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REVIEW

Current State of Knowledge in Ocular Blood Flow in Glaucoma: A Narrative Review

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Abstract: Glaucoma is a multifactorial disease that is dependent on Intra Ocular Pressure (IOP) and associated with risk factors related to reduced ocular blood flow (OBF). In clinical practice, it is instrumental to update and review the considerable evidence of the current imaging technologies utilized in the investigation of OBF involved in both the onset and progression of glaucoma. Bibliographic databases, including PubMed and Google Scholar, were searched for articles on OBF techniques published between 2018 and 2023 using keywords such as “ocular blood flow”, “glaucoma”, “invasive ocular blood flow measurement”, and “non-invasive ocular blood flow measurement”. All types of methodologies were considered, except for editorials, letters to the editor, and animal studies. This review provides comprehensive information on the recent state-of-the-art imaging innovations used to monitor and measure the ocular blood flow in glaucoma.

Keywords: ocular blood flow, glaucoma, laser speckle, color Doppler, Doppler Fourier domain optical coherence tomography, optical coherence tomography

Introduction

Adequate oxygen and nutrient supply to the eye are the main functions of the ocular blood flow (OBF). Ocular blood flow related to glaucoma is a widely explored area of study.[1] Owing to slow glaucomatous progression, ocular blood flow cannot be clearly linked to progression of glaucoma.[2] In glaucoma eyes the OBF is lower, although raised Intra Ocular Pressure (IOP) is the most important risk factor for the development and progression of glaucoma.[3] Glaucoma is known to progress in some patients in spite of a lower IOP. Upregulation of hypoxia-related factors in glaucomatous eyes indicates depletion of oxygen, and oxidative stress caused by the fluctuation of the oxygen supply, along with low perfusion pressure and disturbed autoregulation, are the major causes of tissue damage. This is identifiable as splinter hemorrhages which typically are attributed to a regional breakdown of the blood vessels and associated venous blockage due to regional venous reasons.[4,5]

Glaucoma identification and differentiation can be built on the understanding of its vascular dysfunctions which characterize its etiology and pathogenesis.[6] Thus a direct and broad assessment of OBF calls for the assessment of OBF in diverse tissues of the eye.[7] This makes the qualitative assessment of OBF important for the early diagnosis and management of glaucoma.

With the accelerated dynamics of imaging technologies, various invasive and non-invasive techniques are currently available for evaluating OBF in glaucoma.[8] These technologies discussed and available for glaucomatous OBF assessment have inherent advantages and limitations in measuring the different aspects of OBF. Thus, there exists a need for continuous efforts to develop definite and dependable methods for assessing the ocular BF in glaucoma.

The purpose of this study was to comprehensively review and appraise innovative imaging technologies frequently applied to probe into ocular blood flow dynamics in glaucoma. Subsequently this review is expected to provide physicians with clinically relevant information in identifying the most beneficial imaging diagnostic modality available for evaluating OBF in glaucoma.

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For the methodology of this narrative review article, a bibliographic literature search was undertaken from the online databases like MEDLINE, Embase, Cochrane Reviews, Web of Science, the Allied and Contemporary Medicine (AMED) for articles published on ocular BF techniques published from 2018 to 2023. Boolean logics with keywords such as "ocular blood flow", "glaucoma", "invasive ocular blood flow measurement", "non-invasive ocular blood flow measurement" were used to guarantee the systematic searching. All types of methodologies were considered, except editorials, letters to the editor, and animal studies. The articles identified were filtered by screening their titles and abstracts, and the full-texts of those were retrieved. Eligible studies were selected from the criteria designed to match the current study's aims and objectives. A bibliographic sampling from the articles was selected to further identify other potential sources of information related to the study. Studies were further sieved with regard to imaging mode and clinical use in glaucoma addressed. Thus, this study is presented as a narrative review briefing the capabilities of the imaging technologies in addressing the glaucomatous OBF pathology, along with the barriers characteristic to each technology discussed.

