± 0.78 mm/s in retinal capillaries of rhesus monkey.[110] From these results, it is clear that fluorescein labelled microspheres in circulation do not reasonably approximate RBCs and, therefore, flow results are difficult to transpose onto RBC flow.

2.2. Using fluorescein labelled leukocytes

Scanning laser leukocyte angiography provides real time imaging of the retinal and choroidal circulation using fluorescein labelled leukocytes and scanning laser

Measurement of leukocyte velocity may help detect the relative blood flow in retinal and choroidal tissue that can subsequently be applicable to detecting flow dynamics changes in animal models of DR, vascular occlusion, and occlusive vasculitis.[159] Using a scanning laser ophthalmoscope (SLO) system, digital sequences of moving leukocytes are obtained and, by calculating the movement of leukocytes from one frame to another, the velocity of leukocytes calculated. From the scanning time, the distance in pixels, as well as the velocity, can be calculated using customized software.[159] This approach has been used to study the retinal circulation in rats[112] as well as in non-human primates.[159] The velocity of fluorescently labelled leukocytes in the retinal capillaries of the cynomolgus monkeys was measured to be 0.92 ± 0.32 mm/s.[159]

Improving the labelling further, concanavalin A was substituted for sodium fluorescein as a fluorescent marker, providing a brighter and more stable fluorescent cell label.[88] Yang and co-workers were able to observe leukocyte trafficking using autologous sodium fluorescein labelled leukocytes in humans.[271] This was the first ever study of cellular (inflammatory cells) imaging in human retinal circulation, and the reported mean flow velocity of labelled leukocytes in retinal capillaries was 1.41 +/- 0.29 mm/s.[271] The technique was, however, not followed further for clinical use because of the high experimental efforts and potential safety issues.

Numerous researchers have tried using fluorescein or FITC labeled red blood cells to assess hemodynamics in retinal or systemic circulation. Khoobehi and Peyman used fluorescein labeled RBCs with SLO to assess velocity in retinal arteries of rats but they did not measure velocity in retinal veins or capillaries.[185] There are numerous other studies that have investigated velocities of normal RBCs in retinal circulation in different species.[95,99,109,271]

Wajer and coworkers reported velocity measurements of normal and sickle cell RBCs in the rat retinal and choroidal vasculature.[253] They measured the velocities of RBCs in retinal and choroidal capillaries, as well as in retinal arteries and veins, using FITC labelled rat RBCs and human normal and sickle cell RBCs. By employing SLO, the authors were able to compute velocity in retinal and choroidal circulation from ADPase processed flat mount preparations of the retina.[131] They used a bolus dose of 300 µL of labelled erythrocytes. With a 10% hematocrit and total blood volume of rats being 17 mL, this did not cause a significant increase in hematocrit. They concluded that RBC velocities in retinal capillaries were approximately 4 times higher than in choroidal capillaries, and retention of sickle cell RBCs was shown in ocular vasculatures.[253]

Khoobehi and coworkers obtained RBC velocities of 18.4 ± 1.6 mm/s in retinal arteries and 14.5 ± 3.9 mm/s in retinal veins using a similar method.[108] Jensen and Glucksberg found a large regional distribution of RBC speeds and reported between 0.09 to 2.73 mm/s in peripheral cat retina.[99] In this work, however, they used an endoscope to measure the blood flow velocity, which may not only damage the

The disparity in velocity measurements in retinal circulation between RBC, microspheres and leukocytes may result from size, surface properties (adhesion molecules, receptors, etc.) and membrane stiffness. The difference in velocity of RBC in retinal and choroidal circulation could be attributed to the lobular arrangement and larger volume of the choroidal vasculature and also to the larger luminal diameters of the choroidal capillaries and the numerous flow paths, which is in striking contrast to end arterial system for retinal circulation. The slower flow of RBC in choroidal circulation allows more efficient oxygen exchange that is imperative for higher oxygen demand and higher oxygen consumption in the outer retina as compare to inner retina.[177]

3. Non-invasive tools for assessment of ocular hemodynamics

3.1. Laser Doppler technique for quantitative blood flow analysis

The Doppler effect is the frequency shift of a wave reflected from a moving object. This shift in frequency is proportional to velocity of the moving object and depends on the angle between the velocity vector and the light propagation vector. In the case of retinal blood vessel, the movement of RBCs produce a Doppler shift. The advent of lasers that emit monochromatic coherent light has allowed detection with extremely high resolution of Doppler shift that light undergoes when scattered by a moving particle. As a result, the velocity that can be measured by laser Doppler technique ranges from µm/sec to km/sec. Pioneering work using laser Doppler technique to assess blood flow was done in skin[232] and was later extrapolated into other microvasculature.[10]

based on the optical Doppler effect.[191] Riva and coworkers developed a bi-directional LDV system that detected scattered laser light along two directions so that absolute RBC velocity measurement can be made independent of direction of incident light.[194] Combined with measurement of retinal vessel caliber from fundus photography, volumetric blood flow rate can be calculated.[196] RBC velocity was reported to be in the range of 7-35 mm/s in retinal arteries with diameter between 40-130 µm, and 5-25 mm/s in retinal veins with diameter of 60-180 µm.[47,74,196] Calculated total retinal blood flow ranged from 30-80 µL/min in normal subjects among studies using the LDV technique.[48,64,65,74,196,274] There are several assumptions to be considered in LDV technique for measuring the blood flow dynamics: 1) RBC velocity in a retinal vessel is calculated as mean value from maximum velocity assuming a parabolic flow profile.[65] 2) Vessel diameters from fundus photography or other imaging techniques are calculated based on the assumption of circular lumen in retinal vessels. Different imaging methods may produce different values of vessel diameters depending on their resolution. 3) Total retinal blood flow (TRBF) is estimated by calculation of blood flow in vessels above 50 µm in diameter only. Smaller vessels are not included, but may not contribute much to TRBF. This technique is only used in research settings at the moment.

3.1.2. Laser Doppler flowmetry

Laser Doppler flowmetry (LDF) is another non-invasive technique for assessment of blood flow in vascular tissue. In LDF a coherent laser light illuminates the vascular tissue and measures the Doppler shift induced by moving RBCs.[11] In blood vessels

Based on broadening of the frequency spectrum by moving RBCs, relative blood velocity, volume and flow for a particular amount of tissue can be calculated.[11] The reason why LDF values are expressed in relative units is that Doppler effect is influenced by variations of the optical properties of the tissue arising from differences in structure and vascularization. Therefore comparison between different individuals or between different regions of the same tissue may be problematic.[195] Contrary to blood flow measured by LDV combined with vessel caliber measurement, LDF measures volumetric blood flow by taking into account RBC velocity and RBC volume derived from intensity of signals.[197] Over the last two decades, LDF has been adapted for human use in the measurement of blood flow in the optic nerve head,[197] subfoveal choroid,[193] and iris.[22] LDF values do, however, scale linearly with changes in blood flow. This makes it useful in the assessment of changes in blood flow induced by physiological or pathological stimuli that do not alter optic properties of the tissues.[195] Factors like hyperoxia, hypercapnea, flickering light stimuli, changes in ocular perfusion pressure from isometric exercise and ice water submersion have been shown to change the optic nerve head and choroidal blood flow as measured with LDF.[82,192,213,135] Blood flow measurements using LDF at the peripheral retina appear to be mainly influenced by choroidal blood flow with very little retinal contribution, but that exact sampling depth and the microvessels that contribute most to the signal remain unclear.[180] Apart from interindividual difference in structure and vascularization, blood flow data may also critically depend on the local hematocrit, which is subject to changes induced by pericytes and the endothelium. Hence it is even more difficult to compare healthy and diseased retina.[181,102]

was developed (Heidelberg Retinal Flowmeter, Heidelberg, Germany),[149,150] but is no longer commercially available. It incorporated confocal scanning laser tomography that covers 2560 x 640 μm^2 area with a depth of 400 µm. After confocal scanning is completed, the flowmeter computer system performs a fast Fourier transform to extract the local frequency components of the reflected light. At each point of the scan, a frequency spectrum is computed with blood velocity on x axis of the spectrum and number of the blood cells leading to that frequency pattern on y axis of the spectrum. Integration of spectrum yields local retinal blood flow.[149,150] The flowmeter is designed to analyse a block of 10 $pixel^2$ which is equivalent to 100 μm^2 area of the retinal tissue. The CSLDF instrument's penetrance depth induces a mixed signal of retinal and part of choroidal tissue to an unknown extent, heavily limiting interpretation of results. Other limitations include small sampling areas that do not represent perfusion of the entire retina and inadequate long-term reproducibility.[105]

3.2. Doppler optical coherence tomography

Doppler optical coherence tomography (DOCT) is a functional extension of optical coherence tomography (OCT). Similar to the previously discussed laser techniques, measurement of blood flow is extracted from Doppler shift. In addition to being contactless and dye-free, DOCT has the advantages of providing volumetric information of blood flow together with structural and vascular anatomy.[123] As OCT technology improves resolution, sensitivity and acquisition speed, DOCT is also getting a boost in its application. Using Fourier domain DOCT with orthogonal

corroborating with validity of instruments from their system.[123] Hence, it was possible to measure the total retinal blood flow in the human eye including vessels down to size of 30 µm. Using this highly sophisticated technology, the mean arterial flow measured was 35.7±4.1 µL/min, and the mean venous flow was 36.0±4.5 µL/min.[123,42] The technique has been validated against invasive microsphere technology in a non-human primate model with high Pearson r of 0.976.[247] A few other groups have reported total retinal blood flow based on DOCT using different approaches to extract quantitative perfusion and the values range from 29.7 to 51.4 µL/min. [29,38,42,254,257]

3.3. Laser speckle flowgraphy

Laser speckle flowgraphy (LSFG) is a non-invasive method of measuring optic nerve head, retinal and choroidal blood flow based on laser speckle phenomenon in which interference, termed laser speckle, is observed when coherent light is scattered by a sample. This interference and the resulting laser speckle pattern changes when the sample is non-stationary. In biological tissue, the laser speckle pattern varies due primarily to blood flow. Fercher and Briers first proposed this method[49] and Tamaki and coworkers later developed an LSFG apparatus for quantitative ocular blood flow *in vivo*.[239-241] LSFG reports blood flow as arbitrary units using indices termed normalized blur (NB) and square blur ratio (SBR) in early generation and mean blur rate (MBR) in later development.[118,233] Attempts have also been made to quantify blood flow in single retinal blood vessels by using retinal flow volume (RFV), but the values do not scale linearly with blood flow values.[130,218] Recently new software is developed for LSFG that allows analysis of MBR pulse waveform.[249] Among the new

heartbeats and high blowout score indicates a high constancy of blood flow during the cardiac cycle.[130] The limitations of LSFG include use of arbitrary units which makes comparison or comparison with another technique difficult. It also requires clear media and subject fixation to generate images of good quality.

3.4. Blue-field entoptic simulation

Blue-field entoptic simulation technique, a non-invasive means for measurement of the number and velocity of leukocytes in the human macula, is based on the entoptic phenomenon of observation of one's own leukocytes' movement when looking in to a blue background.[126,198] Test subjects are required to match the global motion of simulated leukocytes displayed on a monitor to that of their own leukocytes by adjusting the number, velocity and velocity pulsatility.[198] Mean leukocyte velocity measured using this method was in the range of 0.23 to 1.9 mm/s.[45,60,128,129,199] The use of this technique is limited by its highly subjective nature.

