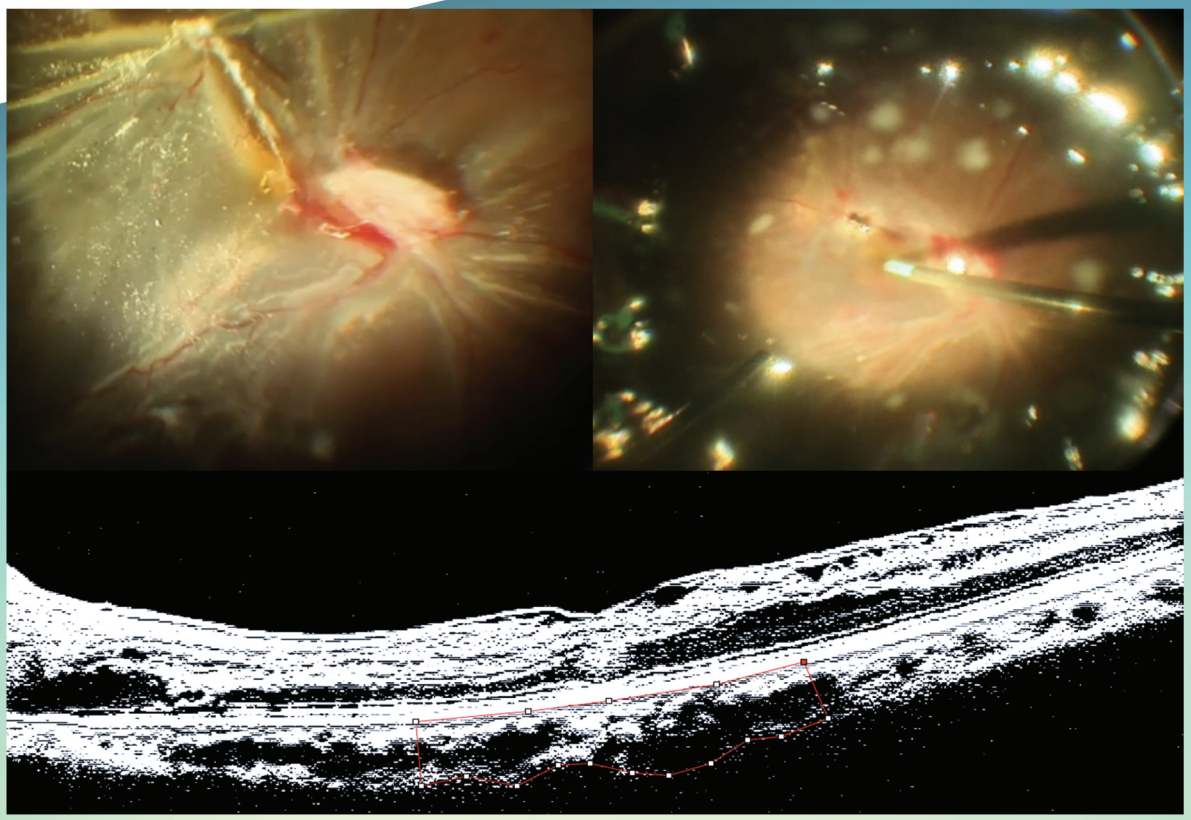
OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY FOR CHOROIDAL AND VITREORETINAL DISORDERS - PART 1



Editors:
Miguel A. Quiroz-Reyes
Virgilio Lima-Gomez

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Optical Coherence Tomography Angiography for Choroidal and Vitreoretinal Disorders Part 1

Edited By

Miguel A. Quiroz-Reyes
Oftalmologia Integral ABC, Retina Department
Medical and Surgical Assistance Institution (Nonprofit Organization)
Affiliated with the Postgraduate Studies Division
National Autonomous University of Mexico
Mexico City, Mexico

&

Virgilio Lima-Gomez
Ophthalmology Service, Hospital Juarez de Mexico
Public Assistance Institution (Nonprofit Organization)
Mexico City, Mexico

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Editors: Miguel A. Quiroz-Reyes & Virgilio Lima-Gomez

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FOREWORD

There is no doubt that serendipity plays an important role in many scientific developments. One very clear example is the evolution of Ophthalmic Coherence Tomography (OCT) in Ophthalmology.

In the early 1970s, Michel Duguay at the AT & T Bell Laboratories published "Light photographed in flight", where he proposed that echoes of light could be used to examine biological tissue. In the mid-1970s, Erich Ippen, of Massachusetts Institute of Technology (MIT), further developed femtosecond optics. Both discoveries built the foundation of the concept called optical reflectivity, with the idea that light interference could be used to obtain a non-invasive "biopsy" of translucid tissues. In the late 1980s, corneal refractive surgery was at its summit. It required an accurate measurement of corneal thickness. James Fujimoto of MIT collaborated with Ophthalmologists Joel Schuman, David Huang and Carmen Puliafito to refine this measurement, using low-coherence interferometry with only partial success. Nevertheless, in a poorly focused image of the cornea, Huang noticed what appeared to be an optical section of the retina in the background. Instead of dismissing this poorly defined image as useless, Huang continued experimenting until he was able to obtain an optical transverse image of the retina. Thus, retinal and choroidal OCT was born. Today OCT constitutes the most important ancillary test and standard of care in Ophthalmic practice, not only in vitreoretinal pathology, but also in glaucoma and problems of the anterior segment.

More recently, swept-source OCT, which can produce 500,000 scans per second and OCT angiography, employing motion contrast imaging, allow us to image retinal capillaries and the smallest neo-vessels in the retinal tissues. Also, enhanced penetration has allowed to provide detailed visualization of the choroid. New technologies are in constant development, such as visible light OCT (visOCT) and adaptive optics (AO-OCT) will allow further details and deeper penetration.

In this particular section of the book, after a review of general principles and advances of OCT and OCTa use in vitreoretinal disorders, all the contributors and coauthors engage in describing to us the normal and pathological parameters of macular and choroidal perfusion patterns, followed by a description and findings in several vitreoretinal and choroidal pathological disorders.

There is no doubt that all the new and described findings in this book will widen our knowledge and be of benefit to our ailing patients.

Alexander Dalma M.D.
Mexico City

PREFACE

Optical coherence tomography angiography is one of the most important recent innovations in ophthalmology. The book you have in your hands represents the collaborative efforts of a select team of subject matter experts. This book aims to be a practical, patient-centered guide complemented with a clinical approach and demonstrative clinical cases to assist ophthalmologists and ophthalmology trainees in the evaluation of newly developed perfusion concepts and the diagnosis and management of patients presenting with a wide spectrum of diseases of the retina and choroid, as well as the role of perfusion parameters in the pathogenesis of diverse diseases. As mentioned briefly before, this book describes the journey from basic ophthalmology principles to the most sophisticated current aspects and advances that have resulted in the development of superb technological innovations. We have gone from fundus fluorescein angiography imaging to the evaluation of the perfusional indices of retinochoroidal structures using noninvasive and noncontact imaging techniques that allow a high histopathological correlation of structural tissue characterization with microvascular evaluation on tissue perfusion.

Written by leading international experts in the field, *Optical Coherence Tomography Angiography for Choroidal and Vitreoretinal Disorders* serves as a practical tool for daily work in a retina clinic, helping you through the first steps of perfusion investigation and clinical evaluation, correlation management and treatment decisions for these complex patients. Each chapter details distinct diseases of the retina or choroid, with a focus on signs and perfusion; optical coherent tomography is emphasized, and the chapters are illustrated with many multipaneled images, such that the book may be used as a reference for deciding on diagnostic and treatment options.

This book dissects the basics of angiography by optical coherence tomography and explains the differences in the clinical utility of optical coherence tomography as well as its complementarity. This gives us a broad explanation of the nomenclature and normal perfusional findings in healthy populations.

Several chapters explain macular perfusional findings in different vitreoretinal and choroidal pathologies, including vascular entities commonly seen in daily practice, such as diabetic retinopathy, hemorrhagic and ischemic infarctions of the retina due to vascular disorders, and choroidal pathological neovascularization; most importantly, perfusion parameters are evaluated by quantification and binarization of the different vascular plexuses at the retinal and choroidal level. Additionally, certain tractional entities are evaluated from the point of view of their microstructural findings and perfusional postoperative outcomes, associating them with the final vision.

Some chapters deal with new antivascular endothelial growth factor molecules and new extended-release delivery devices and provide a comparative evaluation of the therapeutic effect on perfusion. In this way, multiple complex pathological disorders of the retina and choroid are more efficiently diagnosed, followed by natural and treated medical or surgical evolution according to the specific cause and consequently, as mentioned before, monitored in response to specific treatments.

We hope that this book, from a multitude of experts, contributes pertinently to academia and achieves the objective of serving as a guide both in the diagnosis and clinical decision-making that those of us who are dedicated to the difficult but beautiful and challenging practice of clinical and surgical retina care perform on a daily basis.

Miguel A. Quiroz-Reyes, MD
Oftalmologia Integral ABC, Retina Department
Medical and Surgical Assistance Institution (Nonprofit Organization)
Affiliated with the Postgraduate Studies Division
National Autonomous University of Mexico
Mexico City, Mexico

&

Virgilio Lima-Gomez, MD
Ophthalmology Service, Hospital Juarez de Mexico
Public Assistance Institution (Nonprofit Organization)
Mexico City, Mexico

List of Contributors

Alan B. Trevino-Herrera	Ophthalmology Department, School of Medicine, and University Hospital "Dr. Jose Eleuterio Gonzalez, UANL, Monterrey, Mexico
Akin Akyurt	Venividigoz Eye Center, Kadikoy-Istanbul, Turkey
Alper Bilgic	Alphavision Augenarztpraxis, Bremerhaven, Germany
Ana L. Diazceballos-Garcia	Institute of Ophthalmology, Fundacion Conde de Valenciana, Private Assistance Institution (Nonprofit Organization), Mexico City, Mexico
Ahmad R. Alsaber	Department of Mathematics and Statistics, University of Strathclyde, Glasgow, UK
Alejandra Nieto-Jordan	Institute of Ophthalmology, Fundacion Conde de Valenciana, Private Assistance Institution (Nonprofit Organization), Mexico City, Mexico
Boris Moreno-Andrade	Institute of Ophthalmology, Fundacion Conde de Valenciana, Private Assistance Institution (Nonprofit Organization), Mexico City, Mexico
Erick A. Quiroz-Gonzalez	Oftalmologia Integral ABC, Retina Department, Medical and Surgical Assistance Institution (Nonprofit Organization), Affiliated with the Postgraduate Studies Division, National Autonomous University of Mexico, Mexico City, Mexico Institute of Ophthalmology, Fundacion Conde de Valenciana, Private Assistance Institution (Nonprofit Organization), Mexico City, Mexico
Felipe Esparza-Correa	Institute of Ophthalmology, Fundacion Conde de Valenciana, Private Assistance Institution (Nonprofit Organization), Mexico City, Mexico
Jesus H. Gonzalez-Cortes	Ophthalmology Department, School of Medicine, and University Hospital "Dr. Jose Eleuterio Gonzalez, UANL, Monterrey, Mexico
Jesus E. Gonzalez-Cantu	Ophthalmology Department "Guillermo Avalos Urzua Institute", Universidad Galileo, Guatemala
Jorge Morales-Navarro	Institute of Ophthalmology, Fundacion Conde de Valenciana, Private Assistance Institution (Nonprofit Organization), Mexico City, Mexico
José Dalma-Weiszhausz	Asociacion para prevenir la Ceguera en Mexico. Mexico City. Mexico
Jennifer H. Kim-Lee	Institute of Ophthalmology, Fundacion Conde de Valenciana, Private Assistance Institution (Nonprofit Organization), Mexico City, Mexico
Martin Flores-Aguilar, MD, MsSc	Unidad de Retina del Centro, Ophthalmology and Retina Specialists Unit. Hermanos Aldama 227-101 Center Celaya, Mexico
Mario Carranza-Casas	Institute of Ophthalmology, Fundacion Conde de Valenciana, Private Assistance Institution (Nonprofit Organization), Mexico City, Mexico
Miguel A. Quiroz-Reyes, MD	Oftalmologia Integral ABC, Retina Department, Medical and Surgical Assistance Institution (Nonprofit Organization), Affiliated with the Postgraduate Studies Division, National Autonomous University of Mexico, Mexico City, Mexico