The technologies reported in this review can be classified as either non-invasive or invasive. Non-invasive techniques include Color Doppler Imaging (CDI), Laser Doppler Velocimetry (LDV), Laser Speckle Technique, Laser Doppler Flowmetry (LDF), Retinal Vessel Analyzer (RVA), retinal oximetry, and blue-field entoptic techniques. The invasive techniques discussed are scanning laser ophthalmoscopic angiography using fluorescein and/or Indocyanine Green (ICG) dye.

Innovative Diagnostic Imaging for Ocular Blood Flow

Non-Invasive Techniques

Color Doppler Imaging (CDI)

CDI is a medical imaging technique providing a comprehensive evaluation that employs ultrasound waves to measure and visualize the velocity of red blood cells in vessels.[9]

First, B-scan grayscale imaging allows for the visualization of anatomical structures detailing with a structural context for the blood flow analysis.[10] Second, colorized representation of blood flow (BF) is achieved by utilizing the Doppler effect, where moving red blood cells alters their frequency on encountering ultrasound waves (Doppler shift).[11] By assigning different colors to varying frequencies, CDI creates a color map representing blood flow patterns.[12] Finally, CDI provides velocity data obtained from the Doppler shift of moving red blood cells. The velocity information allows for quantitative evaluation of blood flow characteristics, including the speed and direction of blood flow within vessels.[12]

CDI studies on orbital hemodynamics can serve as potential biomarkers for progression of glaucoma.[13] CDI, with no ionizing radiation exposure and economic and easy accessibility, has been reported as a useful approach for diagnosing and monitoring glaucoma cases.[14] Although CDI is an effective method for assessing large arteries, it does not provide quantitative information on the vessel diameter. This technique cannot measure vessel diameter; thus, volumetric blood flow calculations are not possible.[15]

Overall, CDI is a valuable non-invasive tool in medicine for assessing blood flow dynamics and evaluating the velocity of red blood cells, providing useful information for diagnosing various vascular conditions.

Laser Speckle Technique (LST)

Laser Speckle Flowgraphy (LSFG) is a fascinating technology based on the laser speckle phenomenon occurring on illumination of surfaces by coherent laser light.[16,17] This is utilized in measuring the ocular blood flow and by analyzing the changes in the laser speckle pattern, LSFG can provide remarkable insights to glaucomatous changes.[18,19]

Structural and functional glaucoma metrics can be associated with the blood flow metrics identified with LST, which can be a critical tool in the identification of glaucoma severity and diagnosis of glaucoma.[20,21] With faster and reliable Optic Nerve Head (ONH) perfusion assessment LST is a promising tool in the later stage management and monitoring of glaucoma.[22] The limitation of LST is that it measures only the velocity and not the diameter of the vessel; hence, it cannot be used to study volumetric blood flow.[23]

Blue Field Entoptic Technique

An interesting technology, the blue field entoptic technique relies on the blue field entoptic phenomenon, caused by the difference in absorption properties between red blood cells and leukocytes.[24] The dynamic red blood cells on the retina absorb the illumination of the 430 nm wavelength blue light, while the leukocytes appear as bright points of light against a dark background. By analysis of the attributes of these bright points, such as their number, velocity, and pulsatility, the blue field entoptic technique feeds valuable information about leukocyte dynamics in the retina.[25] This is a non-invasive technique based on the blue field entoptic phenomenon, manifested due to the difference in the absorption properties of red blood cells and leukocytes.[26] Blue light with a narrow optical spectrum at a wavelength of 430 nm is considered the best to view this phenomenon. When the retina is illuminated with blue light, moving red blood cells absorb light, whereas leukocytes do not absorb light.[26]

The blue arc entoptic phenomenon perception corresponds with the systemic and functional changes associated with glaucoma, and is utilized in this technique, making it an advantage.[27] The subjective nature of the technique demands the cooperative involvement of the patient for precise measurements and presents with a setback of uncertainty as to whether leukocyte dynamics observed correlate to the glaucomatous retinal changes.[28]