3.5. Geometric tool for microcirculations – retinal vasculature assessment using semi-automated imaging software

The retina is a unique site for direct visualisation of microcirculation using fundus examination and imaging. Examination of microvasculature with time can offer insight into microcirculatory disturbances in blood flow. Using computer assisted, non-invasive and semi-automated imaging tools, microvasculature can be quantified using numerous different geometric parameters.[125,169] Significant progress and validation of this non-invasive tool in last two decades has provided the ability to measure and quantify changes in microcirculation, and monitor and predict the risk

validate the automated analysis using computer algorithms.[90] Studies have now established strong associations between the microvascular signs on retinal fundus photography and clinical/subclinical outcomes in metabolic, cerebrovascular, and cardiovascular diseases.[125,138,235,267,275] The utility of this tool has been established in atherosclerosis, cardiovascular diseases, hypertension, cerebrovascular diseases, diabetic retinopathy and has also been investigated in patients with HIV disease as a marker for disease progression.[125,235,267,268]

This technique essentially involves assessment of fundus photographs and further assessment of arteriolar calibre, venular calibre and other geometric markers. The software program identifies any vessel larger than 25 µm in diameter and identifies its edges using pixel density histogram. Average cross-sectional diameter of the retinal arterioles and venules is computed from repeated measurements. Intergrader reliability for this method was found to be more than 80% making this tool a very useful non-invasive tool for monitoring of microcirculation.[235,267,268] Individual arteriolar and venular diameters are combined into a summary statistic named arteriole-to-venule ratio (AVR). The AVR accounts for magnification differences between photographs as well as refractive error.[90]

Currently retinal vessel caliber measurement has a few limitations. Data obtained from vessel calibre measurements undergo a significant transformation before converting from pixels to micrometres. Empirical models are used to combine individual retinal vessel calibre into summary measures. In addition, the caliber assessment does not provide information about the relation of the blood flow column

3.6. Retinal function imager

Retinal function imager (RFI) (Optical Imaging, Rehovot, Israel; and Topcon Imaging, Oakland, New Jersey, USA) is a non-invasive imaging technique that visualizes the retinal microvasculature by using hemoglobin in RBCs as an intrinsic contrast agent.[97] RFI uses a computerized camera to take high-resolution fundus images and recognizes the motion of RBCs in retinal vessels by comparing eight images of the retina within a single short interval of 0.14 s. The average RBC velocity measured by RFI in healthy eyes was 4.2 ± 0.9 mm/s in retinal arteries and 3.3 ± 0.8 mm/s in retinal veins.[16] It is the multimodal imaging device that can measure retinal microcirculation, microvascular network and oxygen concentration of the retina in health and disease. Using recently developed algorithms, blood flow and oximetry components of the RFI has been automatized and can help in establishing the value of the RFI in different pathologes.[13-15,17,27,100] The advantages of RFI include direct imaging in the blood flow plane, short image acquisition time, and simultaneous measurement of all vessels in the field of view (20° or 35°). It also provides measurement in standard unit (mm/s) rather than arbitrary unit, which allows comparison between patients.[27] Limitations of the RFI technique include an inability to distinguish different vascular slabs in the retina and choroid and to measure blood flow, because vessel diameters cannot be quantified. Blood velocity values obtained with RFI have not been directly validated against other technologies.

3.7. Color Doppler imaging (CDI)

described in detail.[179] In the central retinal artery, the posterior ciliary arteries and the ophthalmic artery peak systolic velocity (PSV) and end diastolic velocity (EDV) can be measured using this technique. Many authors calculate a resistive index (RI) as (PSV-EDV)/PSV, as a measure of vascular resistance, but there are doubts whether this is an adequate measure in the retina because the relationship between RI and vascular resistance is rather complex.[179] The technique has various limitations that have been discussed in detail.[230] Limitations of CDI include the Doppler probe itself influencing readings when applied to the closed eye lid leading to an increase in intraocular pressure, insufficient resolution to allow measurement of retrobulbar vessel diameters leading to an inability to calculate volumetric blood flow, and poor reproducibility, particularly when measuring small posterior ciliary arteries. For CDI of the ophthalmic artery it needs to be considered that only approximately 25% of the blood flowing through this vessel supplies the eye.[113] In all the measured vessels, ocular blood flow and blood velocities can easily be uncoupled.[53] Results of perfusion parameters from CDI studies in diabetes may be also considerably influenced by a diameter change of retrobulbar arteries, which has been calculated as increased in patients with type 1 diabetes.[171]

3.8. Pneumotonometry for assessment of pulsatile ocular blood flow (POBF)

Pneumotonometry assess the pulsatile ocular blood flow (POBF) by measuring the changes in intraocular pressure (IOP) caused by the pulsatile rhythmic filling of the intraocular vessels during the cardiac cycle. In pneumotonometry, the outcome measure pulse amplitude (PA) refers to the maximum IOP change during the cardiac cycle, and the calculation of POBF from IOP changes with time is based on

studied the POBF levels in patients with untreated diabetic retinopathy and reported increased POBF in diabetic retinopathy compared to controls. The background and pre-proliferative/proliferative retinopathy patients had significantly increased POBF levels compared to controls.[134] Similarly Geyer and coworkers also reported increased POBF with the severity of the retinopathy.[66] Savage and coworkers reported significantly decreased POBF in PDR patients treated with panretinal photocoagulation and no change in diabetic patients with no retinopathy or mild NPDR.[207] Hommer and coworkers reported decreased PA in the patients with primary open-angle glaucoma (POAG) compared to healthy controls.[86]

3.9. Laser interferometry for pulsatile blood flow

Laser interferometry assesses the relative distance changes between cornea and retina during the cardiac cycle and the maximum change in corneo-retinal distance during the cardiac cycle is termed as fundus pulsation amplitude (FPA). FPA is a measure of the pulsatile component of ocular blood flow.[211] Laser interferometry uses a 783 nm wavelength single-mode laser diode with a power of approximately 80 µW to illuminate the eye. The laser beam is reflected at the corneal anterior surface and the retina. The interference fringes produced by the two re-emitted waves from cornea and the retina are captured by a CCD array and forms an interferogram from which the corneo-retinal distance changes during the cardiac cycle can be calculated.[211,212]

Schmetterer and coworkers reported the reduced FPA in AMD patients with classic neovascular membranes.[210] Boltz and coworkers studied the FPA and subfoveal

that the patients with lower choroidal blood flow were associated with higher risk of developing of CNV in the fellow eye.[9] Hommer et al., studied the ocular rigidity calculated from the ratio between PA and FPA measured by using pneumotonometry and laser interferometry, respectively in patients with POAG. They have reported increased ocular rigidity and reduced FPA and PA in POAG patients compared to healthy controls.[86] Both pneumotonometry and laser interferometry measure pulsatile component of ocular blood flow and show a significantly higher association between FPA and PA and FPA and POBF.[208]

3.10. Optical coherence tomography angiography (OCTA)

Optical coherence tomography angiography (OCTA) is a recently developed noninvasive, high contrast and high resolution imaging technique for assessment of ocular blood flow and visualization of the retinal and choroidal vasculature. OCTA is a functional extension of structural OCT that detects motion contrast produced by moving blood cells in retinal vessels by multiple repeated B-scans of the same area of the tissue over a period of time. OCTA assesses the blood flow and generate high resolution microcirculation map by analyzing the variations in signal amplitude and /or phase properties between repeated B-scans. Blood flow in the retinal vessels will produce variation and areas with no blood flow (vessel walls) produce no variation on repeated B-scans.[226,21,225]

There are several algorithms have been developed to compute blood flow measurements from the sequential B-scans. These algorithms are based on OCT signal phase or amplitude or both phase and amplitude (complex signal-based

amplitude-decorrelation angiography (SSADA) algorithm, Speckle-variance OCT, and correlation-mapping OCT; Complex-signal-based OCTA techniques are Optical microangiography (OMAG), Multiple signal classification OMAG and Imaginary part-based correlation mapping OCT.[106] The commercially available OCTA systems include SSADA algorithm based AngioVue system (Optovue, Inc., Fremont, CA, USA),[89] OMAG algorithm based AngioPlex system (Carl Zeiss Meditec Inc., Dublin, CA, USA) spectral domain OCTA,[202] amplitude decorrelation algorithm based swept-source optical coherence tomography Angio (Topcon Corp., Japan),[231] and OCTA ratio analysis algorithm based Heidelberg Spectralis OCTA (Heidelberg, Germany).[227]

OCTA has potential applications in evaluation and management of various eye diseases like age related macular degeneration,[201,237,32] diabetic retinopathy,[136,92] diabetic macular edema,[40] choroidal neovascularization,[39] retinal vascular occlusion,[162] glaucoma,[23] uveitis and ocular inflammation.[175] Though OCTA is a non-dye based method that acquires volumetric angiographic information and allows visualization of all layers of retinal blood vessels, it cannot identify the leakage patterns, staining, and pooling seen in conventional fluorescein angiogarphy.[227] Presence of motion artifacts in the background is the most common problem in OCTA from eye movement, intrinsic ocular features, image processing and display strategies. With OCTA steady fixation is necessary to acquire high quality images.[226]

4. Fluorescein and Indocyanine green angiogram for flow dynamics assessment

estimating retinal blood flow. SLO is based on principle of confocal microscopy and is designed for clinical ophthalmoscopy and fluorescein and indocyanine green angiography. With better understanding of this instrument and technology, the applications of scanning laser ophthalmoscopy has broadened to assess hemodynamics in retinal and, possibly, choroidal circulation.[43,165] It uses a finely focused laser beam scanned at video rates across the inside of the eye. Light reflected from the retina and choroid is focused using confocal optics at a pinhole aperture placed in front of the light detector.[43] Taking advantage of scattered light removal by the confocal effect, the resultant image signal is of very high contrast and clearly defined to produce final images of the retina and choroid. As it does not need high amount of irradiation, it is an eye-safe method to image the retina and choroid at low light intensity. SLO also has the advantage of depth discrimination and, by using confocal effect, it can separately image retinal and choroidal vessels of the eye.

4.1.1. Fluorescein angiography

Fluorescein angiography is an important clinical tool for retinal blood flow assessment.[163] While usually yielding qualitative information, quantitaative infomation about retinal blood flow can be achieved, especially when using an SLO.

Fluorescein angiography was originally performed using a fundus camera providing measurements such as mean circulation time (MCT) and arteriovenous passage time (AVP). Relative concentration of fluorescein in retinal vessels can be obtained from densitometric measurements on retinal photographs. Dye dilution curves are

average time it takes for dye molecules to travel from entry to exit of a vascular segment.[85] This technique is further refined using videoangiography.[19,188] AVP, defined as the time between the first appearance of the dye in a retinal artery and in the corresponding vein, is developed as an alternative to MCT.[262] While MCT gives more weight to peripheral retinal circulation, AVP represents the passage time of dye through the shortest segment close to the papilla. An important limitation to this technique is the assumption that all the blood of a volume supplied by a specific artery is drained by a specific vein. Leakage and vasodilation from various pathologies may also affect MCT and AVP measurements.

SLO allows visualisation of retinal, especially perifoveal, microcirculation.[243,262] Using SLO-based fluorescein angiography, quantitative assessment of perifoveal capillary circulation can be achieved using manual tracking (plotting method) or tracing method.

Plotting method: Using 10% sodium fluorescein and an SLO system at an angle of 20^0, macular images can be obtained within 1 min of dye injection. Digital images are subsequently analysed offline to identify fluorescent dots moving in perifoveal capillaries. Frame rate of 30 frames per second are used to identify and trace movement of fluorescent dots. Time sequenced images are analysed to calculate the velocity of fluorescent dots hence quantitative assessment of the blood flow using fluorescent dots was obtained.[271] Littmann curve formula using corneal curvature, refraction, and axial length was used to correct for anatomical variations between individual eyes.[5] As fluorescence of the moving dots can be of inadequate intensity, it is not considered a practical method.

In this method, the entire capillaries are traced and 150 images collected during 5 second periods, and these images are placed next to each other. Movement of the fluorescent bright dots is detected as a continuous shadow image along the reconstructed image. The blood flow velocity is then calculated from the total time period (distance between start and end points of the inclined shadow).[62] A major advantage of this method is that movements of almost all the fluorescent dots within a particular vessel could be analysed by tracing the target capillary.

Nature of fluorescent dots on tracing or plotting method is controversial. The fluorescent dots are well defined and discrete with a size that can be larger than diameter of perifoveal capillary. As postulated by Yang and coworkers the fluorescent dots are unlikely to be stained plasma as plasma fluorescence is not detectable in microcirculation.[272] It is likely that fluorescent dots are stained leukocytes as they could be seen in microcirculation, and erythrocytes do not take up stain. Therefore blood flow velocity by tracing or plotting method may be actually representing leukocyte velocity. The variations in the flow velocity of multiple fluorescent dots moving through the same capillary are accounted for by the shape of the capillary, variable dot size, and pulsations of the blood flow. Nevertheless, as circulating leukocytes move more slowly than erythrocytes owing to their larger size, reduced deformability and increased tendency to adhere to the vascular endothelium, it is difficult to postulate actual blood flow velocity using this technique.

4.1.2. Indocyanine green (ICG) angiography

affinity for plasma protein. Extraction of quantitative blood flow parameters is, however, difficult and there is no automated software to generate choroidal blood flow parameters in SLO ICG angiogram. Harris and coworkers described a technique called area dye-dilution analysis that generates 3 parameters: 10% filling time that represents rapidity of early choroidal filling phase, the slope of curve that represents the overall speed of blood entering the choroid, and maximum intensity of brightness that represents the overall vascular density of choroid.[83] The technique has, however, not gained wide-spread use.

