

THE EYE AS A WINDOW FOR EARLY DIAGNOSIS OF OBSTRUCTIVE SLEEP APNEA

Objective measures on OCTA may allow more effective management of this common condition.

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Retinal angiography is a well-known imaging technique that has been used for the past few decades to assess the retinal vasculature and perfusion. It is useful in the evaluation, diagnosis, and management of patients with numerous retinal pathologies. The angiographic gold standards are fluorescein angiography (FA) and indocyanine green angiography (ICGA), but optical coherence tomography (OCT) technology has given rise to a new vasculature

imaging technique, OCT angiography (OCTA). This technique detects vasculature structures by using motion contrast imaging to obtain high-resolution volumetric blood flow information.¹

OCTA provides a number of advantages over older angiographic methods: It is faster, it is noninvasive, and it can be used to visualize all layers of the retinal vasculature in detail.¹ This method of imaging may provide new insights into the diagnosis, follow-up, and management of retinal diseases. Because of the noninvasive character of this technology, it may also be helpful to define and delineate retinal changes that occur as a result of systemic diseases.

Researchers at the University of Massachusetts Medical School investigated whether obstructive sleep apnea (OSA) can be correlated with retinal vasculature findings.² The researchers compared OCTA images of the retina taken in patients with OSA and in age-matched control individuals free from disease. The purpose of the study was to characterize qualitative and quantitative anatomic changes in the retinal microvasculature of OSA patients using OCTA. Preliminary results of this ongoing study are summarized in this article.

WHAT IS OSA?

OSA is a chronic disorder that is clinically characterized by shallow or paused breathing and snoring during sleep and by sleepiness during the day. These symptoms are a direct result of the repetitive collapse of the upper airway, causing at least five respiratory events of stopped breathing per hour of sleep.³ These episodes cause decreases in blood oxygen desaturation and fragmented sleep due to sudden awareness of oxygen deprivation. The prevalence of OSA is approximately 2% in women and approximately 4% in men, although it is estimated that 82% of men and 93% of women with moderate to severe OSA remain undiagnosed.³

Unfortunately, OSA is not well defined, and therefore it is often underdiagnosed. Objective and unbiased diagnosis of OSA is vital in order to determine the level of severity of the disorder and to choose appropriate treatment options.



AT A GLANCE

- Objective and unbiased diagnosis of obstructive sleep apnea (OSA) is vital in order to determine the level of severity of the disorder and to choose appropriate treatment options.
- An ongoing study using OCTA found that patients with OSA had on average a larger foveal avascular zone area and a smaller average bifurcation angle compared with controls; more study is needed.
- Identifying measurable objective parameters on OCTA could lead to better diagnosis, staging, and management of OSA.