Miguel A. Quiroz-Gonzalez	Oftalmologia Integral ABC, Retina Department, Medical and Surgical Assistance Institution (Nonprofit Organization), Affiliated with the Postgraduate Studies Division, National Autonomous University of Mexico, Mexico City, Mexico
Margarita Montano	Oftalmologia Integral ABC, Retina Department, Medical and Surgical Assistance Institution (Nonprofit Organization), Affiliated with the Postgraduate Studies Division, National Autonomous University of Mexico, Mexico City, Mexico
Renata Garcia-Franco	Instituto de la Retina del Bajio, Queretaro, Mexico
Selma Alin Somilleda-Ventura, DSc	Biomedical Research Center, Fundacion Hospital Nuestra Señora de la Luz, Private Assistance Institution (Non-profit Organization), Mexico City, Mexico Interdisciplinary Center of Health Sciences at the National Polytechnic Institute, Mexico City, Mexico
Sergio E. Hernandez Da Mota, MD	Servicio de Retina, Clinica David and Michoacan University School of Medicine, Morelia, Mexico
Sanjay Marasini	Department of Ophthalmology, The University of Auckland, Auckland, New Zealand
Virgilio Lima-Gómez, MD	Ophthalmology Service, Hospital Juarez de Mexico, Public Assistance Institution (Nonprofit Organization), Mexico City, Mexico

CHAPTER 1

Principles of Optical Coherence Tomography Angiography in Ophthalmology

Selma Alin Somilleda-Ventura, DSc[1,2,*]

[1] *Biomedical Research Center, Fundacion Hospital Nuestra Señora de la Luz, Private Assistance Institution (Non-profit Organization), Mexico City, Mexico*

[2] *Interdisciplinary Center of Health Sciences at the National Polytechnic Institute, Mexico City, Mexico*

Abstract: Optical coherence tomography (OCT) has proven to be an effective diagnostic technique for evaluating ocular structures, particularly for studying retinal layers and other areas of the posterior segment of the eye. The incorporation of strategies and algorithms that allow the observation of the retinal microvasculature and the flow of red blood cells currently represents important advances in the diagnosis and treatment of inflammatory, neural, and vascular retinal diseases. The advantage is that OCT is a non-invasive method that does not require the use of contrast dyes. For this reason, OCT combined with angiography (OCTA) is one of the most important techniques for the study of vitreoretinal disorders. Its optical principle, which is based on the Doppler technique, allows us to understand how OCTA equipment acquires and processes images to facilitate visualization and interpretation through their two- and three-dimensional reconstructions. In addition, OCTA allows the identification of signal alterations that could appear as artifacts on each tomography or angiographic scan. This chapter aims to explore the characteristics and further applications of OCTA in addition to its relevance in ophthalmological clinical practice.

Keywords: Algorithms, Angiography, Artifacts, Choriocapillaris, Contrast dye, Cross-sectional scans, Deep vascular plexus, Doppler technic, En face image, Foveal avascular zone, Image visualization, Inner limiting membrane, Interferometry, Interscan time, Optical coherence tomography, Red blood cells, Retinal layers, Retinal microvasculature, Retinal pigment epithelium, Signal intensity, Spectral domain, Spectrometer, Superficial vascular plexus, Vessel density, Vitreoretinal disorders.

[*] **Corresponding author Selma Alin Somilleda-Ventura, DSc:** Biomedical Research Center, Fundacion Hospital Nuestra Señora de la Luz, Private Assistance Institution (Non-profit Organization), Mexico City, Mexico;
Tel: +52 55 5128 1140; Tel: +52 55 5729 6000; E-mail: ssomilleda@ipn.mx

Miguel A. Quiroz-Reyes and Virgilio Lima-Gomez (Eds.)

INTRODUCTION

The study of ocular anatomy is a fundamental part of understanding the physiological and pathophysiological processes related to this organ. Using imaging methods that have evolved over more than three decades [1], it has been possible to observe ocular structures such as the retina and develop lines of research focused on evaluating blood flow in the retinal microvasculature.

Although fluorescein angiography (FA) has demonstrated its usefulness in the study of the main ocular irrigation pathways (central retinal artery and vein and their derivations) [2, 3], it cannot provide an image of the deep vascular plexus (DVP), which plays an important role in the oxygenation and functioning of the cells of the retinal neural axis. After the introduction of optical coherence tomography (OCT) as a noninvasive and painless imaging technique that uses light to create cross-sectional and three-dimensional highly detailed images of the retina, it is possible to obtain good resolution views of the segmented retina [4], which can provide information that is not visible with other imaging techniques. However, it became evident that the study of this tissue in *quasi-histological* sections [5, 6] was insufficient to fully evaluate this tissue because it was not possible to visualize the blood flow of the superficial and deep plexuses.

Given the existence of methods (such as Doppler techniques) that allow blood flow measurements of other structures, such as the skin [7 - 10], adaptation to the spectral domain and swept-source OCT models is necessary. However, to understand the operation of OCT with angiography (OCTA), it is necessary to explain the optical principles of conventional OCT to establish their relationship with and influence in this field.

OCT: OPTICAL PRINCIPLE

OCT is a high-resolution, non-invasive imaging technique that allows visualization of retinal layers in real time [11, 12]. The initial model called time-domain OCT (TD-OCT) uses light from the infrared spectral range, which is divided into two light beams: (1) the first is reflected in a reference mirror and (2) the second is directed toward the sample tissue (test beam), after which a measurement of the backscattered light is performed by low-coherence interferometry [3, 10, 13]. As the reference mirror changes, the depth of the analyzed section also changes because of the variation in the intensity of the backscattered light.

This full depth profile is called an amplitude scan (A-scan); on the other hand, if the beam performs a lateral scan of the tissue, a cross-sectional image known as a B-scan is obtained (Fig. **1**). The next generation of OCT (frequency domain or

FD-OCT) no longer requires manual scanning of the length of the optical path [13] because it has spectral information from the interferometric signal to form the image.

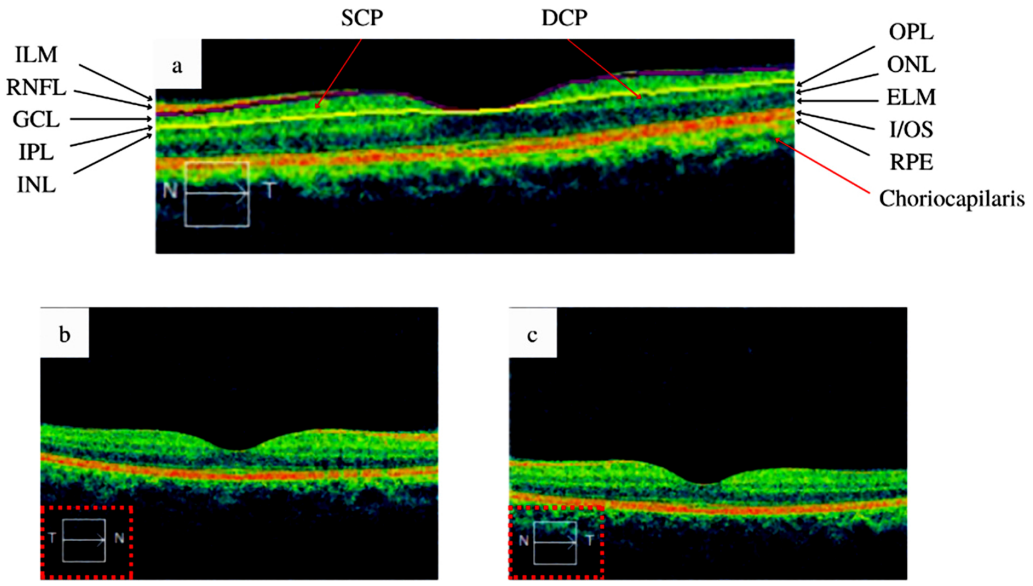

Fig. (1). Quasi-histological section of the retina. (**a**) The spectral domain optical coherence tomography (SD-OCT) image allows visualization of the layers that integrate the retina with the inner limiting membrane (ILM) to the choriocapillaris. Construction of the color image facilitates the identification of each layer. Automatic segmentation lines mark the perimeter between the retinal nerve fiber layer (RNFL) and ganglion cell layer (GCL, purple line), and the perimeter between the inner plexiform layer (IPL) and inner nuclear layer (INL, yellow line). (**b**) and (**c**) Horizontal sections (B-scans) of two healthy retinas, namely the right eye and left eye, respectively. The OCT image automatically provides the scan direction (commonly at the left of each scan).

The incorporation of the spectrometer into the new OCT models known as spectral domain OCT (SD-OCT) changed its optical principle because it used a diffraction element to separate the different wavelengths emitted toward the spectrometer, which were subsequently captured as a superposition of fringe patterns by a high-speed camera (Fig. **2**) [13 - 15]. However, swept-source OCT (SS-OCT) replaces the diffraction element with a high-speed photodetector that allows the interferometric signal to be scanned, equivalent to the spectral interferogram of SD-OCT [16, 17].

CHAPTER 2

Contributions of Optical Coherence Tomography Angiography to the Current Study and Treatment of Eye Diseases

Jesus H. Gonzalez-Cortes[1,*], Alan B. Trevino-Herrera[1], Alper Bilgic[2], Sergio E. Hernandez Da Mota[3], Jesus E. Gonzalez-Cantu[4], Akin Akyurt[5] and **Renata García Franco[6]**

[1] *Ophthalmology Department, School of Medicine, and University Hospital "Dr. Jose Eleuterio Gonzalez, UANL, Monterrey, Mexico*

[2] *Alphavision Augenarztpraxis, Bremerhaven, Germany*

[3] *Servicio de Retina, Clinica David and Michoacan University School of Medicine, Morelia, Mexico*

[4] *Ophthalmology Department "Guillermo Avalos Urzua Institute", Universidad Galileo, Guatemala*

[5] *Venividigoz Eye Center, Kadikoy-Istanbul, Turkey*

[6] *Instituto de la Retina del Bajio, Queretaro, Mexico*

Abstract: Optical coherence tomography angiography (OCT-A) is an advanced noninvasive retinal blood flow imaging technique. It uses motion-contrast imaging to obtain high-resolution volumetric blood flow information to enhance the study of retinal and choroidal vascular pathologies. OCT-A can obtain detailed images of the radial peripapillary network, the deep capillary plexus (DCP), the superficial capillary plexus (SCP) and the choriocapillaris. In addition, compared to fluorescein angiography (FA), this technique does not require the use of injected dye. This chapter aims to present OCT-A technology and clarify its terminology and limitations. The discussion summarizes the potential application of the technology in different retinal and choroidal diseases.

Keywords: Optical coherence tomography angiography, Principles, Clinical relevance, Retinal diseases, Choroidal diseases.