5. Applications of flow dynamics assessment in ocular pathology

5.1. Diabetic retinopathy

For 4 decades, diabetic retinopathy (DR) has been implicated in alterations of retinal blood flow.[117] Various modalities of blood flow assessment were carried out to investigate the extent of such disturbance.

LDV predominates in early studies comparing retinal blood flow in diabetic patients. Calculated total retinal blood flow using LDV was similar in normal patients and diabetics with no DR, background DR, proliferative diabetic retinopathy (PDR); however, it was reduced after panretinal photocoagulation (PRP).[69,76] Lorenzi amd coworkers also showed no significant change in retinal blood flow in type 1 diabetes mellitus (T1DM) patients with no or minimal retinopathy who maintained relatively good glycemic control.[127] This observation was, however, not consistent with Patel and coworkers who reported total retinal blood flow was significantly increased in all stages of DR in comparison with non-diabetic controls and diabetics with no

T1DM. With longer duration of DM and more severe DR, there was a transition from negative to positive retinal blood flow slopes.[119] Pemp and coworkers demonstrated that T1DM patients with no or mild DR had fluctuating retinal blood flow with fluctuating plasma glucose level, which may contribute to microvascular changes.[173] For type 2 diabetes mellitus (T2DM), retinal blood flow was reported as significantly lower in eyes with no DR or mild non-proliferative DR (NPDR) compared to non-diabetic eyes.[155]

Assessment of retinal blood flow using CSLDF and LDF became available over the last 15 years or so. Findl and coworkers reported no significant differences in retinal blood flow with progression of DR in patients with T1DM.[51] Another study, however, reported retinal blood flow in the perifoveal and nasal areas was associated with the level of diabetic retinopathy, with reduction in blood flow in PDR compared to NPDR or pre-PDR.[37] LDF allowed assessment of choroidal blood flow.[193] Foveal choroidal blood flow was shown to be significantly decreased in patients with NPDR, especially those with macular edema,[154] and with PDR.[215] After PRP treatment, an increase in foveal choroidal blood flow has been reported.[236] CSLDF results and also measurements with LDF in macular edema are difficult to interpret due to interindividual variability of tissue properties.[37,51] In LDF the laser penetrates only 300-500 µm. Hence increased tissue thickness in diabetic macular edema may influence the reflected signal of the power Doppler spectrum. Subfoveal choroidal blood flow, however, seems to be more consistently reduced in diabetes.

Research on retinal and choroidal blood flow in DR using LSFG is limited at the moment. Nitta and coworkers showed blood flow as measured by MBR in the retinal

Okamoto et al. reported subfoveal choroidal blood flow decreased significantly after PRP treatment.[164]

Wang et al. first used DOCT to study retinal blood flow and reported a diabetic patient with PDR had reduced total retinal blood flow while diabetic patient with no DR had similar total retinal blood flow compared to control;[255] however, there was only 1 patient in each group. Recently, studies have shown that total retinal blood flow was significantly lower in eyes with all stages of NPDR and PDR.[111,229,244] Lee and coworkers reported retinal blood flow in patients with PDR were decreased at baseline, but did not decrease further after PRP.[122]

Blue field entoptic simulation technique was used to assess perifoveal capillary blood flow in DR. Sinclair reported increased capillary flow velocity with decreased density of the entoptically perceived leukocytes in diabetic eyes.[223] It was later shown that increased flow in the macular microcirculation may be associated with progression of DR;[75] however, a more recent report on T1DM patients with no or minimal retinopathy did not show significant difference in macular capillary blood flow.[166] Abnormal autoregulation of capillary blood flow was also demonstrated by this technique. Patients with DR showed a blunted response of macular capillary blood flow to isocapnic hypoxia and intraocular pressure changes.[46,222]

Retrobulbar hemodynamics was evaluated with CDI. Studies have shown that perfusion velocity was reduced in eyes with DR in central retinal artery,[68,133,41] ophthalmic artery[94] or both.[139] RI was shown to be increased in diabetic patients with or without retinopathy in ophthalmic artery[41,242] and central retinal artery.[1]

observed by CDI. There was an increase in perfusion velocities in ophthalmic artery, posterior ciliary artery and central retinal artery shortly (30 minutes) after PRP treatment; however the same group reported a reduction in the perfusion velocity in ophthalmic artery 6 months to 2 years after PRP treatment.[140] After vitrectomy, there were conflicting reports on changes of perfusion velocity in central retinal artery and posterior ciliary artery.[120,234]

Few reports have been published on ocular blood flow measured by RFI and SLO FA/ICGA. Using RFI, interesting observations were made indicating that diabetic patients with no DR had increased flow velocity while those with NPDR had reduced flow velocity compared to normal.[13,18] Using SLO FA by the tracing method, perifoveal capillary blood flow velocity was shown to be significantly decreased in patients with clinically significant macular edema (CSME) (0.94+/-0.09 mm/s) compared with patients without CSME (1.22+/-0.20 mm/s) and healthy volunteers (1.49+/-0.11 mm/s).[206]

5.1.1. Factors associated with blood flow changes in diabetic retinopathy

Retinal blood flow was found to be higher in diabetic patients, with or without diabetic retinopathy, compared to healthy controls.[173,157] Retinal blood flow rate was proportional to plasma glucose levels[12] and positively associated with severity of the diabetic retinopathy.[157] In long term hypertensive patients significantly reduced retinal capillary flow and retinal capillary rarefaction was observed compared to the healthy subjects.[12] Intensive glycemic and blood pressure control showed no effect of on incidence and progression of DR and suggest that there might be other processes

venular calibers are associated with presence, progression and severity of DR and incident of PDR[217,248,203,115] and wider retinal arterioles are associated with risk of DR.[26,200] Retinal arteriolar diameters were significantly reduced in patients with improved DR in a longitudinal study.[170] Foveal superficial capillary plexus showed capillary rarefaction with nonperfusion areas in patients with DR.[36] The retinal microvascular changes in DR may be related to retinal blood flow alterations secondary to the retinal hypoxia and metabolism. Sousa and coworkers studied mild hypoxia-induced retinal microvascular changes in healthy subjects using OCTA. Parafoveal and peripapillary vessel densities were significantly increased in both eyes of subjects under hypoxic conditions and in post-hypoxic conditions vessel densities were decreased to near-baseline values.[224] Vascular response to a vasoactive stimulus (hypoxia and hyperoxia) is called as vascular reactivity which plays key role in maintaining homeostasis in hemodynamics against various pathophysiological conditions. In healthy subjects retinal vascular diameter and retinal blood flow increases in response to hypoxia and decreases with hyperoxia.[25] In patients with diabetes and DR, vascular reactivity was impaired.[104,67]

In summary, substantial research has been performed to elucidate retinal and choroidal blood flow disturbances in the pathogenesis and progression of DR. However, results are often conflicting, likely due to differences in measurement techniques, inclusion criteria and sample sizes. Comparison of the techniques in a carefully selected patient cohort with adequate size would be helpful in the future.

5.2. Glaucoma

Therefore, the main interest of research on blood flow in glaucoma lies in studying perfusion in the ONH.

Jonas and coworkers reported decreased peripapillary vessel diameter in glaucoma patients, which was also associated with increased severity.[103] Hamard and coworkers used LDV, but actually applied the LDF technique to study ONH blood flow in glaucoma patients and shown that capillary RBC flow velocity was reduced in primary open angle glaucoma (POAG) and normal tension glaucoma (NTG).[81]

The bulk of research on ocular blood flow and glaucoma came from studies with LDF and CSLDF. ONH flow and juxtapapillary blood flow were shown to be decreased in POAG patients[52,72,73,147,148] and NTG patients.[30] This, however, was not repeated in one report by Nicolela and coworkers. Using the same technique, they showed POAG patients had less blood volume, flow, and velocity in the lamina cribrosa and upper temporal peripapillary retina, but there was no difference in blood flow in the neuroretinal rim.[158] It was further shown that ONH blood flow was reduced in POAG suspects who did not manifest visual field abnormalities compared to normal patients, but similar to POAG patients.[176] Hafez and co-workers showed that ONH blood flow was reduced in POAG patients but not in ocular hypertension (OHT) patients compared to normal.[79] With progression of glaucoma, Ciancaglini and coworkers showed change in blood flow to the lamina cribrosa, but not to neuroretinal rim, was associated with visual field damage in POAG using CSLDF.[31] It was also shown that reduced ONH blood flow, rather than retinal or choroidal blood flow, was associated with more visual field loss and disc morphological changes in

Regional distribution of ONH blood flow was studied with LDF and it was shown that temporal neuroretinal rim blood flow was lower on the nasal side in normal patients, which might underscore the increased susceptibility of temporal rim in glaucoma.[8] Comparing POAG and OHT, a significant reduction in blood flow has been observed at the lamina cribrosa and the temporal neuroretinal rim, but not at the nasal neuroretinal rim or the nasal juxtapapillary retina in POAG.[107] Interestingly, following a similar percentage of IOP reduction, POAG patients, but not OHT patients, had a statistically significant improvement of blood flow in the neuroretinal rim of the ONH.[80] This might suggest ONH blood flow autoregulation was defective in POAG while intact in OHT. Vascular dysregulation was supported by studies from Fuchsjäger-Mayrl and coworkers which showed reduced ONH blood flow and an abnormal correlation with mean arterial blood pressure in POAG/OHT patients[61] and from Pemp and coworkers that showed patients with POAG have a larger diurnal fluctuation of ONH blood flow parameters.[172] Weigert and cowrkers did not find significant difference in ONH blood flow after moderate change in IOP between POAG and control using CSLDF, but the changes in ocular perfusion pressure were too small to draw conclusion on disturbance of autoregulation.[258] In NTG patients, there was also no significant change in ONH blood flow following an increase in perfusion pressure after exercise, but again the change in ocular perfusion pressure was small.[184]

Retinal and choroidal blood flow was also studied using LDF in glaucoma patients. Retinal blood flow was shown to decline with time in POAG patients and it was associated with structural glaucomatous progression.[245] Subfoveal choroidal blood

be statistically different between POAG and normal eyes.[116] Subfoveal choroidal blood flow did display increased short-term variability[116] as well as stronger increase in response to exercise-induced blood pressure change[182] in POAG patients, supporting a vascular dysfunction theory.

There has also been substantial research on ocular blood flow in glaucoma patients using CDI. A meta-analysis that included 23 prospective studies showed reduced PSV, reduced EDV and increased RI in all retrobulbar vessels (ophthalmic artery, central retinal artery and short posterior ciliary artery) in POAG patients.[141] Decreased perfusion velocity and increased RI were also demonstrated in some or all of the retrobulbar vessels in angle-closure glaucoma (ACG)[24] and NTG.[178] In addition, CDI was implicated in glaucoma prognosis. Perfusion velocity in ophthalmic artery was shown to correlate with functional and structural progression in POAG patients.[63,152]

Studies using newer techniques such as LSFG and DOCT were only available more recently. Using LSFG, blood flow to the neuroretinal rim measured by SBR was associated with visual field defect in NTG but not POAG group.[273] ONH blood flow measured by LSFG was shown to be reduced in preperimetric glaucoma and mild NTG patients.[219] LSFG measurements of waveform changes in ONH blood flow could differentiate NTG eyes from normal.[220] In contrary to a study using CSLDF, ONH blood flow measured by NB using LSFG did not change significantly with trabeculectomy.[238] DOCT studies mainly focused on retinal blood flow and glaucoma. Retinal blood flow as measured by DOCT was reduced in glaucomatous eyes[91,256] and was a predictor of visual field loss independent of structural loss

the affected hemisphere, which was also associated with thinner RNFL.

Blue-field entoptic simulation, RFI and SLO FA/ICGA have been less commonly used to investigate glaucoma. An early report showed blunted hyperemic response, as measured by macular blood flow using blue-field entoptic simulation following induced IOP change was evident in POAG eyes, suggesting an abnormal autoregulation.[77] Another study showed higher leucocyte velocity was associated with less visual field loss in glaucoma patients.[228] Using RFI, changes in retinal blood flow velocity were only evident in pre-perimetric glaucoma, but not in perimetric glaucoma.[15] Using SLO fluorescein angiography, prolonged arteriovenous passage time and reduced mean dye velocity were associated with glaucoma group.[260,3]

In summary, even though there are some contradictory results, most evidence from available studies appears to support the notion of compromised blood flow and loss of effective autoregulation in the ONH in glaucoma patients. With newer techniques of measurement available, more research would be needed to find out whether this was the cause or the result of glaucomatous damage.