Heidelberg Retinal Flowmetry (HRF)

HRF, an innovative non-invasive technique, is essentially a scanning version of Laser Doppler Technology, which assesses the Doppler shift in laser light.[29] HRF emits low power and as the light interacts with the moving blood cells in the retinal vessels, it undergoes the well-known Doppler shift. On analyzing this shift, HRF provides precious blood flow velocity and volume information in the retinal vasculature.[30] In suspected glaucoma cases, capillary density in the superior and inferior parapapillary retina can be monitored using HRF.[31]

Retinal Oximetry

A non-invasive technique, retinal oximetry has been used since the 1950s to measure relative oxygen saturation in retinal blood vessels.[32] This technique involves capturing images at two wavelengths at a wavelength sensitive to oxyhemoglobin 600 nm, and 570 nm which is not sensitive to oxyhemoglobin.[33] Comparing the brightness of the reflectance from the retinal vessels at these two different wavelengths gives an indirect evaluation of the level of oxygenation. Retinal oximetry aids in the diagnosis and monitoring of various ocular disorders, with details of retinal health and vasculature.[34]

Impaired blood supply to the retina and optic nerve head (ONH) in primary open-angle glaucoma (POAG) can be investigated using retinal oximetry as it can give insights to the retinal metabolic oxygen requirements.[35]

Retinal Vessel Analyzer (RVA)

The RVA is a non-invasive instrument used to assess the pattern of large retinal vessels based on diameter measurements, which is useful information in evaluating retinal blood dynamics.[36] A valuable measurement in ophthalmology, retinal vessel diameter is a major determinant of retinal blood flow and structural changes in retinal vessels and has been linked to several vascular-related systemic pathologies.[37] RVA is an amazing tool to assist in achieving precise recording of the measurements of retinal vessel diameter to evaluate the ocular blood flow and its regulators.[38]

RVA can detect reduced macular vessel density, which is typical in glaucoma and can detect microstructural deformations, and can be utilized to assist in glaucoma diagnosis.[39] One of the limitations of the RVA instrument, however, is obtaining the right quality images of media opacities in cases such as cataracts and corneal pathologies.[40] The RVA image quality is also dependent on the fixation stability and even slight eye movements; it can lead to straying away from right in measurements.[41]

Laser Doppler Velocimetry (LDV)

A non-invasive technique, LDV involves using two separate laser Doppler velocimeters (LDVs) to measure the blood flow velocities in both directions in the retinal arteries and veins.[42] This bidirectional technique provides a comprehensive assessment of the absolute blood flow velocities in these blood vessels. Clinicians and researchers can get a better understanding of the hemodynamics of the retinal circulation using this BF assessment as it can also provide information on the resistance and pulsatility indices of the retinal blood vessels.[43] This technique is helpful in studying various retinal vascular conditions such as diabetic retinopathy, retinal vein occlusion, and hypertensive retinopathy.[44]

The main setback of this technique is that it may be staggered by eye movements and other displacements, media opacities can give rise to blurred images and thus cannot measure circulation in the optic nerve head (ONH).[45] LDV without ionizing radiation is a useful approach for diagnosing and monitoring glaucoma patients.[46]

Laser Doppler Flowmetry (LDF)

A laser Doppler flowmeter is a non-invasive device that works by emitting a low-power laser beam onto the surface of the retina or choroid and utilizes laser Doppler technology to measure blood flow in the retinal and choroidal capillaries. By analyzing the frequency shift, the device can quantify the velocity and volume of blood flow in the retinal and choroidal capillaries.[47]

It typically consists of a laser light source, a modified fundus camera to capture images of the retinal or choroidal vasculature, and a digital system to analyze the images and to calculate blood flow parameters such as blood flow velocity, blood volume, and blood flow rate.[48]

Laser Doppler flowmetry is a valuable tool in ophthalmology and can provide important information about the microcirculation in the retina and choroid.[48] It is used in research and clinical settings to study various retinal and choroidal diseases, such as diabetic retinopathy, age-related macular degeneration, and retinal vascular occlusions.