[*] **Corresponding author Jesus H. Gonzalez-Cortes:** Ophthalmology Department, School of Medicine, and University Hospital "Dr. Jose Eleuterio Gonzalez, UANL, Monterrey, Mexico; Tel: +52 8154 5652; E-mail: drjesusgzz@gmail.com

Miguel A. Quiroz-Reyes and Virgilio Lima-Gomez (Eds.)

INTRODUCTION

Optical coherence tomography angiography (OCT-A) is a new non-invasive imaging technology of the retinal and choroidal perfused microvasculature that was developed to improve the study and understanding of vascular pathologies. The OCT-A technique is based on the principle of mapping the movement of erythrocytes over time, comparing the motion contrast on sequential OCT B-scans, and allowing high-resolution three-dimensional volumetric reconstruction and analysis of the perfused vessels in a matter of seconds [1].

In order to create a map of blood flow, OCT-A analyses the decorrelation signal, which is defined as the differences in the backscattered optical coherent tomography (OCT) signal intensity or amplitude, between successive OCT b-scans obtained at the exact same cross-section. Sites of motion between consecutive OCT b-scans indicate solely erythrocyte movement in retinal blood vessels since axial bulk motion from patient movement is excluded [1].

OCT-A technology does not require intravascular dyes since it properly depicts vessels at different levels of segmentation by using laser light reflected from the surface of moving red blood cells [2]. OCT-A can image detailed flow in the radial peripapillary network (RPN), the superficial capillary plexus (SCP), the deep capillary plexus (DCP), and the choriocapillaris layer. Fundus fluorescein angiography (FA) is an imaging technique that continues to be the gold standard for retinal vascular pathology assessment. Unlike FA, OCT-A does not require contrast medium injections, associated with potential adverse reactions ranging from nausea to complete anaphylaxis. In addition, OCT-A allows images to be acquired in seconds compared to the minutes required for FA.

The two most popular OCT-A devices are spectral domain (wavelength: 840 nm) and swept-source (SS) devices (wavelength: 1050 nm). Overall, the longer wavelength of the SS device is clinically significant. The longer wavelengths in SS devices, provide greater choroid visualization and enhanced penetration into the retinal pigment epithelium (RPE), despite the reduction in axial resolution [3, 4].

Recently, OCT-A technology has developed extended retinal acquisitions that allow assessment beyond the posterior pole. OCT-A technology has enabled the increase in the field of view, which enhances the sensibility in retinal and choroidal pathology detection. The increase in the field of view is a product of faster-capturing devices, reduced resolution of the scans, and improved montage techniques. The future of OCT-A will be focused on improving the resolution of the scans, reducing the acquisition time with the option of wide and ultra-wide imaging [5].

OCT-A is gaining ground in the diagnosis of retinal and choroidal diseases, and it is likely that in the future, it may displace FA as the diagnostic tool of choice for these diseases.

HISTORY

Since the late 1930s, there has been growing interest in the study of the retinal vasculature, and different observations have been published on the coloration and caliber of the retinal vasculature under oxygen inhalation [6]. There is a growing need to develop methods to visualize the retinal vasculature. It was not until 1961 that Novotny and Alvis developed a method of photographing fluorescence in the human retina, today known as fundus fluorescein angiography [7]. This was a major advance for the physiologic and pathologic study of the choroidal and retinal vasculature. However, it was not until 1992 that Yannuzzi *et al.* described digital indocyanine green videoangiography that provided enhanced imaging of the choroidal circulation [8].

Different imaging techniques have been developed for the study of the retinal vasculature, including ultrasound color Doppler, laser Doppler velocimetry, laser speckle assessment and blue field entopic techniques; however, they are not widely used clinically due to difficulty of use, limited availability and poor reproducibility [9].

In 1991, Huang *et al.* described the OCT technique, which became the diagnostic gold standard for macular pathology [10]. From then on, different techniques were progressively developed in the quest to find a tool for blood flow imaging based on time domain OCT. One of them was Doppler OCT, based on the flow-induced Doppler phase shift between A-scans that enabled the calculation of the axial vascular velocity [11]. This technique allowed us to measure blood flow in parallel vessels and in great retinal vessels but not in perpendicular vessels or in the microvasculature [12]. Volumetric angiography did not develop until the advent of spectral domain OCT (SD-OCT) and swept source OCT (SS-OCT).

In 2006, Makita *et al.* used SD-OCT to perform volumetric angiography for retinal and choroidal vascular assessment [13]. In 2008, An *et al.* reported the optical microangiography (OMAG) technique, which was capable of providing volumetric vasculature images in the retina and choroid at a capillary level of resolution [14]. In 2005, Baston *et al.* used speckle analysis in time domain OCT images to determine depth-resolved flow [15]. In 2008, Mariampillai *et al.* presented speckle variance detection in microvasculature using SS-OCT. In 2011, Enfield *et al.* proposed correlation mapping OCT that enabled mapping of vascular networks, and parameters such as capillary density and vessel diameter were determined [16].

CHAPTER 3

Optical Coherence Tomography *vs* Optical Coherence Tomography Angiography in the Differential Diagnosis of Choroidal and Vitreoretinal Diseases

Martin Flores-Aguilar, MD, MsSc[1,*]

[1] *Unidad de Retina del Centro, Ophthalmology and Retina Specialists Unit. Hermanos Aldama 227-101 Center Celaya, Mexico*

Abstract: Optical coherence tomography (OCT) is a practical and common imaging method for the study of diseases of the retina, choroid, and vitreoretinal interface. Software and technological advances have allowed us to observe changes in the retinal at resolutions less than 5 μm; the development of angiography with OCT (OCTA) allows us to three-dimensionally evaluate the existing perfusion in the analyzed retina and choroid non-invasively and without a specific dye, such as fluorescein or indocyanine green angiography. We can detect important clinical differences between OCT and OCTA, although these approaches are complementary. Diabetic retinopathy, vascular occlusions, and choroidal neo-vascularization secondary to age-related macular degeneration and other causes are among the conditions whose diagnosis, treatment, and follow-up benefit from applying these techniques. Leak quantification in cases of macular edema is a good candidate for future objective evaluation; currently, its existence is only demonstrable in structural OCT, although it can be indirectly inferred in OCTA by observing vascular displacements and deformity of the capillary walls. Using OCTA, it is possible to detect intravascular flow even in fibrous tissue, thereby allowing the evaluation of neo-vascular activity in vasoproliferative diseases.

Keywords: OCT, OCTA, Segmentation, Macular telangiectasia, Diabetic retinopathy, Macular degeneration, Vascular occlusion, Arterial occlusion, Venous occlusion, Choroidal neo-vascularization, Macular ischemia, Macular edema, Myopic neo-vascularization.

[*] **Corresponding author Martin Flores-Aguilar, MD, MsSc:** Unidad de Retina del Centro. Ophthalmology and Retina Specialists Unit. Hermanos Aldama 227-101 Center Celaya, Mexico; Tel: +52 4616123581; Fax: +52 4616123581; E-mail: martinretina@yahoo.com

INTRODUCTION

Current advances in retinal imaging technology have allowed access to accurate diagnosis and early treatment in the field of retinal pathology. Optical coherence tomography (OCT) is a non-invasive, practical imaging technique that can be performed in an outpatient setting providing useful information from the anterior segment of the eye, retina, choroid, and optic nerve. Much has been said that it provides an optical biopsy of the retina structure. The first commercial version of the OCT appeared in 2022 (Stratus OCT, Carl Zeiss Meditec Inc, Dublin California EEUU) based on Time-Domain technology with capture speeds of up to 400 scans per second and axial and transverse resolution of 10 and 20 microns respectively. Subsequently, equipment based on Spectral-Domain technology appeared being up to 200 times faster than previous models and with an axial resolution of 5 microns and transversal resolution of 15 microns with acquisition speeds of up to 40,000 scans per second. Currently, in their latest versions, these devices have improved their acquisition speeds of up to 130,000 scans per second (Revo Nx 130, Optopol Technology, Zawercie, Poland). There are also devices based on Swept Source technology allowing scanning speeds up to 100,000 scans per second and better visualization of deep structures under the retinal pigmented epithelium (DR OCT Triton, Topcon Medical Systems, Japan). The best structural images are obtained by averaging many scans over the same point and will depend on the device technology and be influenced by the tracking systems to compensate for saccadic eye movements. Also, optical coherence tomography angiography (OCTA) can be performed to obtain three-dimensional visualization of perfused vessels of the retina and choroid [1]. OCTA, using special algorithms, analyzes the temporal changes in the OCT signal (not only the reflected light). Based on repetitive OCT sampling (B-Scans) from the same retinal segment, it is possible to analyze temporal changes in the signal caused by moving particles (such as those due to the movement of erythrocytes through blood vessels), being able to discern these from those caused by other sources of changes in the signal (such as eye movements or noise in the OCT signal), pixels that change over time are shown white and those that do not change appear in black. Because several algorithms and a wide variety of clinical devices are used for the construction of OCTA images, the images obtained may have significant variations, even when obtained from the same patient.

Any system that performs OCTA has some basic requirements, such as: the structural image of the OCT on which a functional image is obtained using a decorrelation algorithm (SSADA Split-Spectrum Amplitude Decorrelation Angiography was the first developed), very high scan speed between 65,000 and 100,000 scans per second, en face 3D analysis showing the presence or absence of flow in the different layers of the retina, motion correction technology and parallel

processing architecture. Using sets of multiple scans (dense volume), it is possible to obtain OCTA images similar to those obtained by fluorescein angiography, which remains the gold standard. OCTA has the advantage of not requiring the injection of any dye for obtaining images, also allowing visualization of the circulation in the retina (superficial and deep plexus) and the choroid separately if the appropriate segmentation is used (usually performed automatically) [2]. If there is pathology on the retina, the automatic segmentation might fail, both when performing OCT and OCTA, so in some equipment, the segmentation must be performed manually in some scans with the subsequent correction of the entire volume. Also, each of the algorithms has characteristics that can limit the efficiency of image acquisition, such as: the reduction of light penetration to the deepest layers and the appearance of artifacts projected from the most superficial layers to the deepest. Artifacts can be multivariate in origin and generated during image acquisition due to eye movements, the processing of the set of images obtained, and display strategies [3]. Another important characteristic of OCTA is that the intensity of the vessels that we observe is directly related to the amount of flow detected by the equipment, which can be a source of artifacts since there is a threshold for flow detection. For example, we could find areas with a very slow flow that are interpreted as no flow, with important clinical repercussions for decision-making. Perhaps the two most important limitations of the OCTA are the size of the image obtained and the inability to detect leakage. Currently, the devices released for clinical use allow obtaining sample sizes of 3 × 3, 6 × 6, 8 × 8, and 12 × 12 mm, thereby limiting the visualization of the circulation at the equator and the retinal periphery. With the most current devices, it is possible to assemble several images reaching mosaics up to 31 x 27 mm (Xephilio OCT-S1 Canon Medical Systems). On the other hand, there are some algorithms under study to detect changes in cell density and their correlation with increased retinal thickness in macular edema.

For practical purposes, we can classify retinal pathology as those of the inner retina (retinopathies, congenital and acquired vascular defects) and those of the outer retina and choroid (choroidal neo-vascularization or CNV).