5.3. Age-related macular degeneration (AMD)

Pathogenesis of AMD is again multifactorial, and ocular perfusion abnormalities, especially disturbance on choroidal blood flow may be a contributing factor to the pathological changes.[35,174] Inconsistent observations existed regarding retinal vessel calibre measured on fundus photograph and AMD. Early AMD was associated with wider venular diameter in a Singaporean study[98] and with wider arteriolar diameter in

Again, LDF and CSDLF provided significant contribution to the understanding of retinal and choroidal blood flow in AMD. In patients with dry AMD, subfoveal choroidal blood flow was reduced compared to normal.[70] This reduction was associated with increased drusen extent[6] and other features associated with risk for development of choroidal neovascularization (CNV).[71] Reduction in subfoveal choroidal blood flow in dry AMD patients was augmented by systemic hypertension, which might contribute to progression of disease.[146] In a longitudinal study on patients with dry AMD, lower choroidal blood flow at baseline was associated with the development of CNV and reduction in the foveolar choroidal circulation precede the development of CNV in AMD.[144] This observation was supported by another longitudinal study on fellow eyes of AMD patients with unilateral CNV.[9] A similar design to study vascular autoregulaton in glaucoma patient was adopted in AMD. Pournaras and coworkers showed subfoveal choroidal blood flow increased in neovascular AMD patients and remained stable in normal patients in response to moderate increase in ocular perfusion pressure induced by isometric exercise, indicating altered regulation of choroidal blood flow in neovascular AMD;[183] however, this was not the case in dry AMD patients.[145]

With LDF and CSLDF, blood flow changes in response to treatment were studied. Patients with dry AMD who underwent low intensity photocoagulation had an increase in choroidal blood flow 28 months after treatment.[50] In patients with subfoveal CNV secondary to AMD, there was no significant change in choroidal blood flow after photodynamic therapy.[132,252] Fontaine and coworkers showed retinal arteriolar diameter decreased and arterial blood flow remained stable after

in retinal arteriolar diameter, arteriolar blood flow velocity, and blood flow in patients who have received <1.50 mg of ranibizumab.[151] No reports on choroidal blood flows changes after intravitreal anti-vascular endothelial grow factor in AMD patients have yet been published.

Using CDI, a decreased perfusion velocity and increased pulsatility index (defined as (PSV-EDV)/temporal average of velocity) was reported in posterior ciliary artery in patient with AMD,[33,59,87] and the observation was more pronounced in neovascular AMD.[250] After intravitreal bevacizumab treatment, Mete and coworkers noted reduction in perfusion velocity in posterior ciliary ateries.[143] In addition, Toklu and coworkers reported bevacizumab therapy decreased perfusion velocities and increased RI in both posterior ciliary artery and central retinal artery in the early postoperative period and returned to preoperative values at 1 month.[246] Mixed results (unchanged or increased blood flow) were reported after ranibizumab therapy in neovascular AMD patients.[142,205] There were no significant changes in retrobulbar blood flow after combined treatment of intravitreal triamcinolone and photodynamic therapy.[20]

Using SLO ICG angiography, delayed and heterogeneous choroidal filling pattern was shown in non-neovascular AMD patients.[34] Research on retinal blood flow and AMD is rather limited so far. Burgansky-Eliash and coworkers reported decreased retinal arterial flow velocity in AMD patients using RFI.[14] Currently there was no published studies using LSFG, DOCT, or blue field entoptic simulation on blood flow in AMD patients.

relationship. There is also a lack of evidences using newer techniques to evaluate retinal and choroidal blood flow in AMD patients. Further studies are warranted.

6. Applications of flow dynamics assessment in systemic pathology

The easy accessibility of retinal and choroidal microvasculature permits non-invasive evaluation of systemic diseases that affect microcirculation. As mentioned in section 3.5, the association between retinal vessel calibre and systemic diseases, such as diabetes, hypertension, stroke, and coronary artery disease, are evident in a number of large scale studies.[263-266] There is also literature on retinal and choroidal blood flow in association with systemic diseases, although the evidence is relatively weak.

Atherosclerosis is a systemic vasculopathy that affects several arterial beds. Using LDV, it was shown that in patients with coronary artery disease, the retinal blood velocity correlated independently with intima-media thickness (IMT), a marker of carotid atherosclerosis.[153] Retinal arteriolar blood flow measured by RFI was found to be inversely associated with coronary blood flow.[2] This may help detect individuals who are at risk of developing coronary atherosclerosis. Using LSFG, it was noted that parameters of pulse waveform analysis in the ONH including blowout time and blowout score were associated with parameter of carotid atherosclerosis, such as IMT and severity of carotid arterial plaque.[190] Multiple sclerosis (MS) is an inflammatory disease of the central nervous system. It was suggested that MS would result in primary retinopathy reflecting global central nervous system atrophy.[204] Using RFI, Jiang and coworkers first reported significant reduction in retinal blood flow velocity and volume in patients with relapsing remitting MS.[101]

and monitor disease progression by non-invasive evaluation of retinal and choroidal microvasculature. With more techniques available, more studies in the future are expected.

7. Summary and future scope

We present various methods of assessing retinal and choroidal blood flow. One important limitation of current research in ocular blood flow is that there is no gold standard technique. Therefore, it is difficult to compare results arising from different assessment techniques. Nevertheless, each method is able to evaluate certain aspects of ocular hemodynamics from which important knowledge about pathophysiology can be derived. DR, glaucoma, and AMD are three of the most common ocular diseases that significantly burden global health. Disturbance of ocular blood flow has been implicated in all three disorders to varying degrees. Assessment of retinal and choroidal blood flow is also a window to evaluate systemic diseases that affects microvasculature. As technology evolves, better evaluation of blood flow in various ocular and systemic diseases will likely bring new perspectives into clinical practice and translate to better diagnosis and treatment.

scanning the database for all literature published to date in English language.

1. Arai T, Numata R, Tanaka R, et al. Ocular arterial flow hemodynamics in patients with diabetes mellitus. J Ultrasound Med. 1998;17(11):675-81
2. Arbel Y, Sternfeld A, Barak A, et al. Inverse correlation between coronary and retinal blood flows in patients with normal coronary arteries and slow coronary blood flow. Atherosclerosis. 2014;232(1):149-54
3. Arend O, Remky A, Plange N, et al. Capillary density and retinal diameter measurements and their impact on altered retinal circulation in glaucoma: a digital fluorescein angiographic study. Br J Ophthalmol. 2002;86(4):429-33
4. Behrendt T, Wilson LA. Spectral reflectance photography of the retina. Am J Ophthalmol. 1965;59:1079-88
5. Bennett AG, Rudnicka AR, Edgar DF. Improvements on Littmann's method of determining the size of retinal features by fundus photography. Graefes Arch Clin Exp Ophthalmol. 1994;232(6):361-7
6. Berenberg TL, Metelitsina TI, Madow B, et al. The association between drusen extent and foveolar choroidal blood flow in age-related macular degeneration. Retina. 2012;32(1):25-31
7. Berisha F, Schmetterer K, Vass C, et al. Effect of trabeculectomy on ocular blood flow. Br J Ophthalmol. 2005;89(2):185-8
8. Boehm AG, Pillunat LE, Koeller U, et al. Regional distribution of optic nerve head blood flow. Graefes Arch Clin Exp Ophthalmol. 1999;237(6):484-8
9. Boltz A, Luksch A, Wimpissinger B, et al. Choroidal blood flow and progression of age-related macular degeneration in the fellow eye in patients with unilateral choroidal neovascularization. Invest Ophthalmol Vis Sci. 2010;51(8):4220-5

11. Bonner RF, Nossal R. Chapter 2. Principles of laser-Doppler flowmetry. In: Shepherd AP, Oberg PA, eds. Laser-Doppler Blood Flowmetry. Kluwer Academic Publishers, 1990: p. 17-45
12. Bosch AJ, Harazny JM, Kistner I, Friedrich S, Wojtkiewicz J, Schmieder RE. Retinal capillary rarefaction in patients with untreated mild-moderate hypertension. BMC Cardiovasc Disord. 2017; 17(1):300
13. Burgansky-Eliash Z, Barak A, Barash H, et al. Increased retinal blood flow velocity in patients with early diabetes mellitus. Retina. 2012;32(1):112-9
14. Burgansky-Eliash Z, Barash H, Nelson D, et al. Retinal blood flow velocity in patients with age-related macular degeneration. Curr Eye Res. 2014;39(3):304-11
15. Burgansky-Eliash Z, Bartov E, Barak A, et al. Blood-Flow Velocity in Glaucoma Patients Measured with the Retinal Function Imager. Curr Eye Res. 2016;41(7):965-70
16. Burgansky-Eliash Z, Lowenstein A, Neuderfer M, et al. The correlation between retinal blood flow velocity measured by the retinal function imager and various physiological parameters. Ophthalmic Surg Lasers Imaging Retina. 2013;44(1):51-8
17. Burgansky-Eliash Z, Lowenstein A, Neuderfer M, et al. The Correlation Between Retinal Blood Flow Velocity Measured by the Retinal Function Imager and Various Physiological Parameters. Ophthalmic Surg Lasers Imaging Retina. 2013;44(1):51-8

19. Bursell SE, Clermont AC, Shiba T, King GL. Evaluating retinal circulation using video fluorescein angiography in control and diabetic rats. Curr Eye Res. 1992;11(4):287-95
20. Cekic O, Bardak Y, Yesildag A. Color Doppler imaging of ocular blood flow after combined photodynamic therapy with intravitreal triamcinolone in age-related macular degeneration. Curr Eye Res. 2011;36(2):149-53
21. Chalam KV, Sambhav K. Optical coherence tomography angiography in retinal diseases. J Ophthalmic Vis Res. 2016; 11(1):84-92
22. Chamot SR, Movaffaghy AM, Petrig BL, Riva CE. Blood flow in the human iris measured by laser Doppler flowmetry. Microvasc Res. 1999;57(2):153-61
23. Chen CL, Bojikian KD, Wen JC, et al. Peripapillary Retinal Nerve Fiber Layer Vascular Microcirculation in Eyes With Glaucoma and Single-Hemifield Visual Field Loss. JAMA Ophthalmol. 2017; 135(5): 461–8
24. Cheng CY, Liu CJ, Chiou HJ, et al. Color Doppler imaging study of retrobulbar hemodynamics in chronic angle-closure glaucoma. Ophthalmology. 2001;108(8):1445-51
25. Cheng RW, Yusof F, Tsui E, et al. Relationship between retinal blood flow and arterial oxygen. J Physiol. 2016; 594(3):625-40
26. Cheung N, Rogers SL, Donaghue KC, et al. Retinal arteriolar dilation predicts retinopathy in adolescents with type 1 diabetes. Diabetes Care 2008; 31:1842–1846

Clin Exp Ophthalmol. 2013;251(12):2665-70

28. Chin YC, Wong TY, Cheung CM, et al. Retinal vascular caliber and age-related macular degeneration in an Indian population from Singapore. Ophthalmic Epidemiol. 2014;21(4):224-9
29. Choi W, Baumann B, Liu JJ, et al. Measurement of pulsatile total blood flow in the human and rat retina with ultrahigh speed spectral/Fourier domain OCT. Biomed Opt Express. 2012;3(5):1047-61
30. Chung HS, Harris A, Kagemann L, Martin B. Peripapillary retinal blood flow in normal tension glaucoma. Br J Ophthalmol. 1999;83(4):466-9
31. Ciancaglini M, Carpineto P, Costagliola C, Matropasqua L. Perfusion of the optic nerve head and visual field damage in glaucomatous patients. Graefes Arch Clin Exp Ophthalmol. 2001;239(8):549-55
32. Cicinelli MV, Rabiolo A, Sacconi R, et al. Optical coherence tomography angiography in dry age-related macular degeneration. Surv Ophthalmol. 2017; pii: S0039-6257(17)30059-0. doi: 10.1016/j.survophthal.2017.06.005. [Epub ahead of print]
33. Ciulla TA, Harris A, Chung HS, et al. Color Doppler imaging discloses reduced ocular blood flow velocities in nonexudative age-related macular degeneration. Am J Ophthalmol. 1999;128(1):75-80
34. Ciulla TA, Harris A, Kagemann L, et al. Choroidal perfusion perturbations in non-neovascular age related macular degeneration. Br J Ophthalmol. 2002;86(2):209-13