The non-invasive nature of the laser Doppler flowmeter makes it a safe and efficient tool for assessing blood flow in the retinal and choroidal capillaries. It can aid in the diagnosis, monitoring, and treatment evaluation blood flow in the optic nerve in eyes with primary open-angle glaucoma.[49]

Doppler Fourier Domain Optical Coherence Tomography (Doppler FD OCT)

A non-invasive imaging technique, Doppler OCT measures blood velocity and volumetric flow rate in retinal branch vessels and is based on the principle of Doppler shift. Doppler OCT combines the principles of traditional OCT imaging with Doppler flowmetry to provide information about blood flow in the retina.[50] It uses a low-coherence light source to generate interference patterns, which are then analyzed to create high-resolution cross-sectional images of the tissue.[51]

By analyzing the frequency shift of the backscattered light caused by moving blood cells, Doppler OCT can quantify the velocity and direction of blood flow in retinal vessels. This information can be used to assess blood flow abnormalities, such as occlusions, stenosis, or abnormal vessel dilation, which may be indicative of various retinal vascular diseases.[52]

Doppler OCT has become a new imaging biomarker in ophthalmology for studying and diagnosing retinal vascular disorders, by providing detailed and quantitative information about blood flow dynamics in the retina, allowing for earlier detection and more accurate monitoring of various ocular conditions especially glaucoma.[53]

The drawbacks include the compromised image quality due to the phase artifacts that occur in vessels with high BF velocities, and being sensitive to BF parallel to the OCT beam.[54]

Optical Coherence Tomography Angiography (OCTA)

OCTA uses the principles of optical coherence tomography (OCT) and works by measuring the variations in the reflectivity of different layers of the retina to capture high-resolution three-dimensional images of the retinal and choroidal blood vessels without the need for contrast agents or dye injection.[55] One of the key advantages of OCTA is its ability to selectively visualize the blood vessels without the interference of other retinal structures, such as the retinal pigment epithelium (RPE) or the choroid. This allows for more accurate assessment of the characteristics of the blood vessels, such as their density, diameter, and flow velocity.[56]

OCTA being non-invasive with high-resolution imaging capabilities has various clinical applications, including the monitoring of treatment response and disease progression over time for ocular conditions such as diabetic retinopathy, age-related macular degeneration, and glaucoma, thus making this technique the most favored and advantageous.[56] Many artifacts, such as motion, attenuation, segmentation, and projection artifacts, impose limitations on OCTA and can critically interfere with the interpretation of OCT-A images.[57]

Table 1 provides a brief summary of the non-invasive techniques discussed, with glaucoma imaging being addressed.

Table 1 Summary of the Non-Invasive Techniques Used for OBF Measurement with Mention of Glaucoma Imaging