INNER RETINAL ABNORMALITIES

Vitreoretinal Interface

The study of the retinal surface, as well as the vitreous interface, has been greatly facilitated with the use of OCT; vascular changes of the inner surface of the retina secondary to traction are evaluated by OCTA. Macular holes, epiretinal membranes, and tractional syndromes are evaluated in detail. The International Vitreomacular Traction Study Group classification provided new definitions for

CHAPTER 4

Nomenclature and Current Indications of Optical Coherence Tomography Angiography in Diseases of the Choroid and Retina

Sergio E. Hernandez Da Mota, MD[1,*], Jesus H. Gonzalez-Cortes[2] and **Renata Garcia-Franco[3]**

[1] *Servicio de Retina, Clinica David and Michoacan University School of Medicine, Morelia, Mexico*

[2] *Ophthalmology Department, School of Medicine, and University Hospital "Dr. Jose Eleuterio Gonzalez," UANL, Monterrey, Mexico*

[3] *Instituto de la Retina del Bajio, Queretaro, Mexico*

Abstract: One of the most significant developments in ocular imaging in the last century was optical coherence tomography (OCT). OCT angiography (OCT-A), an extension of OCT technology, offers depth-resolved images of the blood flow in the choroid-retina that are much more detailed than those produced by earlier imaging techniques such as fluorescein angiography (FA). Due to its requirements of novel tools and processing methods, the prevailing imaging constraints, the rapid improvements in imaging technology, and our knowledge of the imaging and relevant pathology of the retina and choroid, this novel modality has been challenging to implement in daily clinical practice. Even those familiar with dye-based ocular angiography will find that mastering OCT-A technology requires a steep learning curve due to these issues. Potential applications of OCT-A include almost all diseases of the choroid and retina, as well as anterior segment diseases. Currently, the most common indications are age-related macular degeneration and ischemic retinopathies, including diabetic retinopathy and retinal occlusive vascular disorders. Incorporating OCT-A into multimodal imaging for the comprehensive assessment of retinal pathology is a fast-growing area, and it has expanded our knowledge of these complex diseases in terms of diagnosis and treatment. This review describes the current main indications of OCT-A in retinal and choroidal diseases.

Keywords: OCT-angiography, OCT, Retinal diseases, Macular diseases, Choroidal diseases, Fluorescein angiography.

[*] **Corresponding author Sergio E. Hernandez-Da Mota, MD:** Servicio de Retina, Clinica David and Michoacan University School of Medicine, Morelia, Mexico; Tel: +52 443 314 4362; E-mails: tolodamota@yahoo.com.mx and tolodamota@cloud.com

Miguel A. Quiroz-Reyes and Virgilio Lima-Gomez (Eds.)

INTRODUCTION

A-scan and B-scan cross-sectional reconstruction after optical coherence tomography (OCT) scanning has been used to produce two-dimensional (2D) and three-dimensional (3D) images of various eye tissues. Furthermore, spectral-domain OCT (SD-OCT) has an improved sensitivity and signal-to-noise ratio [1 - 5].

The OCT scanning velocity (approximately 25,000 to 85,000 scans per second) makes it extensively applied in monitoring and diagnosing many retinal and other eye diseases. Swept-source OCT (SS-OCT) is a more recently developed OCT variant. Wavelengths of approximately 800 nm are used by SD-OCT, while a longer wavelength (1000 nm) is used by SS-OCT [1].

SS-OCT scans across a narrower spectrum of wavelengths using a center light source at 1μm, compared to SD-OCT. SS-OCT's longer wavelength provides a deeper penetration of retinal layers and an improved visualization of the choroid [1].

Optical coherence tomography angiography (OCT-A) is an imaging technology, an extension of OCT technology, that allows for three-dimensional viewing of the choroid's and retina's perfused vasculature and is non-invasive. OCT-A measures the intensity of the reflected light and the fluctuations of the optical coherence tomography (OCT) signal in contrast to conventional structural OCT [2].

Conventional OCT is excellent at obtaining static 3D structural data from the retina. Nonetheless, it is insufficient for producing helpful angiograms since it only detects the image contrast from blood vessel walls. Conversely, OCT-A utilizes blood cell movement to produce angiograms with excellent picture contrast [1].

OCT-A systems collect several B-scans at the same area in the retina to derive information about blood cell mobility. Clinical OCT-A is now feasible due to recent advancements in OCT data collecting speeds, which made it possible to adopt intricate scanning methods promptly. Then, methods for separating motion contrast from the shifting dispersion of moving blood cells were established. Erythrocytes, for instance, disperse differently based on their velocity, shape, and orientation.

To create the 3D OCT-A volume and its en-face projection, OCT-A algorithms separate OCT signals with unaltered scattering from static tissue and preserve the OCT signals associated with motion [1].

OCT-A algorithms can compare the phase and the amplitude between B-scans since the raw data from OCT A-scans is complex-valued [3].

The split-spectrum amplitude-decorrelation algorithm, known as SSADA, is one of the algorithms used by OCT-A devices that examine amplitude differences between B-scans. Conversely, the optical microangiography algorithm compares phase and amplitude discrepancies. Additionally, the OCT spectrum is divided into eleven sub-bands by the SSADA algorithm, which is known to boost the signal-to-noise ratio but reduces the axial resolution of the final image [1].

Obtaining OCT-A images equal to fluorescein angiography (FA) images is feasible using these dense volume scans. Moreover, OCT-A does not require any dye injection, unlike FA. In addition, although FA only provides two-dimensional images of the fundus, OCT-A allows for distinct observation of the structure and blood flow inside the choroid, vitreous, and retina [2 - 4].

It is possible to assess the different retina capillary networks using correctly adjusted segmentation boundaries [2]. OCT-A-developed algorithms are used in clinical devices and research for OCT-A image creation. As a result, the appearance of OCT-A images from other devices varies [4], potentially leading to differing clinical diagnostic interpretations.

While each OCT-A algorithm has its own set of restrictions due to its general approach, some confounding factors affect all algorithms and are inherent aspects of this imaging technique. These issues are examples of decreased light penetration in the outer layers of the retina and artifacts projected from more superficial levels to deeper layers of the retina. Image acquisition, eye movements, image processing, and display techniques can all cause different artifacts [1].

Dynamic features, such as dye pooling, staining, and leakage can be seen with FA. Since there is no movement of blood cells, these dynamic phenomena cannot be seen with OCT-A. While these features are also used in clinical diagnosis [3], leakage or hemorrhage can potentially mask retinal disease. OCT-A can produce well-defined, high-contrast images of the microvessels beneath leaky or hemorrhaging areas [3 - 5]. As a result, dye-based angiography and OCT-A provide complementary data.

An additional restriction of commercially available OCT-A devices is their narrow visualization field compared to modern ultra-widefield fluorescein angiography systems [6]. A broader visualization is essential since many retinal entities have early manifestations in the mid-peripheral and peripheral retinal

CHAPTER 5

Normative Perfusion Indices in the Emmetropic Nondiabetic and Healthy Highly Myopic Adult Population

Virgilio Lima-Gómez, MD[1,*] and **Miguel A. Quiroz-Reyes, MD**[2]

[1] *Ophthalmology Service, Hospital Juarez de Mexico, Public Assistance Institution (Nonprofit Organization), Mexico City, Mexico*

[2] *Oftalmologia Integral ABC, Retina Department, Medical and Surgical Assistance Institution (Nonprofit Organization), Affiliated with the Postgraduate Studies Division, National Autonomous University of Mexico, Mexico City, Mexico*

Abstract: Reference values of optical coherence tomography angiography metrics vary according to the device used to measure them and even based on the software on the same device. There might exist measurement differences between different maps within the same device: Variables such as age, gender, and signal strength might induce changes in the measurement outputs.

This chapter deals with the values of vessel length and vessel area densities, and foveal avascular zone values of healthy emmetropic people via the 3 × 3 mm map used in the most common equipment that are available commercially. The text includes metrics of the parafovea and fovea at the superficial, intermediate, and deep capillary plexuses. These measurements corresponded to the adult non-diabetic population and were distributed as center (foveal), inner (parafoveal) and full (whole map) densities, depending on the evaluated region, according to densities in the foveal, parafoveal, and whole map measurements. Metrics of the parafovea by subfield were also included. We also report current cut-off values that have been proposed as normality references in some variables. Values for the remaining metrics and devices can later be proposed. We dedicate a special section to non-diabetic patients with high myopia without pathology, which includes the same metrics as in emmetropic patients. The evaluation of perfusion indices benefits from the simultaneous measurement of metrics as well as regional evaluation. The signal strength is a key variable to consider.

Keywords: Area, Deep capillary plexus, Emmetropia, Foveal avascular zone, Middle capillary plexus, Myopia, Perimeter, Superficial capillary plexus, Vessel area density, Vessel length density.

[*] **Corresponding author Virgilio Lima-Gómez, MD:** Ophthalmology Service, Hospital Juarez de Mexico, Public Assistance Institution (Nonprofit Organization), Mexico City, Mexico; Tel: +525 55747 7560; E-mail: forscher7@gmail.com

Miguel A. Quiroz-Reyes and Virgilio Lima-Gomez (Eds.)

CAPILLARY CIRCULATION OF THE MACULA

Blood circulation in the retina adjusts to the needs of a complex neural network whose oxygen needs vary according to the cell layer as well as to the neural activity under different illumination conditions. Histologic studies and now optical coherence tomography angiography (OCTA) allow to define three retinal capillary plexuses: superficial, middle (intermediate) and deep.

The middle and deep plexuses come from the superficial plexus (SCP), and there are connections between plexuses that allow the interchange of blood flow from one to another [1]. The superficial SCP lies at the nerve fiber layer and ganglion cell layer. The middle (intermediate) plexus (MCP) follows the limit between the inner nuclear and inner plexiform layers, and the deep plexus (DCP) is located where the inner nuclear and the outer plexiform layers meet.

Optical coherence tomography (OCT) uses the principles of interferometry to produce high-definition microscopic images of retinal structures in vivo; its definition has been compared to that of optic microscopy, with the added benefit of lacking fixation artifacts. The resolution of spectral domain OCT devices allows to identify both neural and vascular structures in the retina, though the definition of capillaries required additional analysis, which eventually led to the development of OCTA; the principles of OCT and OCTA are reviewed extensively in previous chapters of this book.

As a general principle, OCTA compares the changes in structure within the retinal tissues, which reflect the movement of erythrocytes inside the capillaries. As no other retinal element changes within a short time span, OCTA uses the differences between a region with erythrocytes and the same region without them to outline the capillary plexuses.

A problem that arose as OCTA devices appeared was that they used different methods to outline the capillaries. The algorithms applied to build the maps of the capillary plexuses use phase-signal, amplitude signal and complex signal methodologies. The first are not available commercially, because they require to remove noise from the background, which can occur form eye motion or instabilities in the system. Methods that are based on amplitude are used by most commercial devices, and complex signal algorithms, which are highly sensible to low-speed flow, are also used by other commercial devices [1].

Some OCTA devices further process acquired images to improve the quality of their images, which reduces eye motion related disturbances. Each device offers a high internal reproducibility, but its measurements cannot be interchanged directly with those of other devices. The resulting problem is that comparisons

across studies depend on the availability of data for comparison, which come from the same device, the same area of evaluation, and the same segmentation (even the same software).

OCTA devices define the segmentation of the retina used to measure the different plexuses; some measurements are acquired automatically, and others are manually calculated from image slabs [1]. The retinal circulation is heterogeneous, and it requires regional references to detect changes indicating a pathologic condition in different diseases [2].