36. Couturier A, Mane V, Bonnin S, et al. Capillary plexus anomalies in diabetic retinopathy on optical coherence tomography angiography. Retina. 2015; 35(11):2384-91
37. Cuypers MH, Kasanardjo JS, Polak BC. Retinal blood flow changes in diabetic retinopathy measured with the Heidelberg scanning laser Doppler flowmeter. Graefes Arch Clin Exp Ophthalmol. 2000;238(12):935-41
38. Dai C, Liu X, Zhang HF, et al. Absolute retinal blood flow measurement with a dual-beam Doppler optical coherence tomography. Invest Ophthalmol Vis Sci. 2013;54(13):7998-8003
39. de Carlo TE, Bonini Filho MA, Chin AT, Adhi M, Ferrara D, Baumal CR, et al. Spectral‐domain optical coherence tomography angiography of choroidal neovascularization. Ophthalmology. 2015; 122(6):1228‐38
40. de Carlo TE, Chin AT, Joseph T, et al. Distinguishing diabetic macular edema from capillary nonperfusion using optical coherence tomography angiography. Ophthalmic Surg Lasers Imaging Retina. 2016; 47(2):108e14
41. Dimitrova G, Kato S, Tamaki Y, et al. Choroidal circulation in diabetic patients. Eye (Lond). 2001 Oct;15(Pt 5):602-7
42. Doblhoff-Dier V, Schmetterer L, Vilser W, et al. Measurement of the total retinal blood flow using dual beam Fourier-domain Doppler optical coherence tomography with orthogonal detection planes. Biomed Opt Express. 2014;5(2):630-42

Lippincott-Raven; 1997

44. Evans DW, Harris A, Danis RP, et al. Altered retrobulbar vascular reactivity in early diabetic retinopathy. Br J Ophthalmol. 1997;81(4):279-82
45. Fallon TJ, Maxwell D, Kohner EM. Measurement of autoregulation of retinal blood flow using the blue field entoptic phenomenon. Trans Ophthalmol Soc U K. 1985;104 (Pt 8):857-60
46. Fallon TJ, Maxwell DL, Kohner EM. Autoregulation of retinal blood flow in diabetic retinopathy measured by the blue-light entoptic technique. Ophthalmology. 1987 Nov;94(11):1410-5
47. Feke GT, Goger DG, Tagawa H, Delori FC. Laser Doppler technique for absolute measurement of blood speed in retinal vessels. IEEE Trans Biomed Eng. 1987;34(9):673-80
48. Feke GT, Tagawa H, Deupree DM, et al. Blood flow in the normal human retina. Invest Ophthalmol Vis Sci. 1989;30(1):58-65
49. Fercher AF, Briers JD. Flow visualization by means of single-exposure speckle photography. Optics Communications. 1981;37(5):326-30
50. Figueroa M, Schocket LS, DuPont J, et al. Long-term effect of laser treatment for dry age-related macular degeneration on choroidal hemodynamics. Am J Ophthalmol. 2006;141(5):863-7
51. Findl O, Dallinger S, Rami B, et al. Ocular haemodynamics and colour contrast sensitivity in patients with type 1 diabetes. Br J Ophthalmol. 2000;84(5):493-8
52. Findl O, Rainer G, Dallinger S, et al. Assessment of optic disk blood flow in patients with open-angle glaucoma. Am J Ophthalmol. 2000;130(5):589-96

54. Flammer J, Orgul S, Costa VP, et al. The impact of ocular blood flow in glaucoma. Prog Retin Eye Res. 2002;21(4):359-93
55. Flammer J, Orgul S. Optic nerve blood-flow abnormalities in glaucoma. Prog Retin Eye Res. 1998;17(2):267-89
56. Flammer J. The vascular concept of glaucoma. Surv Ophthalmol. 1994;38 Suppl:S3-6
57. Flower RW. Extraction of choriocapillaris hemodynamic data from ICG fluorescence angiograms. Invest Ophthalmol Vis Sci. 1993;34(9):2720-9
58. Fontaine O, Olivier S, Descovich D, et al. The effect of intravitreal injection of bevacizumab on retinal circulation in patients with neovascular macular degeneration. Invest Ophthalmol Vis Sci. 2011;52(10):7400-5
59. Friedman E, Krupsky S, Lane AM, et al. Ocular blood flow velocity in age-related macular degeneration. Ophthalmology. 1995;102(4):640-6
60. Fuchsjager-Mayrl G, Malec M, Polska E, et al. Effects of granulocyte colony stimulating factor on retinal leukocyte and erythrocyte flux in the human retina. Invest Ophthalmol Vis Sci. 2002;43(5):1520-4
61. Fuchsjager-Mayrl G, Wally B, Georgopoulos M, et al. Ocular blood flow and systemic blood pressure in patients with primary open-angle glaucoma and ocular hypertension. Invest Ophthalmol Vis Sci. 2004;45(3):834-9
62. Funatsu H, Sakata K, Harino S, et al. Tracing method in the assessment of retinal capillary blood flow velocity by fluorescein angiography with scanning laser ophthalmoscope. Jpn J Ophthalmol. 2006;50(1):25-32

64. García JP, Jr., García PT, Rosen RB. Retinal blood flow in the normal human eye using the canon laser blood flowmeter. Ophthalmic Res. 2002;34(5):295-9
65. Garhofer G, Werkmeister R, Dragostinoff N, Schmetterer L. Retinal blood flow in healthy young subjects. Invest Ophthalmol Vis Sci. 2012;53(2):698-703
66. Geyer O, Neudorfer M, Snir T, et al. Pulsatile ocular blood flow in diabetic retinopathy. Acta Ophthalmol Scand. 1999; 77(5):522-5.
67. Gilmore ED, Hudson C, Nrusimhadevara RK, et al. Retinal arteriolar diameter, blood velocity, and blood flow response to an isocapnic hyperoxic provocation in early sight-threatening diabetic retinopathy. Invest Ophthalmol Vis Sci. 2007; 48(4):1744-50
68. Goebel W, Lieb WE, Ho A, et al. Color Doppler imaging: a new technique to assess orbital blood flow in patients with diabetic retinopathy. Invest Ophthalmol Vis Sci. 1995;36(5):864-70
69. Grunwald JE, Brucker AJ, Petrig BL, Riva CE. Retinal blood flow regulation and the clinical response to panretinal photocoagulation in proliferative diabetic retinopathy. Ophthalmology. 1989;96(10):1518-22
70. Grunwald JE, Hariprasad SM, DuPont J, et al. Foveolar choroidal blood flow in age-related macular degeneration. Invest Ophthalmol Vis Sci. 1998;39(2):385-90
71. Grunwald JE, Metelitsina TI, Dupont JC, et al. Reduced foveolar choroidal blood flow in eyes with increasing AMD severity. Invest Ophthalmol Vis Sci. 2005;46(3):1033-8
72. Grunwald JE, Piltz J, Hariprasad SM, DuPont J. Optic nerve and choroidal circulation in glaucoma. Invest Ophthalmol Vis Sci. 1998;39(12):2329-36

74. Grunwald JE, Riva CE, Baine J, Brucker AJ. Total retinal volumetric blood flow rate in diabetic patients with poor glycemic control. Invest Ophthalmol Vis Sci. 1992;33(2):356-63
75. Grunwald JE, Riva CE, Petrig BL, et al. Strict control of glycaemia: effects on blood flow in the large retinal vessels and in the macular microcirculation. Br J Ophthalmol. 1995;79(8):735-41
76. Grunwald JE, Riva CE, Sinclair SH, et al. Laser Doppler velocimetry study of retinal circulation in diabetes mellitus. Arch Ophthalmol. 1986;104(7):991-6
77. Grunwald JE, Riva CE, Stone RA, et al. Retinal autoregulation in open-angle glaucoma. Ophthalmology. 1984;91(12):1690-4
78. Guthoff RF, Berger RW, Winkler P, et al. Doppler ultrasonography of the ophthalmic and central retinal vessels. Arch Ophthalmol. 1991;109(4):532-6
79. Hafez AS, Bizzarro RL, Lesk MR. Evaluation of optic nerve head and peripapillary retinal blood flow in glaucoma patients, ocular hypertensives, and normal subjects. Am J Ophthalmol. 2003;136(6):1022-31
80. Hafez AS, Bizzarro RL, Rivard M, Lesk MR. Changes in optic nerve head blood flow after therapeutic intraocular pressure reduction in glaucoma patients and ocular hypertensives. Ophthalmology. 2003;110(1):201-10
81. Hamard P, Hamard H, Dufaux J, Quesnot S. Optic nerve head blood flow using a laser Doppler velocimeter and haemorheology in primary open angle glaucoma and normal pressure glaucoma. Br J Ophthalmol. 1994;78(6):449-53

perturbations. J Glaucoma. 1996;5(4):258-65

83. Harris A, Chung HS, Ciulla TA, Kagemann L. Progress in measurement of ocular blood flow and relevance to our understanding of glaucoma and age-related macular degeneration. Prog Retin Eye Res. 1999;18(5):669-87
84. Harris NR, Watts MN, Leskova W. Intravital video microscopy measurements of retinal blood flow in mice. J Vis Exp. 2013;(82):51110
85. Hickam JB, Frayser R. Aphotographic method for measuring the mean retinal circulation time using fluorescein. Invest Ophthalmol. 1965;4(5):876-84
86. Hommer A, Fuchsjäger-Mayrl G, Resch H, Vass C, Garhofer G, Schmetterer L. Estimation of ocular rigidity based on measurement of pulse amplitude using pneumotonometry and fundus pulse using laser interferometry in glaucoma. Invest Ophthalmol Vis Sci. 2008; 49(9):4046-50
87. Hosal BM, Karakoc G, Gursel E, Camur M. Color Doppler imaging of the retrobulbar circulation in age-related macular degeneration. Eur J Ophthalmol. 1998;8(4):234-8
88. Hossain P, Liversidge J, Cree MJ, et al. In vivo cell tracking by scanning laser ophthalmoscopy: quantification of leukocyte kinetics. Invest Ophthalmol Vis Sci. 1998;39(10):1879-87
89. Huang D, Jia Y, Gao SS, et al. Optical Coherence Tomography Angiography Using the Optovue Device. Dev Ophthalmol. 2016; 56:6e12
90. Hubbard LD, Brothers RJ, King WN, et al. Methods for evaluation of retinal microvascular abnormalities associated with hypertension/sclerosis in the

91. Hwang JC, Konduru R, Zhang X, et al. Relationship among visual field, blood flow, and neural structure measurements in glaucoma. Invest Ophthalmol Vis Sci. 2012;53(6):3020-6
92. Hwang TS, Jia Y, Gao SS, et al. Optical coherence tomography angiography features of diabetic retinopathy. Retina. 2015; 35(11):2371e6
93. Ikram MK, van Leeuwen R, Vingerling JR, et al. Retinal vessel diameters and the risk of incident age-related macular disease: the Rotterdam Study. Ophthalmology. 2005;112(4):548-52
94. Ino-ue M, Azumi A, Yamamoto M. Ophthalmic artery blood flow velocity changes in diabetic patients as a manifestation of macroangiopathy. Acta Ophthalmol Scand. 2000;78(2):173-6
95. Ishikawa M, Sekizuka E, Shimizu K, et al. Measurement of RBC velocities in the rat pial arteries with an image-intensified high-speed video camera system. Microvasc Res. 1998;56(3):166-72
96. Iwase T, Kobayashi M, Yamamoto K, Ra E, Terasaki H. Effects of photocoagulation on ocular blood flow in patients with severe non-proliferative diabetic retinopathy. PLoS One. 2017;12(3):e0174427
97. Izhaky D, Nelson DA, Burgansky-Eliash Z, Grinvald A. Functional imaging using the retinal function imager: direct imaging of blood velocity, achieving fluorescein angiography-like images without any contrast agent, qualitative oximetry, and functional metabolic signals. Jpn J Ophthalmol. 2009;53(4):345-51

2008;146(6):954-9.e1

99. Jensen PS, Glucksberg MR. Regional variation in capillary hemodynamics in the cat retina. Invest Ophthalmol Vis Sci. 1998;39(2):407-15