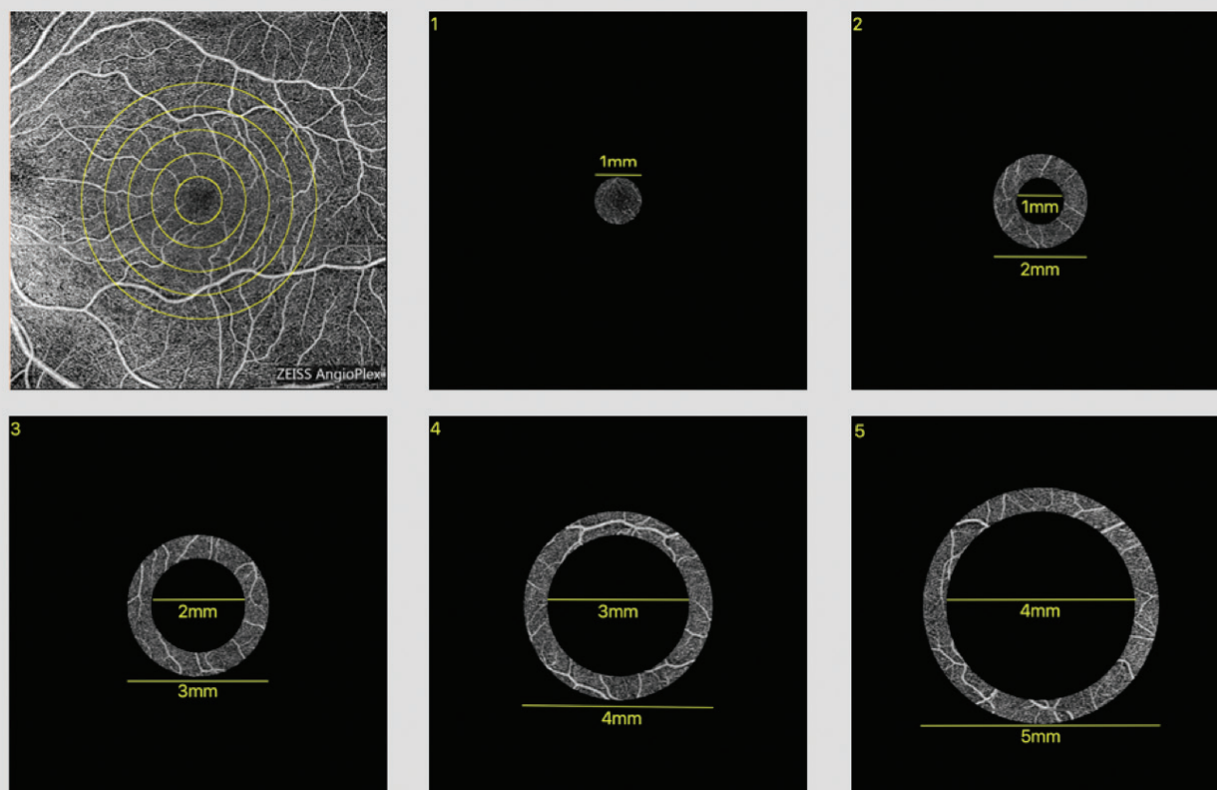


Figure. A concentric series of area slices taken around the foveal avascular zone for measurements of vascular density and flow. The software used for image analysis was the freeware ImageJ v1.33, developed by the US National Institutes of Health and available for download at: <https://imagej.nih.gov/ij/index.html>.

Today, there are two accepted methods for diagnosing OSA: polysomnography, which is done in a sleep lab, and home testing with the use of a portable monitor.³ Both of these methods, however, are considered unsatisfactory, and new diagnostic measures are needed.

Treatment of OSA is most often attempted with the use of continuous positive airway pressure, or CPAP. For those who do not tolerate CPAP well, there are also bilevel and autotitrating positive airway pressure modes.

SYSTEMIC DISORDERS ASSOCIATED WITH OSA

Early detection of OSA is important because of the many complications and secondary diseases associated with this disorder. The apneic episodes of OSA correlate with a number of alterations, including, but not limited to, sustained sympathetic activation, oxidative stress, endothelial damage, platelet activation, and increased inflammation, which, together, may contribute to these complications.³

For example, apneic episodes produce surges in systolic and diastolic blood pressure, keeping mean blood pressure levels elevated at night and thereby contributing as a secondary cause of hypertension.³ Because hypertension can lead to heart attack and stroke, this is a serious risk for OSA patients. Other complications linked to sleep apnea include depression, daytime sleepiness, insulin resistance, intrathoracic pressure changes, and thrombosis.^{3,4} Clinical sampling at sleep labs

has found a 21% to 41% prevalence of depression in patients with OSA.⁴ There is also a high prevalence of hypertension in patients with sleep apnea; an estimated 40% of patients diagnosed with OSA are hypertensive.³ With the variety of complications associated with OSA, it is crucial to develop reliable diagnostic methods for its early detection and management.

EYE PATHOLOGY RELATED TO OSA

The retina is one of the tissues in the body that consumes the most oxygen. It is thus plausible that changes ensue, specifically in the retinal vasculature, when oxygen is reduced as in OSA. The first described effect of OSA in the eye was the mechanical rubbing of the eyelid in restless sleep, causing floppy eyelid syndrome.⁵ More recently, OSA-associated vascular complications have been linked to several ophthalmic diseases, including glaucoma, nonarteritic anterior ischemic optic neuropathy, optic disc edema, retinal vein occlusion, and diabetic retinopathy.⁶

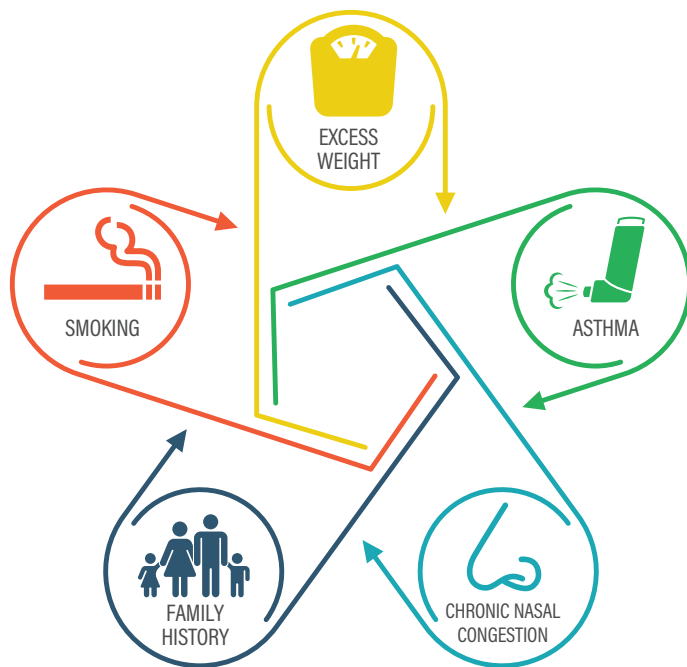
Not only has OSA been associated with increased risk for ophthalmic disease, but also recent studies have shown that it may be a factor in some patients' lack of response to anti-VEGF therapy. In 2014, Nesmith et al suggested a relationship between nonresponse to anti-VEGF therapy and OSA.⁶ Their study found that poor responders to anti-VEGF therapy had a higher risk for OSA compared with controls. In 2016, Schaal et al found that untreated OSA hindered the response to bevacizumab (Avastin, Genentech) in patients with age-related macular degeneration.⁷

What Is Obstructive Sleep Apnea?