OCTA produces information that helps to define the proportion of the scanned retinal area, where there is blood circulation using mainly two metrics: vessel area density (VAD) and vessel length density (VLD). VAD represents the percentage of the retina where there are blood vessels (the pixels in white within the output image). Changes in VAD include variations in both length of patent vessels and vessel caliber. A decrease of capillaries may be accompanied by vasodilatation, which VAD might not reflect, this variable is the best for estimating an actual density of retinal vessels and is useful to detect ischemia. VAD is s currently preferred over terms like "vessel density" and "perfusion density" [3]. Vessel length density (VLD) represents the total length of patent vessels within the evaluated retinal area, measured in mm/mm^2 or mm^{-1}). In this chapter, we use VLD rather than "skeletonized vessel density", as used in other studies. As this variable excludes vessel caliber, it rules out vasodilatation from larger vessels and accounts preferably for the capillary networks. OCTA combines both variables to calculate the boundaries of the foveal avascular zone, as well as its circularity, diameter and area. A 3 x 3 mm circular map centered in the foveola is the most frequently used OCTA output; it is divided into a central 1 mm diameter area, and an "inner" parafoveal zone, divided into superior, inferior, temporal and nasal subfields. Densities at the 1 mm diameter area are labelled as "center", while the ones of the parafoveal zone are labelled as "inner". The mean densities at the entire 3 × 3 mm are labelled as "full densities"; depending on the devices, there are maps of 6, 9, and 12 mm diameter, with different strategies for measuring within and between devices. For instance, the measurements of the 3 × 3 mm AngioPlex map and those of their corresponding fields of the 6 × 6 mm map differ because the 3 × 3 mm map measures more points in the parafovea; the 6 × 6 mm map measures more points in the perifovea [4, 5].

There are automatic SCP outputs in every OCTA device, and usually DCP outputs, except for the AngioPlex device. Researchers who use the AngioPlex measure the MVP and the DCP manually. As the measurements from different OCTA devices cannot be interchanged directly, this chapter presents information from the commercially available devices that are most used.

CHAPTER 6

Normative Perfusion Indices in the Diabetic Population

Virgilio Lima-Gómez, MD[1,*] and **Miguel A. Quiroz-Reyes, MD**[2]

[1] *Ophthalmology Service, Hospital Juarez de Mexico, Public Assistance Institution (Nonprofit Organization), Mexico City, Mexico*

[2] *Oftalmologia Integral ABC, Retina Department, Medical and Surgical Assistance Institution (Nonprofit Organization), Affiliated with the Postgraduate Studies Division, National Autonomous University of Mexico, Mexico City, Mexico*

Abstract: Diabetes damages retinal capillaries before clinical changes appear. Optical coherence tomography can quantify changes in vessel length density and vessel area density in diabetics without retinopathy and can lead to a reduction of these metrics in different capillary plexuses. The mean values of vessel densities vary according to the device used. Here, we review the values of vessel length density, vessel area density, and foveal avascular zone metrics in diabetics without retinopathy in a 3 x 3 mm map of the most used commercially available devices. We included measurements for the superficial, intermediate, and deep capillary plexuses in the parafoveal region. The information refers to adult type 2 diabetic people according to densities in the foveal, parafoveal, and whole map measurements. We also included parafoveal distribution by field as well. There are references to the foveal avascular zone—a common variable measured to detect ischemia in patients with diabetic retinopathy—and we report them for both superficial and deep capillary plexuses. We also include the proposed cut-off values for normality for metrics of the superficial capillary plexus and propose an explanation for the differences that exist between measurements with the same device as related to diabetes duration.

Keywords: Area, Deep capillary plexus, Diabetes, Foveal avascular zone, Middle capillary plexus, Perimeter, Superficial capillary plexus, Vessel area density, Vessel length density.

VESSEL CHANGES IN DIABETES BEFORE THE ONSET OF DIABETIC RETINOPATHY

Diabetic retinopathy is a chronic and specific complication of diabetes that may take time to appear after the onset of metabolic disease. Although some patients

[*] **Corresponding author Virgilio Lima-Gómez, MD:** Ophthalmology Service, Hospital Juarez de Mexico, Public Assistance Institution (Nonprofit Organization), Mexico City, Mexico; Tel: +525 55747 7560; E-mail: forscher7@gmail.com

already have retinopathy when diabetes is diagnosed, most of them have a clinically normal retina for years.

Retinal fluorescein angiography has shown that there might be subclinical microaneurysms that might go undetected during dilated ophthalmoscopy and even at a fundus photograph. Although both ancillary tests have been of use to evaluate the retinal circulation in diabetes, they lack a volumetric perspective, which prevents detecting regional differences in the capillary plexuses resulting from hyperglycemia.

Optical coherence tomography changed the evaluation of the retina in diabetes because it allowed to measure retinal thickness and detect structural tissue changes. The principles of interferometry used by this device have led to obtaining high-definition images of all the retinal layers, especially by commercially available spectral domain machines. Although the immediate application of retinal thickness quantification was the evaluation of macular edema, the scope expanded to analyze eyes with subclinical macular edema and people without retinopathy.

The alterations in retinal thickness that were found in diabetic people without retinopathy focused on thinning at specific retinal layers, particularly the retinal ganglion cell layer. The decrease in retinal ganglion cell layer thickness supported the concept of neurodegeneration, which is still a remarkably interesting topic; however, it could not be linked to capillary disease by measuring only retinal thickness, because the vessel evaluation that could be provided by fluorescein angiography.

Optical coherence tomography angiography (OCTA) used the advantage of OCT to identify the changes in structures in specific retinal layers. At first it focused on the nerve fiber layer and the inner nuclear layer, where traditional histologic studies had located the capillary plexuses. Using temporal differences in structure, OCTA defined the pathways where erythrocytes circulated, and produced the architecture of superficial and deep capillary plexuses at the retina. A more detailed explanation of the principles of OCT and OCTA is discussed in previous chapters of this book.

With the resource of volumetric evaluation, OCTA allows to link structural retinal changes (such as localized thinning) and circulatory alterations. It also allows to map regional capillary deficits in a two-dimensional approach, increasing the value of analyzing specific macular areas, such as the foveal avascular zone. The combination of vessel and neuronal changes in the retina has led to approaching the neurovascular unit and neurovascular coupling, which may be impaired in diabetics before clinical retinopathy appears.

OCTA has revealed that there are changes in vessel length density (VLD) and vessel area density (VAD) that precede the development of the first detectable anatomic signs of diabetic retinopathy.

Current studies emphasize the role of neurovascular coupling in the development of early capillary changes in the retina, while other authors explain the changes from a vascular damage perspective. Still, others suggest that early neurodegeneration occurs, eventually altering vessel densities.

Both vessel and neural dysfunction before the onset of diabetic retinopathy represent a preclinical form of the disease that occurs without impairment of visual function. Combined with functional evaluations, the metrics of OCTA produce quantitative and reproducible data that can identify early preclinical changes in diabetics.

One of the earliest functional changes yet described is a reversal of neurovascular coupling, *i.e.,* changing from dark-adapted eyes to light-reduced VAD in the SCP and in the MCP in diabetics without retinopathy. VAD was lower in the DCP during dark adaptation; both changes are the opposite of what is seen in healthy people, where VAD in the capillary plexuses increases to meet the metabolic demands of the most active neural layer: ganglion cells in light and photoreceptors in the dark [1]. Another early change is an increase in VAD in the ring area of 200 μm outside the FAZ. This is thought to represent a response to higher metabolic demands before capillary damage starts [2].

Regardless of the functional evaluations, they need a reference for comparison. Although healthy control is always needed, there are values of vessel densities in diabetics without retinopathy that can be used to standardize the baseline measurements, which have already been published—in some cases, in patients with a long duration of diabetes.

Macular vessel densities in diabetic patients without retinopathy are usually lower than in healthy people. As in emmetropic and myopic eyes, measurements of different OCTA devices are not interchangeable in diabetic patients without retinopathy. It is better to have a reference for the device, and preferably, the software version that is used.

The information provided by optical coherence tomography angiography sets references about the extension of the evaluated area of the retina where there is circulation from two measurements:

• Vessel area density (VAD) is the proportion of the evaluated area covered by vessels (white pixels in the digital image) divided by the total area and expressed

CHAPTER 7

Correlation of the Structural and Perfusion Findings in Patients with Surgically Resolved Myopic Foveoretinal Detachment

Miguel A. Quiroz-Reyes, MD[1,*], Erick A. Quiroz-Gonzalez[1,2], Jorge Morales-Navarro[2], Miguel A. Quiroz-Gonzalez[1], Ana L. Diazceballos-Garcia[2], Sanjay Marasini[3], Mario Carranza-Casas[2] and **Virgilio Lima-Gomez[4]**

[1] *Oftalmologia Integral ABC, Retina Department, Medical and Surgical Assistance Institution (Nonprofit Organization), Affiliated with the Postgraduate Studies Division, National Autonomous University of Mexico, Mexico City, Mexico*

[2] *Institute of Ophthalmology, Fundacion Conde de Valenciana, Private Assistance Institution (Nonprofit Organization), Mexico City, Mexico*

[3] *Department of Ophthalmology, The University of Auckland, Auckland, New Zealand*

[4] *Ophthalmology Service, Hospital Juarez de Mexico, Public Assistance Institution (Nonprofit Organization), Mexico City, Mexico*

Abstract: Myopia is a global public health problem leading to visual impairment and blinding complications. Myopic foveoschisis (MF)/foveoretinal detachment (FRD) might be responsible for progressive visual loss in eyes with macular traction maculopathy (MTM). An assessment of the macular microcirculation might identify defects that are potentially implicated in subsequent pathological changes. In the present chapter, macular perfusion in normal eyes was compared with that in highly myopic eyes with MF/FRD. Vessel density (VD) differed between the groups, and the superficial area of the foveal avascular zone (FAZ) was significantly larger in the control groups. Better final visual acuity results were significantly correlated with fewer structural findings and greater VD ($p < 0.05$). The central subfoveal thickness was significantly larger in the control groups and significantly smaller in the surgery group. These findings suggested a higher incidence of macular perfusional VD deficiencies and abnormalities in the FAZ area in the highly myopic eyes.

[*] **Corresponding author Miguel A. Quiroz-Reyes, MD:** Oftalmologia Integral ABC, Retina Department, Medical and Surgical Assistance Institution (Nonprofit Organization), Affiliated with the Postgraduate Studies Division, National Autonomous University of Mexico, Mexico City, Mexico; Tel: +52 55 5217 2732; Fax: +52 55 1664 7180; E-mails: drquiroz@prodigy.net.mx and drquirozreyes7@gmail.com

Keywords: Choriocapillaris flow area, Choriocapillaris subfoveal plexus, Choroidal vascular index, Deep vascular plexus, Foveal avascular zone, Foveoretinal detachment, High myopia, Myopic foveoschisis, Myopic macular degeneration, Myopic macular hole-associated retinal detachment, Myopic macular hole, Myopic traction maculopathy, Posterior staphyloma, Superficial vascular plexus, Vessel density, Vitreomacular traction.

INTRODUCTION

Myopia is a global public health problem leading to visual impairment and blinding complications [1]. Direct and indirect costs related to the loss of productivity were estimated to be $244 billion worldwide in 2015 because of the visual impairment caused by uncorrected myopia. The situation is expected to worsen as the prevalence of myopia is expected to reach 50% of the global population by 2050 [2].

The World Health Organization (WHO) defines myopia as a refractive error with a spherical equivalent of ≤ -0.5 diopters [2]. When the refractive error is more than 6 D, it is usually referred to as high myopia. High myopia differs from pathologic myopia (PM) in its effects on the posterior pole of the eye, leading to retinal lesions. PM is estimated to affect up to 3% of the global population. The consequences of PM include posterior staphyloma (PS) and more severe myopic maculopathy than diffuse chorioretinal atrophy [2]. An estimated 30% of patients with PM develop myopic traction maculopathy (MTM).

The early stage of MTM, also known as myopic foveoschisis (MF), is a schisis-like thickening of the retina in the eyes with high myopia along with PS. The term MTM was first used by Panozzo and Mercanti to describe conditions associated with highly myopic eyes, including macular retinoschisis, foveoretinal detachment (FRD) and macular holes (MHs) [3]. A pulling or stretching force is considered the cause of this disorder, and the clinical presentation has various forms, such as partially detached vitreous with vitreomacular adhesion, epiretinal macular membrane (ERM) proliferation, foveoschisis or maculoschisis, localized foveal detachment, or full macular detachment [2]. The disorder worsens gradually, and spontaneous recovery is rare, causing permanent vision loss, which warrants early treatment [2].