100. Jiang H, Delgado S, Liu C, et al. In Vivo Characterization of Retinal Microvascular Network in Multiple Sclerosis. Ophthalmology. 2016;123(2):437-8

101. Jiang H, Delgado S, Tan J, et al. Impaired retinal microcirculation in multiple sclerosis. Mult Scler. 2016;22(14):1812-1820

102. Joanna Kur, Eric A. Newman, Tailoi Chan-Ling. Cellular and physiological mechanisms underlying blood flow regulation in the retina choroid in health disease. Prog Retin Eye Res. 2012; 31(5): 377–406

103. Jonas JB, Nguyen XN, Naumann GO. Parapapillary retinal vessel diameter in normal and glaucoma eyes. I. Morphometric data. Invest Ophthalmol Vis Sci. 1989;30(7):1599-603

104. Justesen BL, Mistry P, Chaturvedi N, et al. Retinal arterioles have impaired reactivity to hyperoxia in type 1 diabetes. Acta Ophthalmol. 2010; 88(4):453-7

105. Kagemann L, Harris A, Chung HS, et al. Heidelberg retinal flowmetry: factors affecting blood flow measurement. Br J Ophthalmol. 1998;82(2):131-6

106. Kashani AH, Chen CL, Gahm JK, Zheng F, Richter GM, Rosenfeld PJ, Shi Y, Wang RK. Optical coherence tomography angiography: A comprehensive review of current methods and clinical applications. Prog Retin Eye Res. 2017; 60:66-100

1998;126(1):42-51

108. Khoobehi B, Peyman GA. Fluorescent labeling of blood cells for evaluation of retinal and choroidal circulation. Ophthalmic Surg Lasers. 1999;30(2):140-5

109. Khoobehi B, Peyman GA. Fluorescent vesicle system. A new technique for measuring blood flow in the retina. Ophthalmology. 1994;101(10):1716-26

110. Khoobehi B, Shoelson B, Zhang YZ, Peyman GA. Fluorescent microsphere imaging: a particle-tracking approach to the hemodynamic assessment of the retina and choroid. Ophthalmic Surg Lasers. 1997;28(11):937-47

111. Khuu LA, Tayyari F, Sivak JM, et al. Aqueous humour concentrations of TGF-beta, PLGF and FGF-1 and total retinal blood flow in patients with early non-proliferative diabetic retinopathy. Acta Ophthalmol. 2017;95(3):e206-e211

112. Kimura H, Kiryu J, Nishiwaki H, Ogura Y. A new fluorescent imaging procedure in vivo for evaluation of the retinal microcirculation in rats. Curr Eye Res. 1995;14(3):223-8

113. Kiss B, Dallinger S, Polak K, et al. Ocular hemodynamics during isometric exercise. Microvasc Res 2001; 61(1):1–13.

114. Klein R, Klein BE, Tomany SC, Wong TY. The relation of retinal microvascular characteristics to age-related eye disease: the Beaver Dam eye study. Am J Ophthalmol. 2004;137(3):435-44

115. Klein R, Myers CE, Lee KE, Gangnon R, Klein BE. Changes in retinal vessel diameter and incidence and progression of diabetic retinopathy. Arch Ophthalmol. 2012; 130(6):749–55

primary open-angle glaucoma. Graefes Arch Clin Exp Ophthalmol. 2010;248(6):833-7

117. Kohner EM. The problems of retinal blood flow in diabetes. Diabetes. 1976;25(2 SUPPL):839-44

118. Konishi N, Tokimoto Y, Kohra K, Fujii H. New Laser Speckle Flowgraphy System Using CCD Camera. Optical Review. 2002;9(4):163-169

119. Konno S, Feke GT, Yoshida A, et al. Retinal blood flow changes in type I diabetes. A long-term follow-up study. Invest Ophthalmol Vis Sci. 1996;37(6):1140-8

120. Krepler K, Polska E, Wedrich A, Schmetterer L. Ocular blood flow parameters after pars plana vitrectomy in patients with diabetic retinopathy. Retina. 2003;23(2):192-6

121. Kur J, Newman EA, Chan-Ling T. Cellular and physiological mechanisms underlying blood flow regulation in the retina and choroid in health and disease. Prog Retin Eye Res. 2012;31(5):377-406

122. Lee JC, Wong BJ, Tan O, et al. Pilot study of Doppler optical coherence tomography of retinal blood flow following laser photocoagulation in poorly controlled diabetic patients. Invest Ophthalmol Vis Sci. 2013 Sep 9;54(9):6104-11

123. Leitgeb RA, Werkmeister RM, Blatter C, Schmetterer L. Doppler optical coherence tomography. Prog Retin Eye Res. 2014;41:26-43

124. Lieb WE, Cohen SM, Merton DA, et al. Color Doppler imaging of the eye and orbit. Technique and normal vascular anatomy. Arch Ophthalmol. 1991;109(4):527-31

126. Loebl M, Riva CE. Macular circulation and the flying corpuscles phenomenon. Ophthalmology. 1978;85(9):911-7

127. Lorenzi M, Feke GT, Cagliero E, et al. Retinal haemodynamics in individuals with well-controlled type 1 diabetes. Diabetologia. 2008;51(2):361-4

128. Lotfi K, Grunwald JE. The effect of caffeine on the human macular circulation. Invest Ophthalmol Vis Sci. 1991;32(12):3028-32

129. Loukovaara S, Harju M, Kaaja R, Immonen I. Retinal capillary blood flow in diabetic and nondiabetic women during pregnancy and postpartum period. Invest Ophthalmol Vis Sci. 2003;44(4):1486-91

130. Luft N, Wozniak PA, Aschinger GC, et al. Ocular Blood Flow Measurements in Healthy White Subjects Using Laser Speckle Flowgraphy. PLoS One. 2016;11(12):e0168190

131. Lutty GA, McLeod DS. A new technique for visualization of the human retinal vasculature. Arch Ophthalmol. 1992;110(2):267-76

132. Maar N, Pemp B, Kircher K, et al. Ocular haemodynamic changes after single treatment with photodynamic therapy assessed with non-invasive techniques. Acta Ophthalmol. 2009;87(6):631-7

133. MacKinnon JR, McKillop G, O'Brien C, et al. Colour Doppler imaging of the ocular circulation in diabetic retinopathy. Acta Ophthalmol Scand. 2000;78(4):386-9

134. MacKinnon JR, O'Brien C, Swa K, Aspinall P, Butt Z, Cameron D. Pulsatile ocular blood flow in untreated diabetic retinopathy. Acta Ophthalmol Scand. 1997; 75(6):661-4.

136. Matsunaga DR, Yi JJ, De Koo LO, et al. Optical coherence tomography angiography of diabetic retinopathy in human subjects. Ophthalmic Surg Lasers Imaging Retina. 2015; 46(8):796e805

137. Maumenee AE. Causes of optic nerve damage in glaucoma. Robert N. Shaffer lecture. Ophthalmology. 1983;90(7):741-52

138. McGeechan K, Liew G, Macaskill P, et al. Risk prediction of coronary heart disease based on retinal vascular caliber (from the Atherosclerosis Risk In Communities [ARIC] Study). Am J Cardiol. 2008;102(1):58-63

139. Mendivil A, Cuartero V, Mendivil MP. Ocular blood flow velocities in patients with proliferative diabetic retinopathy and healthy volunteers: a prospective study. Br J Ophthalmol. 1995;79(5):413-6

140. Mendivil A, Cuartero V, Mendivil MP. Ocular blood flow velocities in patients with proliferative diabetic retinopathy before and after scatter photocoagulation: a prospective study. Eur J Ophthalmol. 1995;5(4):259-64

141. Meng N, Zhang P, Huang H, et al. Color Doppler imaging analysis of retrobulbar blood flow velocities in primary open-angle glaucomatous eyes: a meta-analysis. PLoS One. 2013;8(5):e62723

142. Mete A, Saygili O, Mete A, et al. Does ranibizumab (Lucentis(R)) change retrobulbar blood flow in patients with neovascular age-related macular degeneration? Ophthalmic Res. 2012;47(3):141-5

143. Mete A, Saygili O, Mete A, et al. Effects of intravitreal bevacizumab (Avastin) therapy on retrobulbar blood flow parameters in patients with neovascular age-related macular degeneration. J Clin Ultrasound. 2010;38(2):66-70

Ophthalmol Vis Sci. 2008;49(1):358-63

145. Metelitsina TI, Grunwald JE, DuPont JC, Ying GS. Effect of isometric exercise on choroidal blood flow in patients with age-related macular degeneration. Br J Ophthalmol. 2010;94(12):1629-31

146. Metelitsina TI, Grunwald JE, DuPont JC, Ying GS. Effect of systemic hypertension on foveolar choroidal blood flow in age related macular degeneration. Br J Ophthalmol. 2006;90(3):342-6

147. Michelson G, Langhans MJ, Groh MJ. Perfusion of the juxtapapillary retina and the neuroretinal rim area in primary open angle glaucoma. J Glaucoma. 1996;5(2):91-8

148. Michelson G, Langhans MJ, Harazny J, Dichtl A. Visual field defect and perfusion of the juxtapapillary retina and the neuroretinal rim area in primary open-angle glaucoma. Graefes Arch Clin Exp Ophthalmol. 1998;236(2):80-5

149. Michelson G, Schmauss B, Langhans MJ, et al. Principle, validity, and reliability of scanning laser Doppler flowmetry. J Glaucoma. 1996;5(2):99-105

150. Michelson G, Schmauss B. Two dimensional mapping of the perfusion of the retina and optic nerve head. Br J Ophthalmol. 1995;79(12):1126-32

151. Micieli JA, Tsui E, Lam WC, et al. Retinal blood flow in response to an intravitreal injection of ranibizumab for neovascular age-related macular degeneration. Acta Ophthalmol. 2012;90(1):e13-20

152. Moore NA, Harris A, Wentz S, et al. Baseline retrobulbar blood flow is associated with both functional and structural glaucomatous progression after 4 years. Br J Ophthalmol. 2016. doi: 10.1136/bjophthalmol-2016-308460

systemic atherosclerosis. Invest Ophthalmol Vis Sci. 2005;46(2):720-5

154. Nagaoka T, Kitaya N, Sugawara R, et al. Alteration of choroidal circulation in the foveal region in patients with type 2 diabetes. Br J Ophthalmol. 2004;88(8):1060-3

155. Nagaoka T, Sato E, Takahashi A, et al. Impaired retinal circulation in patients with type 2 diabetes mellitus: retinal laser Doppler velocimetry study. Invest Ophthalmol Vis Sci. 2010;51(12):6729-34

156. Newman EA. Functional hyperemia and mechanisms of neurovascular coupling in the retinal vasculature. J Cereb Blood Flow Metab. 2013;33(11):1685-95

157. Nguyen HT, van Duinkerken E, Verbraak FD, et al. Retinal blood flow is increased in type 1 diabetes mellitus patients with advanced stages of retinopathy. BMC Endocr Disord. 2016; 16(1):25

158. Nicolela MT, Hnik P, Drance SM. Scanning laser Doppler flowmeter study of retinal and optic disk blood flow in glaucomatous patients. Am J Ophthalmol. 1996;122(6):775-83

159. Nishiwaki H, Ogura Y, Kimura H, et al. Quantitative evaluation of leukocyte dynamics in retinal microcirculation. Invest Ophthalmol Vis Sci. 1995;36(1):123-30

160. Nitta F, Kunikata H, Aizawa N, et al. The effect of intravitreal bevacizumab on ocular blood flow in diabetic retinopathy and branch retinal vein occlusion as measured by laser speckle flowgraphy. Clin Ophthalmol. 2014;8:1119-27

162. Novais EA, Waheed NK. Optical coherence tomography angiography of retinal vein occlusion. Dev Ophthalmol. 2016; 56:132e8

163. Novotny HR, Alvis DL. A method of photographing fluorescence in circulating blood in the human retina. Circulation. 1961;24:82-6

164. Okamoto M, Matsuura T, Ogata N. Effects of panretinal photocoagulation on choroidal thickness and choroidal blood flow in patients with severe nonproliferative diabetic retinopathy. Retina. 2016;36(4):805-11

165. Ormerod LD, Fariza E, Webb RH. Dynamics of external ocular blood flow studied by scanning angiographic microscopy. Eye (Lond). 1995;9(Pt 5):605-14

166. Palkovits S, Fuchsjager-Mayrl G, Kautzky-Willer A, et al. Retinal white blood cell flux and systemic blood pressure in patients with type 1 diabetes. Graefes Arch Clin Exp Ophthalmol. 2013;251(6):1475-81