Non-Invasive Techniques for OBF			
Studies	**Technique**	**Detail**	**Utilization in Glaucoma**
Zegadło 2021[58]	Color Doppler Imaging (CDI)	CDI quantifies the velocity and direction of blood flow in retinal vessels and this information can be used to assess blood flow abnormalities.	In glaucoma patients, there have been OCT observations of Doppler parameters of retro bulbar arteries in association with thinning of the Retinal Nerve Fiber Layer (RNFL). This information can aid in the diagnosis, monitoring, and treatment of glaucoma, allowing for more proactive management of the glaucoma.
Calzetti 2022[59]	Laser Speckle Technique (LST)	Images the ocular blood flow with high resolution and high speed, utilizing the laser speckle phenomenon.	Correlations with visual field sensitivity and the favorable floor effect compared indicates LST as a promising clinical tool to monitor progression in late-stage glaucoma.
Chen 2022[60]	Blue Field Entoptic Technique	Can measure leukocyte speed in retinal perifoveal vessels	This technique can provide precision measurements of blood flow which can be set as a biomarker of glaucoma related dysregulation of blood flow in glaucoma.
Rolle 2019[61]	Heidelberg Retinal Flowmetry (HRF)	Measures the mean values of velocity, volume, and flow measurements using uses low laser light intensities	HRF has been reported to identify vessel densities and diminished microvascular network in POAG eyes.
Shughoury 2020[62]	Retinal Oximetry	An imaging approach based on the observation that light absorbed by hemoglobin depends upon its oxygen saturation.	Glaucoma pathogenesis is understood from the data of retinal metabolic oxygen demand and retinal oximetry holds great promise in its identification.
Kuerten 2021[63]	Retinal Vessel Analyzer (RVA)	Evaluates retinal vessel diameter by checking the brightness characteristics of the vessel.	Glaucoma patients have significantly altered localized retinal vessel regulation and vascular dysregulation in early glaucoma has been reported to be identified with RVA.
Banou 2023[14]	Laser Doppler Velocimetry (LDV)	Based on the principle of Doppler shift in a laser beam to measure the velocity in the assessment of absolute blood flow velocities in retinal arteries and veins.	Assessing the blood velocities using LDV provides crucial information leading to the diagnosis and monitoring of progression of glaucoma.
Mursch-Edlmayr 2021[44]	Laser Doppler Flowmetry (LDF)	It quantitatively measures the relative average velocity, number times velocity of red blood cells in retinal and choroidal capillaries.	Research evidence suggests that LDV performs well in the identification of abnormal optic nerve head blood flow autoregulation in POAG patients.
Abe 2022[64]	Doppler Fourier Domain Optical Coherence Tomography (DF - OCT)	Based on coherence domain optical technology, DFOCT is an imaging modality which uses coherence gating of backscattered light for tomographic imaging of tissue structure.	DFOCT has been reported to identify the relative blood flow in normal tension glaucoma eyes.
Bekkers 2020,[65] Hou 2020[66]	Optical Coherence Tomography Angiography (OCTA)	OCTA employs motion contrast imaging to high-resolution volumetric blood flow information and generates volumetric angiography images	Evidence suggests that glaucomatous vascular damage can be assessed using OCTA, and adds value to glaucoma diagnosis. The vessel density (VD) in the optic disc and macula can be differentiated using OCTA between POAG and Primary Angle Closure Glaucoma (PACG) eyes.

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Invasive Techniques

Scanning Laser Ophthalmoscope Angiography (SLO)

An invasive technique, SLO produces high-resolution images of the fundus utilizing a scanning laser ophthalmoscope along with different filters to perform fluorescein angiography (FA) and indo cyanine green (ICG) angiography.[58]

During SLO, a contrast agent (either fluorescein or indocyanine green dye) is injected into the patient's bloodstream and the SLO system captures images of the dye as it circulates through the blood vessels in the retina. These images are recorded on videotape or stored digitally at a rate of 30 images per second, allowing for the visualization of the dye's movement and the assessment of blood flow within the retinal vessels.[59]

By analyzing the SLO images, healthcare professionals can evaluate the blood flow patterns, identify any abnormalities or blockages, and assess the health of the retinal vasculature.[60] SLO is particularly useful as multicolor imaging[61] and auto fluorescence imaging to identify reduced blood flow in the retina, choroid, and optic nerve head demonstrating its potential in diagnosing glaucoma.[62]

Scanning Laser Ophthalmoscopic Angiography with Fluorescein and/or Indocyanine Green (ICG) Dye

During digital scanning laser ophthalmoscopic angiography (SLO-A), an invasive technique, a contrast agent, either fluorescein or indo cyanine green dye, is injected into the patient's bloodstream and to capture images of the dye as it circulates through the blood vessels in the retina and choroid.[14] By quantifying various aspects of blood flow, such as vessel diameter, blood velocity, and blood volume, SLO-A provides valuable information about the perfusion of the retina and choroid.[44]

These techniques can help in the diagnosis and monitoring of various ocular conditions, by visualizing the retinal circulation flow index which is evidence of reduced retinal hemodynamics, indicative of glaucoma.[64]

Dye leakage is a drawback of this technique which can interfere with the visualization of fine retinal vascular structures, along with the side effect of invasive dyes such as nausea and local and general allergic reactions.[65]

Table 2 features a brief summary of the invasive techniques discussed, with glaucoma imaging addressed.