MF and FRD are classified based on different stages [2]. This system classifies MF/FRD due to MTM into four retinal stages (1–4) and three foveal stages (a–c) during the evolution of the disorder. Stages 1 (MF) and 2 (FRD) represent the earliest stages of MTM, while stages 3 and 4 are associated with retinal detachment. As the severity changes from stage 1 to 4, an associated worsening of visual acuity is observed [2].

Kelly and Wendel [4] first used vitrectomy to treat idiopathic MHs in 1991, and the method has since become a standard surgical procedure. The stage during which patients with MTM should be treated to obtain the best surgical outcome is currently unknown [5]. Surgical options to treat myopic MHs include macular buckling, classical or modified internal limiting membrane (ILM) peeling, and autologous ILM or full-thickness neuroretinal transplantation. In patients with MTM, a thin retina, abnormal vitreoretinal adhesion, and stiff ILM may contribute to high myopia MTM. Therefore, the remaining vitreous cortex and ILM develop effectively. The literature shows that pars plana vitrectomy (PPV) is the most common treatment for MTM, although no difference in outcomes has been observed among different treatment procedures [2].

Myopic macular degeneration (MMD) is one of the leading causes of blindness or low vision in developed nations, especially where the prevalence of myopia is high. It is characterized by excessive elongation of the eye, scleral thinning, PS, chorioretinal atrophy and choroidal neovascularization. MMD is often associated with MTM. Generally, highly myopic eyes with MF/FRD progress to MH formation [6, 7]. MH is a full-thickness defect of retinal tissue involving the anatomic fovea and was first described by Takano and Kishi based on optical coherence tomography (OCT) [8 - 10]. MF/FRD is presumed to progress slowly over the years, subsequently leading to MTM.

A better understanding of the analysis of perfusion at the macular level has led to improvements in the evaluation techniques and management of the spectrum of macular pathologies [11 - 13]. However, a paucity of data on the long-term macular perfusion findings and quantitative vessel density (VD) evaluations of surgically resolved MF/FRD is available. A better understanding of the differences in these conditions would help a vitreoretinal surgeon plan macular surgical procedures and the timing of the surgery for better surgical outcomes. Recently, we published patient data that met the criteria designed to minimize possible confounding variables [13]. This chapter elaborates on the comparison of the quantitative data on macular microcirculation in the emmetropia control, high myopia control, and operated eye groups in which MF/FRD resolved completely after macular surgery. Due to the significance of the timely detection of visual changes in patients in the early stages of this condition, we consider writing a complete chapter dedicated to the early stages of this myopic tractional pathology of utmost importance (Table **1**).

Preoperative Examination of Highly Myopic Eyes

Highly myopic eyes may show a subclinical loss of vision and might unsuspectingly co-occur with macular visual manifestations that are difficult to

CHAPTER 8

Postoperative Macular Perfusion Evaluation in Eyes with Noncomplicated Retinal Detachment and Macular Involvement Surgically Managed with Primary Vitrectomy

José Dalma-Weiszhausz[1,*]

[1] *Asociacion para prevenir la Ceguera en Mexico. Mexico City. Mexico*

Abstract: Rhegmatogenous retinal detachment (RRD) is fairly common and one of the main causes of blindness if left untreated. In spite of the high anatomical success rate for retinal detachment, visual recovery is lagging. Microvascular changes in the macular area might play a role in determining poor visual outcomes. Methods: Optical coherence tomography (OCT) and OCT angiography (OCT-A) technologies have been used to determine the relationship between microvascular macular changes and visual acuity. Results: RRD seems to alter microcirculatory anatomy in the macular area by increasing the foveal avascular zone (FAZ) and diminishing the vascular density (VD) of the superficial, deep and choroidal capillary plexuses. More so if the macula is detached, these changes appear to recover with time and might be correlated with postoperative visual acuity, but apparently do not entirely explain the sometimes-unexpected poor visual results.

Keywords: Rhegmatogenous retinal detachment, OCT, OCT-A, Foveal avascular zone, Vascular density, Macula.

INTRODUCTION

Rhegmatogenous retinal detachment (RRD) is fairly common and one of the main causes of blindness if left untreated. It is characterized by the separation of the neurosensory retina from the pigment epithelium caused by the presence of a retinal break through which fluid from the vitreous cavity may gain access to the virtual space between both layers, facilitated by vitreous traction and fluid currents in the vitreous cavity. Several treatment methods, most of them surgical, have been described. Currently, pneumatic retinopexy (PR), scleral buckle (SB) and pars plana vitrectomy (PPV), either combined or as single procedures, have

[*] **Corresponding author José Dalma-Weiszhausz:** Asociacion para prevenir la Ceguera en Mexico. Mexico City, Mexico; Tel: +52 55 5540 34 28. E-mails: jose@dalma.org and dalmayasoc@prodigy.net.mx

Miguel A. Quiroz-Reyes and Virgilio Lima-Gomez (Eds.)

reported single-surgery anatomic success rates above 85%. Unfortunately, visual recovery has not been as good as would be expected. Several preoperative and postoperative reasons have been proposed for this lack of adequate visual recuperation [1-8]. Most of them have focused on microstructural and/or microvascular changes since, on retinal biomicroscopy, the postoperative fundus may appear normal.

When the retina becomes detached, the external retinal layers, usually supplied by the choriocapillaris, lose their source of nourishment and oxygen, showing hypoxia. The tissue response involves the production of vasoactive mediators such as prostaglandins, cytokines and growth factors which bring vascular changes to the adjacent capillary circulation, causing occlusions, vasodilation and hyperpermeability [9 - 11]. Cytotoxic enzymes and photoreceptor apoptosis have been documented since the early stages of retinal detachment and may continually deteriorate as long as the retina remains separated [10].

More apparent complications have been implicated such as macular edema and epiretinal membrane formation. The appearance of optical coherence tomography (OCT) has allowed for the *in-vivo*, non-invasive analysis of retinal microstructure. The use of OCT techniques has focused on the anatomical integrity of photoreceptors and outer limiting membrane to try and justify the lack of adequate visual recovery in RRD patients but has been unable to prove a causative effect since patients with apparently normal anatomy continue to show subnormal visual improvement [12 - 14].

OCT angiography (OCT-A), has been employed to investigate retinal and choroidal microcirculation in retinal detachment patients and its possible impact on final visual function. This method not only allows visualization and grading of the macular microvasculature but it permits the spatial separation of the superficial and deep retinal plexuses as well as the choriocapillaris. Vessel density (VD) as well as flow density (FD) may be graded and compared. Unfortunately, the algorithms used on different equipment may vary, making inter-apparatus comparisons impossible [15].

Several papers have been published describing the microvascular changes in OCT-A in postoperative patients having undergone a vitrectomy for RRD repair. These works have focused on the anatomic characteristics of the macular microcirculation measuring the foveal avascular zone (FAZ) area in the superficial plexus as well as the deep plexus plain. Vessel density (VD) in the superficial and deep capillary plexus as well as the choriocapillary plexus.

One of the first papers to be published found a relationship between superficial FAZ and central foveal thickness, confirming other reports [16, 17] but found no

relation with the deep FAZ and no relation to final visual acuity. OCT-A measurements taken of the foveal avascular zone area in patients with macula-on and macula-off RRD and comparing them to control measurements taken from the unaffected eye of the same subjects show that the superficial and deep plexus FAZ were found to be unchanged in the macula-on RRD *vs.* control [18 - 22]. Macula-off RRD patients had a significantly larger FAZ. Superficial and deep FAZ areas showed a negative correlation with visual acuity in macula-off RRD after surgical repair; the deep FAZ showed a greater difference, especially in RRD with a macular detachment of more than 10 days [20, 23]. This data seems to hold true in other series. The repair procedure also appears to show a difference since SB showed less change in FAZ and superficial capillary plexus architecture than vitrectomy as compared to control eyes [21, 24] and with the use of silicone oil instead of gas as a tamponade [18, 25, 26]. Some series show no difference between using gas or silicone oil as tamponade [23].

FAZ areas appear to recover, at least partially, at 3, 6 and even 12 months after surgery [24, 25, 27]. The relationship of FAZ enlargement with visual recovery is controversial, but it seems to be moderately and inversely correlated to final visual acuity [18, 21, 22].

These differences seem to indicate that retinal microvascular changes may be responsible for the altered retinal function and diminished visual acuity observed even after successful RRD repair.

Trying to find a more specific biomarker for postoperative visual acuity has prompted several papers.

Superficial plexus vascular density (SVD) has been extensively analyzed. Most papers describe a decreased VD in macula-off RRD and especially in detachments of more than 10 days duration [18, 20, 23, 24]. One has associated this to decreased flow density [20]. The evidence of its relationship to decreased visual acuity is debatable since some papers report no relationship [24] while other do find a statistically significant correlation [20, 28]. The long-term follow-up accounts tend to report an almost complete recovery after 3 months as compared to the contralateral healthy eye, even after removal when silicon oil has been used [29].

Deep plexus VD (DVD) has also been reported to be decreased in macula-off RRD [18, 21, 26, 28]. Its measurements have been slightly more erratic since obtaining clear images is more cumbersome. Its relationship with final visual acuity has been less reliable [28], but several reports show a correlation between vessel density and final visual acuity [17, 20, 30].

CHAPTER 9

Postoperative Analysis of Macular Perfusional Status in Giant Retinal Tear-Related Retinal Detachments

Miguel A. Quiroz-Reyes, MD[1,*], Erick A. Quiroz-Gonzalez[1,2], Miguel A. Quiroz-Gonzalez[1], Ahmad R. Alsaber[3], Sanjay Marasini[4] and **Virgilio Lima-Gomez[5]**

[1] *Oftalmologia Integral ABC, Retina Department, Medical and Surgical Assistance Institution (Nonprofit Organization), Affiliated with the Postgraduate Studies Division, National Autonomous University of Mexico, Mexico City, Mexico*

[2] *Institute of Ophthalmology, Fundacion Conde de Valenciana, Private Assistance Institution (Nonprofit Organization), Mexico City, Mexico*

[3] *Department of Mathematics and Statistics, University of Strathclyde, Glasgow, UK*

[4] *Department of Ophthalmology, The University of Auckland, Auckland, New Zealand*

[5] *Ophthalmology Service, Hospital Juarez de Mexico, Public Assistance Institution (Nonprofit Organization), Mexico City, Mexico*

Abstract: Rhegmatogenous retinal detachment (RRD) associated with giant retinal tears (GRTs) can cause significant visual impairment due to structural or perfusional macular sequelae. This condition is an acute-onset incident that leads to a full-thickness circumferential retinal tear of at least 90°. Limited data are available concerning the patients´ long-term perfusional status after successful surgery for GRTs with macula-off RRD. This chapter examines the long-term outcomes of eyes treated with varying degrees of GRT-associated RRD extensions and compares them with those of two control groups. The surgical group was subdivided according to GRT-associated RRD extension as follows: eyes with extension of <180° and eyes with extension > of >180°. The eyes were further classified according to whether complementary 360° scleral buckle (SB) placement was required. Postoperative optical coherence tomography (OCT) demonstrated that 33.3% of the eyes had abnormal foveal contours, 39.4% had ellipsoid zone (EZ) disruption, 2 had dissociated optic nerve fiber layer (DONFL) defects, and 45.4% had external limiting membrane (ELM) line discontinuities. OCT angiography (OCT-A) revealed abnormal perfusion indices in surgically treated eyes (p<0.0001). Postsurgical best-corrected visual acuity (BCVA) was negatively correlated with the superficial foveal avascular zone area, superficial parafoveal vessel

* **Corresponding author Miguel A. Quiroz-Reyes, MD:** Oftalmologia Integral ABC, Retina Department, Medical and Surgical Assistance Institution (Nonprofit Organization), Affiliated with the Postgraduate Studies Division, National Autonomous University of Mexico, Mexico City, Mexico; Tel: +52 55 5217 2732; Fax: +52 55 1664 7180; E-mails: drquiroz@prodigy.net.mx and drquirozreyes7@gmail.com

density, and central subfoveal thickness but positively correlated with the choriocapillaris flow area (CFA). Moreover, eyes treated surgically for GRT-associated RRD had multiple structural alterations reflected by spectral-domain OCT biomarkers and OCT-A perfusional findings correlated with visual outcomes. Despite successful retinal reattachment without proliferation, management of GRT-associated RRD remains challenging.