167. Patel A, MacMahon S, Chalmers J, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008; 358(24):2560–2572

168. Patel V, Rassam S, Newsom R, et al. Retinal blood flow in diabetic retinopathy. BMJ. 1992;305(6855):678-83

169. Patton N, Aslam TM, MacGillivray T, et al. Retinal image analysis: concepts, applications and potential. Prog Retin Eye Res. 2006;25(1):99-127

170. Pedersen L, Jeppesen P, Knudsen ST, Poulsen PL, Bek T. Improvement of mild retinopathy in type 2 diabetic patients correlates with narrowing of retinal arterioles. A prospective observational study. Graefes Arch Clin Exp Ophthalmol. 2014; 252/10: 1561–7

in type 1 diabetes patients. Acta Ophthalmol. 2013; 91(5):e348-52

172. Pemp B, Georgopoulos M, Vass C, et al. Diurnal fluctuation of ocular blood flow parameters in patients with primary open-angle glaucoma and healthy subjects. Br J Ophthalmol. 2009;93(4):486-91

173. Pemp B, Polska E, Garhofer G, et al. Retinal blood flow in type 1 diabetic patients with no or mild diabetic retinopathy during euglycemic clamp. Diabetes Care. 2010;33(9):2038-42

174. Pemp B, Schmetterer L. Ocular blood flow in diabetes and age-related macular degeneration. Can J Ophthalmol. 2008;43(3):295-301

175. Pichi F, Sarraf D, Arepalli S, et al. The application of optical coherence tomography angiography in uveitis and inflammatory eye diseases. Prog Retin Eye Res. 2017; 59:178-201

176. Piltz-seymour JR, Grunwald JE, Hariprasad SM, Dupont J. Optic nerve blood flow is diminished in eyes of primary open-angle glaucoma suspects. Am J Ophthalmol. 2001;132(1):63-9

177. Pittman RN. Oxygen delivery and transport in the microcirculation. Basel, Karger, 1987

178. Plange N, Remky A, Arend O. Colour Doppler imaging and fluorescein filling defects of the optic disc in normal tension glaucoma. Br J Ophthalmol. 2003;87(6):731-6

179. Polska E, Kircher K, Ehrlich P, et al. RI in central retinal artery as assessed by CDI does not correspond to retinal vascular resistance. Am J Physiol Heart Circ Physiol. 2001;280(4):H1442-7

choroidal circulation. Current Eye Research. 2002; 24(4):318-323.

181. Polska E, Polak K, Luksch A, et al. Twelve hour reproducibility of choroidal blood flow parameters in healthy subjects. Br J Ophthalmol. 2004; 88(4): 533–537

182. Portmann N, Gugleta K, Kochkorov A, et al. Choroidal blood flow response to isometric exercise in glaucoma patients and patients with ocular hypertension. Invest Ophthalmol Vis Sci. 2011;52(10):7068-73

183. Pournaras CJ, Logean E, Riva CE, et al. Regulation of subfoveal choroidal blood flow in age-related macular degeneration. Invest Ophthalmol Vis Sci. 2006;47(4):1581-6

184. Pournaras CJ, Riva CE, Bresson-Dumont H, et al. Regulation of optic nerve head blood flow in normal tension glaucoma patients. Eur J Ophthalmol. 2004;14(3):226-35

185. Pournaras CJ, Riva CE. Retinal blood flow evaluation. Ophthalmologica. 2013;229(2):61-74

186. Pournaras CJ, Rungger-Brändle E, Riva CE, et al. Regulation of retinal blood flow in health and disease. Prog Retin Eye Res. 2008;27(3):284-330

187. Prada D, Harris A, Guidoboni G, et al. Autoregulation and neurovascular coupling in the optic nerve head. Surv Ophthalmol. 2016;61(2):164-86

188. Preussner PR, Richard G, Darrelmann O, et al. Quantitative measurement of retinal blood flow in human beings by application of digital image-processing methods to television fluorescein angiograms. Graefes Arch Clin Exp Ophthalmol. 1983;221(3):110-2

Acta Ophthalmol. 2011;89(7):e544-9

190. Rina M, Shiba T, Takahashi M, et al. Pulse waveform analysis of optic nerve head circulation for predicting carotid atherosclerotic changes. Graefes Arch Clin Exp Ophthalmol. 2015;253(12):2285-91

191. Riva C, Ross B, Benedek GB. Laser Doppler measurements of blood flow in capillary tubes and retinal arteries. Invest Ophthalmol. 1972;11(11):936-44

192. Riva C. E., Falsini B., Logean E. Flicker-evoked responses of human optic nerve head blood flow: luminance versus chromatic modulation. Investigative Ophthalmology and Visual Science. 2001; 42(3):756–762

193. Riva CE, Cranstoun SD, Grunwald JE, Petrig BL. Choroidal blood flow in the foveal region of the human ocular fundus. Invest Ophthalmol Vis Sci. 1994;35(13):4273-81

194. Riva CE, Feke GT, Eberli B, Benary V. Bidirectional LDV system for absolute measurement of blood speed in retinal vessels. Appl Opt. 1979;18(13):2301-6

195. Riva CE, Geiser M, Petrig BL. Ocular blood flow assessment using continuous laser Doppler flowmetry. Acta Ophthalmol. 2010;88(6):622-9

196. Riva CE, Grunwald JE, Sinclair SH, Petrig BL. Blood velocity and volumetric flow rate in human retinal vessels. Invest Ophthalmol Vis Sci. 1985;26(8):1124-32

197. Riva CE, Harino S, Petrig BL, Shonat RD. Laser Doppler flowmetry in the optic nerve. Exp Eye Res. 1992;55(3):499-506

198. Riva CE, Petrig B. Blue field entoptic phenomenon and blood velocity in the retinal capillaries. J Opt Soc Am. 1980;70(10):1234-8

1985;92(8):1130-2

200. Rogers SL, Tikellis G, Cheung N, et al. Retinal arteriolar caliber predicts incident retinopathy: The Australian Diabetes, Obesity and Lifestyle (AusDiab) Study. Diabetes Care 2008; 31:761–763

201. Roisman L, Zhang Q, Wang RK, et al. Optical coherence tomography angiography of asymptomatic neovascularization in intermediate age-related macular degeneration. Ophthalmology. 2016; 123(6):1309e19

202. Rosenfeld PJ, Durbin MK, Roisman L, et al. ZEISS AngioplexTM spectral domain optical coherence tomography angiography: Technical aspects. Dev Ophthalmol. 2016; 56:18e29

203. Roy MS, Klein R, Janal MN. Retinal venular diameter as an early indicator of progression to proliferative diabetic retinopathy with and without high-risk characteristics in African Americans with type 1 diabetes mellitus. Archives of Ophthalmology. 2011; 129(1):8–15

204. Saidha S, Sotirchos ES, Oh J, et al. Relationships between retinal axonal and neuronal measures and global central nervous system pathology in multiple sclerosis. JAMA Neurol. 2013;70(1):34-43

205. Sakalar YB, Senturk S, Yildirim M, et al. Evaluation of retrobulbar blood flow by color doppler ultrasonography after intravitreal ranibizumab injection in patients with neovascular age-related macular degeneration. J Clin Ultrasound. 2013;41(1):32-7

2006;113(8):1385-91

207. Savage HI, Hendrix JW, Peterson DC, Young H, Wilkinson CP. Differences in pulsatile ocular blood flow among three classifications of diabetic retinopathy. Invest Ophthalmol Vis Sci. 2004; 45(12):4504-9

208. Schmetterer L, Dallinger S, Findl O, Eichler HG, Wolzt M. A comparison between laser interferometric measurement of fundus pulsation and pneumotonometric measurement of pulsatile ocular blood flow. 1. Baseline considerations. Eye (Lond). 2000; 14 (Pt 1):39-45

209. Schmetterer L, Garhofer G. How can blood flow be measured? Surv Ophthalmol. 2007;52 Suppl 2:S134-8

210. Schmetterer L, Kruger A, Findl O, Breiteneder H, Eichler HG, Wolzt M. Topical fundus pulsation measurements in age-related macular degeneration. Graefes Arch Clin Exp Ophthalmol. 1998; 236(3):160-3

211. Schmetterer L, Lexer F, Unfried C, Sattrnann H, Fercher AF. Topical measurement of fundus pulsations. Opt Eng. 1995; 34:711-6

212. Schmetterer L, Wolzt M, SalomonA, et al. Effect of isoproterenol, phenylephrine, and sodium nitroprusside on fundus pulsations in healthy volunteers. Br J Ophthalmol. 1996; 80: 217-223

213. Schmidl D, Boltz A, Kaya S, et al. Comparison of choroidal and optic nerve head blood flow regulation during changes in ocular perfusion pressure. Invest Ophthalmol Vis Sci. 2012; 53(8):4337-46

Eye Res. 2011;93(2):141-55

215. Schocket LS, Brucker AJ, Niknam RM, et al. Foveolar choroidal hemodynamics in proliferative diabetic retinopathy. Int Ophthalmol. 2004;25(2):89-94

216. Sehi M, Goharian I, Konduru R, et al. Retinal blood flow in glaucomatous eyes with single-hemifield damage. Ophthalmology. 2014;121(3):750-8

217. Shao Q, Heussen FM, Ouyang Y, Hager A. Retinal vessel diameter changes in different severities of diabetic retinopathy by SD-OCT. Eur J Ophthalmol. 2016; 26(4):342-6

218. Shiga Y, Asano T, Kunikata H, et al. Relative flow volume, a novel blood flow index in the human retina derived from laser speckle flowgraphy. Invest Ophthalmol Vis Sci. 2014;55(6):3899-904

219. Shiga Y, Kunikata H, Aizawa N, et al. Optic Nerve Head Blood Flow, as Measured by Laser Speckle Flowgraphy, Is Significantly Reduced in Preperimetric Glaucoma. Curr Eye Res. 2016;41(11):1447-1453

220. Shiga Y, Omodaka K, Kunikata H, et al. Waveform analysis of ocular blood flow and the early detection of normal tension glaucoma. Invest Ophthalmol Vis Sci. 2013;54(12):7699-706

221. Silver DM, Farrell RA. Validity of pulsatile ocular blood flow measurements. Surv Ophthalmol. 1994; 28(Suppl):S72-80

222. Sinclair SH, Grunwald JE, Riva CE, et al. Retinal vascular autoregulation in diabetes mellitus. Ophthalmology. 1982;89(7):748-50

224. Sousa DC, Leal I, Moreira S, Dionísio P, Abegão Pinto L, Marques-Neves C. Hypoxia challenge test and retinal circulation changes - a study using ocular coherence tomography angiography. Acta Ophthalmol. 2017 Nov 21. doi: 10.1111/aos.13622. [Epub ahead of print]

225. Spaide RF, Fujimoto JG, Waheed NK, et al. Optical coherence tomography angiography. Prog Retin Eye Res. 2017 Dec 8. pii: S1350-9462(17)30056-3. doi: 10.1016/j.preteyeres.2017.11.003. [Epub ahead of print]

226. Spaide RF, Fujimoto JG, Waheed NK. Image artifacts in optical coherence tomography angiography. Retina. 2015; 35(11):2163-80

227. Spaide RF, Klancnik JM Jr, Cooney MJ. Retinal vascular layers imaged by fluorescein angiography and optical coherence tomography angiography. JAMA Ophthalmol. 2015; 133(1):45e50

228. Sponsel WE, DePaul KL, Kaufman PL. Correlation of visual function and retinal leukocyte velocity in glaucoma. Am J Ophthalmol. 1990;109(1):49-54

229. Srinivas S, Tan O, Nittala MG, et al. Assessment of retinal blood flow in diabetic retinopathy using doppler fourier-domain optical coherence tomography. Retina. 2017. doi: 10.1097/IAE.0000000000001479

230. Stalmans I, Vandewalle E, Anderson DR, et al. Use of colour Doppler imaging in ocular blood flow research. Acta Ophthalmol. 2011;89(8):e609-30

231. Stanga PE, Tsamis E, Papayannis A, et al. Swept-source optical coherence tomography Angio(Topcon Corp, Japan): Technology review. Dev Ophthalmol. 2016; 56:13e7

233. Sugiyama T, Araie M, Riva CE, et al. Use of laser speckle flowgraphy in ocular blood flow research. Acta Ophthalmol. 2010;88(7):723-9