OSA is a chronic disorder clinically characterized by shallow or paused breathing and snoring during sleep. Apneic episodes produce surges in systolic and diastolic blood pressure, keeping mean blood pressure levels elevated at night and thereby contributing as a secondary cause of hypertension, which can then lead to heart attack and stroke.³ Other complications linked to sleep apnea include depression, daytime sleepiness, insulin resistance, intrathoracic pressure changes, and thrombosis.^{3,4}



Risk Factors for OSA



According to the Mayo Clinic, anyone can develop OSA, but certain factors put one at increased risk.⁹

OSA Prevalence



4%



2%

Estimated percentage of men and women with moderate to severe OSA that remains undiagnosed.³



82%



93%

OCTA FOR DIAGNOSIS OF OSA

In the study by University of Massachusetts Medical School researchers mentioned above,² the researchers performed 8x8 superficial macular scans using the Cirrus HD-OCT 5000 AngioPlex (Carl Zeiss Meditec) in the eyes of patients with severe OSA with no other known eye pathology.

The scans were captured at a rate of 68,000 A scans per second and were analyzed using a split-spectrum amplitude-decorrelation angiography algorithm. The presence and severity of OSA was determined by limited channel ambulatory monitoring; measures included apnea-hypopnea index (AHI), lowest oxygen saturation, and total time with oxygen saturation level lower than 90%. The data collected by OCTA included foveal avascular zone (FAZ) area, average vein diameter, average bifurcation angle, vasculature density around the FAZ, and intensity correlating with flow. The figure on page 27 depicts the area slices used to measure vasculature density and flow around the FAZ.

The study found that patients with OSA had on average a larger FAZ area and a smaller average bifurcation angle compared with controls. In addition, OSA patients in the study had on average a higher vasculature density in each of the areas analyzed. Evidence of more tortuous vasculature was seen in the OCTA images of OSA patients compared with controls; this phenomenon was first described by Li et al.⁸

The study is ongoing. Recently, researchers at the University of Massachusetts Medical School joined forces with the sleep lab at Baystate Medical Center in Springfield, Mass., in the hope of recruiting and including in the study patients with more severe OSA. The anticipation is that OCTA will be a useful technique to aid in the diagnosis and management of OSA based on objective imaging factors.

GOALS FOR DIAGNOSING AND MANAGING OSA

OSA is a condition with a high prevalence and high number of undetected cases. New approaches to help diagnose OSA early and manage the disease over time could

bring patients relief from some of the negative sequelae and health hazards that result from it and result in a healthier population.

Research in this area is in its pioneering phase and is ongoing. The objective is to detect changes in the retinal microvasculature that can be quantified and correlated with the severity of OSA. The hope is to eventually identify easily measurable objective parameters in OCTA images that could lead to better diagnosis, staging, and management of OSA. Larger-scale studies will be needed to determine the role of OCTA in the ocular and systemic management of patients with OSA. ■

1. Chalam KV, Sambhav K. Optical coherence tomography angiography in retinal diseases. *J Ophthalmic Vis Res*. 2016;11(1):84-92.
2. Lombardi L, Helmy O, Sailer S, Johnson K, Schaal S. Characterization of retinal and choroidal microvasculature changes in obstructive sleep apnea patients by optical coherence tomography angiography analysis. Poster presented at: Association for Research in Vision and Ophthalmology Annual Meeting; May 6-11, 2017; Baltimore.
3. Jean-Louis G, Zizi F, Brown D, Ogedegbe G, Borer J, McFarlane S. Obstructive sleep apnea and cardiovascular disease: evidence and underlying mechanisms. *Minerva Pneumol*. 2009;48(4):277-293.
4. Harris M, Glozier N, Ratnavadivel R, Grunstein RR. Obstructive sleep apnea and depression. *Sleep Med Rev*. 2009;13(6):437-444.
5. McNab AA. Floppy eyelid syndrome and obstructive sleep apnea. *Ophthalm Plast Reconstr Surg*. 1997;13(2):98-114.
6. Nesmith BL, Ihnen M, Schaal S. Poor responders to bevacizumab pharmacotherapy in age-related macular degeneration and in diabetic macular edema demonstrate increased risk for obstructive sleep apnea. *Retina*. 2014;34(12):2423-2430.
7. Schaal S, Sherman MP, Nesmith B, Barak Y. Untreated obstructive sleep apnea hinders response to bevacizumab in age-related macular degeneration. *Retina*. 2016;36(4):791-797.
8. Li DQ, Golding J, Choudhry N. Swept-source optical coherence tomography angiography and vascular perfusion map findings in obstructive sleep apnea. *Ophthalmic Surg Lasers Imaging Retina*. 2016;47(9):880-884.
9. Mayo Clinic. Obstructive sleep apnea. www.mayoclinic.org/diseases-conditions/obstructive-sleep-apnea/symptoms-causes/dxc-20205871. Accessed August 3, 2017.

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