Keywords: Brilliant Blue G dye, Choriocapillaris flow area, Choriocapillaris subfoveal plexus, Deep vascular plexus, Dissociated optic nerve fiber layer defects, Ellipsoid zone, Epiretinal membrane proliferation, External limiting membrane, Foveal avascular zone, Giant retinal tears, Pars plana vitrectomy, Perfluoropropane gas, Postoperative perfusion indices, Proliferative vitreoretinopathy, Retinal pigment epithelium, Rhegmatogenous retinal detachment, Scleral buckle, Superficial vascular plexus, Trypan blue, Vessel density.

INTRODUCTION

A giant retinal tear (GRT) is defined as a full-thickness circumferential break in the retina extending more than three clock hours or 90° [1]. Rhegmatogenous retinal detachment (RRD) associated with GRTs is a rare but devastating condition because of its guarded prognosis and related significant visual morbidity [2]. In GRTs, the vitreous gel remains attached to the anterior flap of the retina, while the posterior retina moves freely and folds upon itself [3]. GRT associated with RRD is acute tractional events in which the posterior vitreous is detached due to pathological contraction of the vitreous at the bed of a normal or predisposed retina [4, 5]. The annual incidence of GRT has not been clearly established in the literature; however, it is estimated that between 0.05% and 0.09% per 100,000 people suffer from this condition [4 - 9]. GRTs predominantly affect males, accounting for up to 91% (range: 65% to 91%) of all patients [4 - 9], and GRT patients represent 1.5% of all RRD individuals, with an average age of 42 years at diagnosis [5, 8]. The disease is estimated to affect approximately 0.05:100,000 individuals annually [3]. Higher rates were reported in studies where patients presented late with more complex RRDs, such as those in East Africa (8.3%) [7] and Argentina (4.31%) [9]. In general, GRTs are most frequently found immediately posterior to the ora serrata (82%), followed by the equator (15%) or posterior to the equator (3%) [10]. It is assumed that the high incidence of proliferative vitreoretinopathy (PVR) from GRT is due to the release and fibrous metaplasia of a large number of retinal pigment epithelial (RPE) cells (RPE cell dispersion), inflammatory breakdown of the retinal–blood barrier, and upregulated release of multiple pro-inflammatory factors and cytokines, resulting in the rapid occurrence of PVR [2].

The predisposing factors associated with GRTs include local and systemic factors as well as idiopathic factors [4, 5, 11 - 13]. Approximately 55% of cases were reported to be idiopathic, according to a large epidemiological study conducted in the United Kingdom (2010). Other risk factors include myopia (25%); hereditary conditions with defects in type 1 and 2 collagen synthesis, such as osteogenesis imperfecta and Marfan's, Stickler–Wagner, and Ehlers–Danlos syndrome (14%); and closed eye blunt trauma (12.3%) [4, 5, 11 - 14]. Other rare conditions include aniridia, lens colobomas, microspherophakia, retinitis pigmentosa, and endogenous endophthalmitis [15]. The most common predisposing factor for the development of GRT is trauma (4-11%) [5]. Different clinical types of GRT are shown in the multipanel (Fig. **1**).

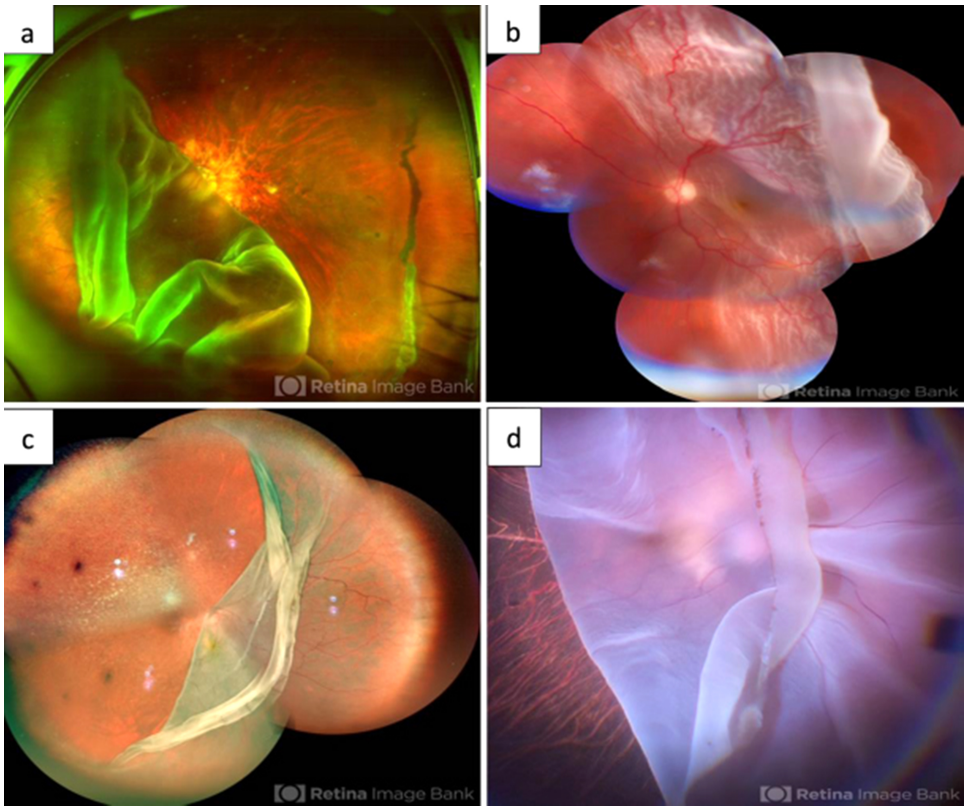

Fig. (1). ***Clinical types of giant retinal tears***. (**a**) Fundus photograph of a 30-year-old woman with giant retinal tear. May 8, 2021. By: ?74785. (**b**) Fundus composite of a 50-year-old man with macula-off retinal detachment due to a temporal giant retinal tear. Lucas Zago Ribeiro. **Jul 6, 2021.** 78893. (**c**) Fundus photograph of a 16-year-old male with a Rhegmatogenous Retinal Detachment secondary to a Giant Retinal Tear in the right eye. Vaidehi Sathaye, MD. April 21, 2021, 93502. (**d**) Intraoperative photo of a 360-degree giant retinal tear folded onto itself as if veiling the macula. Manish Nagpal, MD. Retina Foundation. February 2, 2022. 91319. The images in this modified multipanel figure were originally published in the Retina Image Bank® website. Retina Image Bank. © The American Society of Retina Specialists.

CHAPTER 10

Macular Perfusion in Clinically Significant Diabetic Macular Edema and in Different Stages of Diabetic Retinopathy

Virgilio Lima-Gómez, MD[1,*] and **Miguel A. Quiroz-Reyes, MD**[2]

[1] *Ophthalmology Service, Hospital Juarez de Mexico, Public Assistance Institution (Nonprofit Organization), Mexico City, Mexico*

[2] *Oftalmologia Integral ABC, Retina Department, Medical and Surgical Assistance Institution (Nonprofit Organization), Affiliated with the Postgraduate Studies Division, National Autonomous University of Mexico, Mexico City, Mexico*

Abstract: Diabetic macular edema uses structural features as biomarkers and predictors of treatment response. Optical coherence tomography angiography (OCTA) metrics found a correlation between many structural biomarkers and reduced vessel density. We present recent references of vessel length density, vessel area density, and foveal avascular zone metrics in eyes with diabetic macular edema and comment on the associations found between them and structural biomarkers. Diabetic macular edema can change the level at which the capillary plexuses are located, with retinal cysts altering the strength signal. Though image evaluation requires adjustment, intra-subject comparison before and after treatment can be a useful tool to note changes in vessel perfusion, combined with structural changes, to assess treatment outcomes. Macular ischemia is a variable that can be identified reliably with OCTA and can be detected in different capillary plexuses. For eyes with retinal thickening, OCTA evaluation requires consistency to avoid inter-device variability. It is recommended to use the same device, the same scanning protocol, and preferably the same software, to obtain more reproducible measurements.

Keywords: Area, Deep capillary plexus, Diabetic macular edema, Foveal avascular zone, Middle capillary plexus, Perimeter, Superficial capillary plexus, Vessel area density, Vessel length density.

CLINICALLY SIGNIFICANT DIABETIC MACULAR EDEMA

Clinically significant diabetic macular edema (CSME) was defined by the Early Treatment Diabetic Retinopathy Study (ETDRS), seen as a retinal thickening that

[*] **Corresponding author Virgilio Lima-Gómez, MD:** Ophthalmology Service, Hospital Juarez de Mexico, Public Assistance Institution (Nonprofit Organization), Mexico City, Mexico; Tel: +52 55 5747 7560;
E-mail: forscher7@gmail.com

Clinically significant diabetic macular edema (CSME) was defined by the Early Treatment Diabetic Retinopathy Study (ETDRS), seen as a retinal thickening that

lines in a visual acuity chart. Optical coherence tomography (OCT) has contributed to understanding features and the magnitude of retinal thickening; this is, in addition to antiangiogenic drugs, changing the approach and treatment of diabetic macular edema (DME).

OCT revealed that two eyes with the same thickening topography may have different retinal thickness, and that two eyes with the same retinal thickness may have different structural issues. These differences have led to identifying structural biomarkers, such as central retinal thickness, central foveal subfield thickness, intra-retinal cystoid spaces, hyperreflective retinal foci, hyperreflective retinal spots, disorganization of inner retinal layers, and subfoveal neurosensory detachment. The definition of CSME has not been discarded, as center-involving macular edema (CIME) is another commonly used term; both kinds of thickening represent DME, but the first is more common in eyes with reduced vessel area density (VAD), which is related to ischemia.

In 2020, an international panel proposed a grading system for DME, based on OCT; it used the 3.45 mm maps and evaluated six qualitative parameters:

a) Size of intraretinal cysts

b) Visibility of the external limiting membrane (ELM) at the fovea

c) Visibility of the ellipsoid zone (EZ) at the fovea

d) Presence of disorganization of the retinal inner layers (DRIL)

e) Presence of subretinal fluid

f) Presence of hyperreflective intraretinal foci

g) The vitreoretinal relationship is considered to be two quantitative variables: central subfield thickness (CST) and macular volume (MV in a 1 mm diameter ring). Operative definitions are as follows:

Intraretinal cysts were round, minimally reflective spaces at the outer and inner nuclear or ganglion cell layers.

There was an absence of the EZ or a complete loss of foveal reflectivity at those levels, which are the first and the second hyperreflective bands of the outer retinal layers on OCT. When partially visible in the fovea, but not completely

discernible, these layers are classified as "disrupted." Whenever the EZ is non-gradable (N/G) and has a subretinal fluid, only the ELM is graded.