234. Sullu Y, Hamidova R, Beden U, et al. Effects of pars plana vitrectomy on retrobulbar haemodynamics in diabetic retinopathy. Clin Exp Ophthalmol. 2005;33(3):246-51

235. Sun C, Liew G, Wang JJ, et al. Retinal vascular caliber, blood pressure, and cardiovascular risk factors in an Asian population: the Singapore Malay Eye Study. Invest Ophthalmol Vis Sci. 2008;49(5):1784-90

236. Takahashi A, Nagaoka T, Sato E, Yoshida A. Effect of panretinal photocoagulation on choroidal circulation in the foveal region in patients with severe diabetic retinopathy. Br J Ophthalmol. 2008;92(10):1369-73

237. Takasago Y1, Shiragami C, Kobayashi M, et al. Macular atrophy findings by optical coherence tomography angiography compared with fundus autofluorescence in treated exudative age-related macular degeneration. Retina. 2017; 28. doi: 10.1097/IAE.0000000000001980. [Epub ahead of print]

238. Tamaki Y, Araie M, Hasegawa T, Nagahara M. Optic nerve head circulation after intraocular pressure reduction achieved by trabeculectomy. Ophthalmology. 2001;108(3):627-32

239. Tamaki Y, Araie M, Kawamoto E, et al. Noncontact, two-dimensional measurement of retinal microcirculation using laser speckle phenomenon. Invest Ophthalmol Vis Sci. 1994;35(11):3825-34

speckle phenomenon. Exp Eye Res. 1995;60(4):373-83

241. Tamaki Y, Araie M, Tomita K, et al. Real-time measurement of human optic nerve head and choroid circulation, using the laser speckle phenomenon. Jpn J Ophthalmol. 1997;41(1):49-54

242. Tamaki Y, Nagahara M, Yamashita H, Kikuchi M. Blood velocity in the ophthalmic artery determined by color Doppler imaging in normal subjects and diabetics. Jpn J Ophthalmol. 1993;37(4):385-92

243. Tanaka T, Muraoka K, Shimizu K. Fluorescein fundus angiography with scanning laser ophthalmoscope. Visibility of leukocytes and platelets in perifoveal capillaries. Ophthalmology. 1991;98(12):1824-9

244. Tayyari F, Khuu LA, Flanagan JG, et al. Retinal Blood Flow and Retinal Blood Oxygen Saturation in Mild to Moderate Diabetic Retinopathy. Invest Ophthalmol Vis Sci. 2015;56(11):6796-800

245. Tobe LA, Harris A, Hussain RM, et al. The role of retrobulbar and retinal circulation on optic nerve head and retinal nerve fibre layer structure in patients with open-angle glaucoma over an 18-month period. Br J Ophthalmol. 2015;99(5):609-12

246. Toklu Y, Cakmak HB, Raza S, et al. Short-term effects of intravitreal bevacizumab (Avastin((R))) on retrobulbar hemodynamics in patients with neovascular age-related macular degeneration. Acta Ophthalmol. 2011;89(1):e41-5

247. Told R, Wang L, Cull G, et al. Total Retinal Blood Flow in a Nonhuman Primate Optic Nerve Transection Model Using Dual-Beam Bidirectional Doppler

248. Tsai AS, Wong TY, Lavanya R, et al. Differential association of retinal arteriolar and venular caliber with diabetes and retinopathy. Diabetes Research and Clinical Practice. 2011; 94(2):291–298

249. Tsuda S, Kunikata H, Shimura M, et al. Pulse-waveform analysis of normal population using laser speckle flowgraphy. Curr Eye Res. 2014;39(12):1207-15

250. Uretmen O, Akkin C, Erakgun T, Killi R. Color Doppler imaging of choroidal circulation in patients with asymmetric age-related macular degeneration. Ophthalmologica. 2003;217(2):137-42

251. Venkataraman ST, Flanagan JG, Hudson C. Vascular reactivity of optic nerve head and retinal blood vessels in glaucoma--a review. Microcirculation. 2010;17(7):568-81

252. Vinh Moreau-Gaudry V, Geiser M, Romanet JP, et al. Effects of photodynamic therapy on subfoveal blood flow in neovascular age-related macular degeneration patients. Eye (Lond). 2010;24(4):706-12

253. Wajer SD, Taomoto M, McLeod DS, et al. Velocity measurements of normal and sickle red blood cells in the rat retinal and choroidal vasculatures. Microvasc Res. 2000;60(3):281-93

254. Wang Y, Bower BA, Izatt JA, et al. In vivo total retinal blood flow measurement by Fourier domain Doppler optical coherence tomography. J Biomed Opt. 2007;12(4):041215

255. Wang Y, Fawzi A, Tan O, et al. Retinal blood flow detection in diabetic patients by Doppler Fourier domain optical coherence tomography. Opt Express. 2009;17(5):4061-73

diseases. Invest Ophthalmol Vis Sci. 2011 Feb 11;52(2):840-5

257. Wang Y, Lu A, Gil-Flamer J, et al. Measurement of total blood flow in the normal human retina using Doppler Fourier-domain optical coherence tomography. Br J Ophthalmol. 2009;93(5):634-7

258. Weigert G, Findl O, Luksch A, et al. Effects of moderate changes in intraocular pressure on ocular hemodynamics in patients with primary open-angle glaucoma and healthy controls. Ophthalmology. 2005;112(8):1337-42

259. Wise GN, Dollery CT, Henkind P. The Retinal Circulation. New York, NY, Harper & Row, 1971

260. Wolf S, Arend O, Sponsel WE, et al. Retinal Hemodynamics Using Scanning Laser Ophthalmoscopy and Hemorheology in Chronic Open-angle Glaucoma. Ophthalmology. 1993;100(10):1561-6

261. Wolf S, Arend O, Toonen H, et al. Retinal capillary blood flow measurement with a scanning laser ophthalmoscope. Preliminary results. Ophthalmology. 1991;98(6):996-1000

262. Wolf S, Jung F, Kiesewetter H, et al. Video fluorescein angiography: method and clinical application. Graefes Arch Clin Exp Ophthalmol. 1989;227(2):145-51

263. Wong TY, Klein R, Couper DJ, et al. Retinal microvascular abnormalities and incident stroke: the Atherosclerosis Risk in Communities Study. Lancet. 2001;358(9288):1134-40

264. Wong TY, Klein R, Sharrett AR, et al. Retinal arteriolar diameter and risk for hypertension. Ann Intern Med. 2004;140(4):248-55

Communities Study. JAMA. 2002;287(9):1153-9

266. Wong TY, Klein R, Sharrett AR, et al. Retinal arteriolar narrowing and risk of diabetes mellitus in middle-aged persons. JAMA. 2002;287(19):2528-33

267. Wong TY, Mitchell P. Hypertensive retinopathy. N Engl J Med. 2004;351(22):2310-7

268. Wong TY, Mitchell P. The eye in hypertension. Lancet. 2007;369(9559):425-35

269. Xu L, Wang S, Li Y, Jonas JB. Retinal vascular abnormalities and prevalence of age-related macular degeneration in adult Chinese: the Beijing Eye Study. Am J Ophthalmol. 2006;142(4):688-9

270. Yang K, Zhan SY, Liang YB, et al. Association of dilated retinal arteriolar caliber with early age-related macular degeneration: the Handan Eye Study. Graefes Arch Clin Exp Ophthalmol. 2012;250(5):741-9

271. Yang Y, Kim S, Kim J. Fluorescent dots in fluorescein angiography and fluorescein leukocyte angiography using a scanning laser ophthalmoscope in humans. Ophthalmology. 1997;104(10):1670-6

272. Yang Y, Kim S, Kim J. Visualization of retinal and choroidal blood flow with fluorescein leukocyte angiography in rabbits. Graefes Arch Clin Exp Ophthalmol. 1997;235(1):27-31

273. Yaoeda K, Shirakashi M, Fukushima A, et al. Relationship between optic nerve head microcirculation and visual field loss in glaucoma. Acta Ophthalmol Scand. 2003;81(3):253-9

275. Yoshitomi T, Wong AS, Daher E, Sears ML. Aqueous flare measurement with laser flare-cell meter. Jpn J Ophthalmol. 1990;34(1):57-62

Table 1. Results of different techniques used for measuring ocular blood flow in different disea

Method	Study subjects	Measurements	
Laser Doppler velocimetry[196]	Healthy subjects	Mean total arterial volumetric flow rate	33
		Mean total venous volumetric flow rates	34
Doppler Optical Coherence Tomography[42]	Healthy subjects	Mean retinal arterial flow	35
		Mean retinal venous flow	36
Doppler Optical Coherence Tomography[91]	Glaucoma patients	Total retinal blood flow	34
	Healthy subjects	Total retinal blood flow	45
Doppler Optical Coherence Tomography[216]	Glaucoma patients	Total retinal blood flow	34
	Healthy subjects	Total retinal blood flow	46
Laser Doppler flowmetry[70]	Dry AMD patients	Mean choroidal blood flow in the center of the fovea	8.
		Mean choroidal blood volume in the center of the fovea	0.

		Mean choroidal blood velocity in the center of the fovea	0.
		Mean blood flow pulsatility	0.
	Healthy controls	Mean choroidal blood flow in the center of the fovea	13
		Mean choroidal blood volume in the center of the fovea	0.
		Mean choroidal blood velocity in the center of the fovea	0.
		Mean blood flow pulsatility	0.
Laser Doppler flowmetry[9]	Patients with unilateral choroidal neovascular AMD	Mean subfoveal choroidal blood flow	17
Scanning laser Doppler flowmetry[157]	Proliferative DR	Median retinal blood flow	25
	Non-proliferative DR (NPDR)		22

	Diabetics with no clinical retinopathy		21
	Healthy controls		20
Pneumotonometry[134]	Pre-proliferative / proliferative diabetic retinopathy (DR)	Mean pulsatile ocular blood flow (POBF)	10
	Background DR		10
	Diabetics with no clinical retinopathy		81
	Non-diabetic control subjects		64
Pneumotonometry[86]	Primary open-angle glaucoma (POAG)		87
	Healthy subjects		10
Laser interferometry[210]	AMD patients	Fundus pulsation amplitude (FPA) measurements adjacent to the classic	4.

		neovascular membranes (CNM) (FPA_{out})	
		FPA measurements directly on the CNM (FPA_{in})	3.
	Healthy subjects	FPA_{out}	3.
		FPA_{in}	3.
Laser interferometry[86]	POAG	FPA	3.
	Healthy subjects	FPA	3.
Laser speckle flowgraphy[96]	Severe NPDR patients underwent panretinal photocoagulation (PRP)	Optic nerve head (ONH) mean blur rate (MBR) in the vessel area	29
		ONH MBR in the tissue area	9.
		Choroidal MBR	6.
	Severe NPDR patients without PRP	ONH MBR in the vessel area	40
		ONH MBR in the tissue area	10
		Choroidal MBR	7.
	Healthy controls	ONH MBR in the vessel area	41

		ONH MBR in the tissue area	1
		Choroidal MBR	9.
Retinal function imager[16]	Healthy subjects	Mean RBC velocity in retinal arteries	4.
		Mean RBC velocity in retinal veins	3.
Retinal function imager[14]	Healthy subjects	Mean retinal arterial blood flow velocity	4.
		Mean retinal venous blood flow velocity	2.
	AMD patients	Mean retinal arterial blood flow velocity	3.
		Mean retinal venous blood flow velocity	2.
Color Doppler imaging[143]	AMD patients before intravitreal Bevacizumab injection	Peak systolic perfusion velocity (PSV) in nasal posterior ciliary arteries	16
		End diastolic perfusion velocity (EDV) in nasal posterior ciliary arteries	5.
		PSV in temporal posterior ciliary arteries	16
		EDV in temporal posterior ciliary arteries	5.
	AMD patients post-	PSV in nasal posterior ciliary arteries	13

	intravitreal Bevacizumab injection	EDV in nasal posterior ciliary arteries	4.
		PSV in temporal posterior ciliary arteries	15
		EDV in temporal posterior ciliary arteries	5.
Optical coherence tomography angiography[23]	Eyes with glaucoma	Peripapillary retinal nerve fiber layer (RNFL) blood flux index	0.
	Healthy eyes	Peripapillary RNFL blood flux index	0.

* The difference was significant than controls (p<0.05); # The difference in FPA_{in} was significant than F

values in the severe NPDR with PRP group were significantly lower than that of the severe NPDR with

subjects (p<0.05);