Strengths and Limitations of Review

This review implements a comprehensive search through the PubMed search engine using a wide range of keywords, yielding a panoramic view of the current state-of-the-art imaging technologies used in OBF. While PubMed is a valuable resource, it is important to note that it may have limitations in terms of geographical coverage and language accessibility, and may not include all relevant studies published in non-English languages and in other countries where such technologies are not yet available. This review was also limited by the quality of the available studies, many of which were pilot trials or feasibility studies, with small sample sizes and heterogeneity in data, with no evaluation results. As seen from the limited number of studies available on ocular blood flow imaging in glaucoma cases, this field has enormous potential for improvement and evaluation.

Table 2 Summary of the Invasive Techniques Used for OBF Measurement with Mention of Glaucoma Imaging

Invasive Techniques for OBF			
Studies	**Technique**	**Detail**	**Utilization in Glaucoma Detection**
Stoskuviene 2019[67]	Scanning Laser Ophthalmoscope Angiography (SLO)	Here a collimated laser beam is used for visualizing and providing tomographic imaging of the ocular structures in vivo.	SLO has been identified as valuable method evaluation of vessel pattern and diameter for these capillaries to diagnose and assess glaucoma.
Burn 2022[68]	Ophthalmoscopic Angiography with indocyanine green (ICG) dye	Retinal circulation in great detail, fluid can be imaged due to the physical characteristics of indocyanine green (ICG).	The vascular regression in POAG has been imaged and studied using ophthalmoscopic – angiography with indo cyanine green (ICG) dye.

Conclusion

Ocular blood flow is impaired in glaucoma and its clinical evaluation is complex; thus, it is of interest in ophthalmology. Many state-of-the-art technologies for evaluating OBF in glaucoma have evolved, catering to the early detection and risk of glaucoma progression.

There is a critical lack of scientific evidence from clinical and evaluation studies to support the feasibility of measuring the OBF in glaucoma. Trials should be undertaken using gold-standard normative databases for each measurement technique to correlate the relationship between ocular hemodynamics, metabolism, and glaucoma progression. The non-invasive technique of OCT angiography is currently supported as a great scientific and clinical tool for the identification of glaucoma pathogenesis, which can lead to its earlier detection.

From the discussed techniques, no single technique has become the standard for measuring ocular blood flow (OBF), and each technique has its own limitations. One of the challenges is that these techniques typically measure only one aspect of blood flow, such as velocity or volume, while blood flow involves multiple variables. However, despite these limitations, the collective application of these techniques in numerous studies has provided valuable insights into the hemodynamic changes associated with normal physiology and ocular diseases. By using a combination of techniques, researchers have been able to identify patterns and trends in OBF that can aid in understanding various conditions.

As technology continues to advance, the shortcomings of current methods are gradually being addressed. Newer techniques are being developed, and existing ones are being refined to provide more accurate and comprehensive measurements of OBF. These advancements may include improvements in resolution, increased sensitivity, and the ability to measure multiple variables simultaneously.

In the future, it is likely that physicians will have access to a wider range of OBF measurement methods in the clinical setting.

This expanded toolbox of techniques will provide more comprehensive assessments of ocular blood flow and contribute to better diagnosis, monitoring, and management of ocular diseases. It is important to note that ongoing research and technological advancements are essential in order to validate and establish the clinical utility of these emerging techniques. The field of OBF measurement is evolving, and with further advancements, more standardized and clinically applicable methods may emerge.

Disclosure

The author reports no conflicts of interest in this work.

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