DRIL was the loss of clear demarcation between the outer plexiform layer, the inner nuclear layer, and the ganglion cell layer-inner plexiform layer complex in the fovea.

SF is the presence of a hyporeflective subfoveal neurosensory detachment, resulting from fluid accumulation between the retinal pigment epithelium line and the retina.

Hiperfluorescent retinal spots (HF) are manually counted in each scan, if they fulfill the following features: reflectivity such as that of the nerve fiber layer, and the absence of back shadowing, or a diameter < 30 μm.

The vitreomacular relationship was classified as complete posterior vitreous detachment (PVD), incomplete posterior vitreous detachment (IVD), when vitreoretinal adhesion exists, but did not alter the retinal profile, vitreomacular traction (VTM) when any residual macular vitreous attachment causes anteroposterior traction, and epiretinal membrane (ERM), with evidence of epiretinal tissue adhered to the macular surface, regardless of the effect it causes on the underlying retina [1].

This classification has not considered OCTA yet.

Macular ischemia is a known cause of visual loss; before the introduction of OCT, its diagnosis depended on finding an enlarged foveal avascular zone (FAZ); OCTA now detects subtle and extensive changes in capillary circulation, which represent vessel closure and induce ischemia, without a large impact on the FAZ area. Diabetic retinopathy progresses as capillary closure increases, and OCTA metrics are both a quantitative and objective way of measuring areas without circulation, in patients with and without DME [2]. An advantage of OCTA is that it allows the measurement of three capillary plexuses: the superficial (SCP), which runs in the nerve fiber and ganglion cell layers, the middle (MCP) at the boundary of the inner nuclear layer, the inner plexiform layer, and the deep (DCP) at the union between the inner nuclear layer and the outer plexiform layer.

The information provided by OCTA sets references for the extension of the evaluated area of the retina with circulation. This is based on two measurements:

• Vessel area density (VAD) is the proportion of the evaluated area covered by vessels (white pixels in the digital image) divided by the total area and expressed as a percentage. VAD indicates changes in both the length of vessels with

CHAPTER 11

Evaluation of Macular Perfusion in Successfully Reattached Macula-off Diabetic Tractional Retinal Detachment

Miguel A. Quiroz-Reyes, MD[1,*], Erick A. Quiroz-Gonzalez[1,2], Jorge Morales-Navarro[2], Miguel A. Quiroz-Gonzalez[1], Margarita Montano[1], Felipe Esparza-Correa[2], Jennifer H. Kim-Lee[2], Boris Moreno-Andrade[2], Alejandra Nieto-Jordan[2], Ahmad R. Alsaber[3] and **Virgilio Lima-Gomez[4]**

[1] *Oftalmologia Integral ABC, Retina Department, Medical and Surgical Assistance Institution (Nonprofit Organization), Affiliated with the Postgraduate Studies Division, National Autonomous University of Mexico, Mexico City, Mexico*

[2] *Institute of Ophthalmology, Fundacion Conde de Valenciana, Private Assistance Institution (Nonprofit Organization), Mexico City, Mexico*

[3] *Department of Mathematics and Statistics, University of Strathclyde, Glasgow, UK*

[4] *Ophthalmology Service, Hospital Juarez de Mexico, Public Assistance Institution (Nonprofit Organization), Mexico City, Mexico*

Abstract: Current imaging techniques based on optical coherence tomography (OCT) angiography are useful for observing different retinal microcirculation patterns. The primary purpose of this chapter was to describe the functional, structural, and serial perfusion postoperative outcomes of successfully reattached macula-off tractional retinal detachment (TRD). Patients who underwent a successful diabetic vitrectomy were analyzed. The mean differences between the preoperative best-corrected visual acuity (BCVA), 3-month BCVA, and final postoperative BCVA were statistically significant ($p < 0.05$). The duration of vision loss before surgery was 11.6 ± 2.3 weeks (mean ± standard deviation (SD)).

The mean duration (± SD) of the resolution of macular detachment was 3.6 ± 1.7 weeks in the pure macular TRD group and 1.8 ± 0.8 weeks in the combined tractional and rhegmatogenous macular detachment ($p < 0.05$) group. The mean follow-up duration of all patients was 11.4 ± 5.7 months (mean ± SD). Longitudinal multimodal imaging tests revealed abnormal superficial and deep microcirculation patterns with multiple microabnormalities in the foveal avascular zone and different but distinct areas of the non-perfused macula in different OCT angiography slabs. Additionally, disorganization

* **Corresponding author Miguel A. Quiroz-Reyes, MD:** Oftalmologia Integral ABC, Retina Department, Medical and Surgical Assistance Institution (Nonprofit Organization), Affiliated with the Postgraduate Studies Division, National Autonomous University of Mexico, Mexico City, Mexico; Tel: +52 55 5217 2732; Fax: +52 55 1664 7180;
E-mails: drquiroz@prodigy.net.mx and drquirozreyes7@gmail.com

of the retinal inner layers and chronic ischemic macular edema were observed in 82% of eyes examined using the spectral domain (SD) OCT. Therefore, these data suggest that despite the successful anatomical reattachment of the macula, long-term postoperative microcirculatory abnormalities were detected in both groups; however, these abnormalities were predominantly accompanied by severe persistent ischemia in the recurrent TRD group due to the presence of multiple microcirculatory defects.

Keywords: Choriocapillaris subfoveal plexus, Deep vascular plexus, Disorganization of the retinal inner layers, Long-term proliferative diabetic retinopathy complications, Macula-off tractional retinal detachment, Optical coherence tomography angiography, Macular perfusion indices, Perfusion microcirculatory abnormalities, Ischemic macula, Chromatic visual field testing, Microperimetry, Multifocal electroretinography, Secondary complicated retinal detachment, Superficial vascular plexus, Vessel density.

INTRODUCTION

Diabetes mellitus (DM) is prevalent worldwide, affecting an estimated 285 million adults (6.4%) as of 2010 [1]. It is one of the main causes of visual morbidity worldwide. The estimated prevalence of diabetic retinopathy (DR) and vision-threatening DR from 2005-2008 was 28.5% and 4.4%, respectively, among US adults with diabetes [2]. The main causes of vision loss in these patients include diabetic macular edema (DME), chronic cystic macular edema (CME), and complications related to proliferative diabetic retinopathy (PDR), including recurrent vitreous hemorrhage (VH), tractional retinal detachment (TRD), refractory macular edema associated with posterior hyaloid traction, combined traction and rhegmatogenous retinal detachment, and epiretinal membrane (ERMs) proliferation. These are the most common indications for surgical vitrectomy [3 - 5].

One of the most successful techniques used to manage DR is the administration of vascular endothelial growth factor (anti-VEGF) [6]. Although they are limited by their short-lived effects, they are widely available for use worldwide, especially in the treatment of aggressive proliferative DR [6]. However, some patients are treated with steroids, periocular injections, or intravitreal extended-release devices to maintain long-term visual outcomes. Panretinal photocoagulation (PRP) remains the gold standard of care but is preferred as a second-line treatment, especially in developed countries, owing to the popularity of anti-VEGF treatments [7].

The protocol proposed by Sivaprasad *et al.* (2015) [8] for diabetic retinopathy ‘Clinical efficacy and mechanistic evaluation of aflibercept for proliferative diabetic retinopathy (acronym CLARITY) and Research Network Protocol’ has

been used as a guideline for the surveillance and management of patients with macular edema and complications related to Proliferative DR (PDR). When DR is detected late, advanced pars plana vitrectomy (PPV) is needed [7]. Despite extensive research, the predictive factors for visual outcomes after vitrectomy still largely remain to be elucidated [9 - 11]. Several researchers have used horizontal B-scans of optical coherence tomography (OCT) images to investigate the disorganization of the retinal inner layers (DRIL) [12]. This method was used to assess the boundaries of the ganglion cell layer-inner plexiform layer (GCL-IPL) complex, inner nuclear layer (INL), and outer plexiform layer (OPL). Sun *et al.* (2014) investigated whether DRIL predicts visual acuity (VA) in eyes with central edema (DME). They found that a greater DRIL extent at baseline correlated with worse baseline VA, and an increase in DRIL during 4 months was associated with worsening VA at 8 months [12].

OCT angiography (OCT-A) facilitates visualization of blood flow in biological tissues. It noninvasively creates *in vivo* 3-dimensional composites of separate layers of the retinal and choroidal vasculature without the use of a contrast agent [13]. Using multiple algorithms, the sensitivity of imaging methods is increased for detailed imaging of the superficial and deep retinal capillary plexus and choriocapillaris [13]. The OCT-A method ignores the quantitative measurement of blood flow and uses motion as a contrast mechanism to visualize the location of the moving cells [13]. It eliminates the need for a dye [14, 15] and the 'transit window' effect observed with fundus fluorescein angiography (FFA) and indocyanine (ICG). OCT-A also avoids dark artifacts of retinal and vascular features that may occur owing to dye leakage [16]. This technique provides capillary-level detail at high depth resolution, which is provided only by histological methods [17 - 20].

OCT-A is useful for assessing DR, as it shows retinal foveal avascular zone (FAZ) enlargement and microaneurysms, and facilitates the examination of superficial and deep capillary plexuses in several diabetic lesions. When used along with OCT-A, Optovue AngioVue system technology enables quantitative analysis of the superficial and deep plexuses of the retinal vessels, serving as biomarkers for the diagnosis and monitoring of disease progression or treatment responses [21]. Fluorescein angiography cannot resolve the details of the deep capillary plexus and peripapillary radial capillaries [16, 17, 22]. However, OCT-A is a superior method for the quantitative analysis of retinal perfusion, as it is able to detect all clinically relevant retinal findings in individuals with DR [22, 23]. Additionally, disc neovascularization (NVD) and neovascularization elsewhere (NVE) were reliably detected using OCT-A [24 - 26] (Fig. **1**). Since the assessment of these clinical findings is important for better management of DR, such as during the monitoring of medical and surgical outcomes, OCT-A

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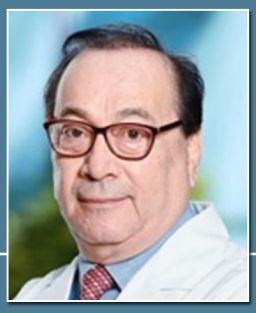

Miguel A. Quiroz-Reyes

Prof. Miguel A. Quiroz-Reyes is an ophthalmologist, retina specialist, and macula surgeon. He is a former president of the Mexican Retina Association and member of the Mexican Society of Ophthalmology, American Academy of Ophthalmology, American Society of Retina Specialists and PAAO. He is certified in ophthalmology and earned his master's degree from the Faculty of Medicine and Mexican Board of Ophthalmology affiliated with The National Autonomous University of Mexico. His goals include teaching, scientific writing, developing state-of-the art surgery techniques and assisting academical activities. His passion for the retina can be traced back to 1989 in Boston, where he specialized from Schepens Eye Research, which is affiliated with Harvard Medical School.

Virgilio Lima-Gomez

Prof. Virgilio Lima-Gomez is an ophthalmologist, retina specialist and a DSc Research in Medicine. He is an attending physician and surgeon, former head of the Ophthalmology Service, and of the Research Division at Hospital Juárez de México. He is a member of the Mexican Ophthalmology Society, Mexican Retina Association, Mexican Academy of Surgery and National Academy of Medicine of Mexico. He is an ophthalmology professor at Universidad Nacional Autonoma de Mexico, member of the National Researchers System. He was awarded the National Research Prize by Fundacion Mexicana para la Salud in 2008. His current research focuses on optical coherence tomography angiography, diabetic retinopathy and myopia.