

# Journal Highlights

NEW FINDINGS FROM THE PEER-REVIEWED LITERATURE

## Ophthalmology

Selected by Stephen D. McLeod, MD

### Glaucoma Presence and Nocturnal Elevation of Systolic BP

October 2019

Although research has revealed links between glaucoma progression and the variability of circadian blood pressure (BP), it is unclear whether glaucoma itself is associated with particular patterns in nighttime BP. Moreover, it can be difficult to recruit healthy subjects for comparison studies. In an observational study, Yoshikawa et al. looked at BP patterns in patients with glaucoma and more than 700 healthy controls. They noted a significant relationship between glaucoma and elevated nighttime BP as well as nondipper status (minimal nocturnal BP reduction). This association was independent of factors such as obesity, diabetes, and older age.

This cross-sectional study included 109 patients with glaucoma and 708 healthy controls. The mean age of both cohorts was 71 years. All study participants underwent ophthalmic examinations, and ambulatory BP was measured every 30 minutes for 48 hours. The nondipper pattern of BP was defined as a decline in mean nighttime systolic BP of <10% of the mean daytime systolic BP.

Daytime and nighttime periods for

each participant were determined from entries in sleep diaries.

After adjustment for potential confounders (including age, weight, and concurrent diabetes), multivariable linear regression analyses showed that nocturnal systolic BP was 4.1 mm Hg higher in the glaucoma group ( $p = .01$ ), and the nondipper pattern was more prevalent in these patients

(45.0 vs. 27.5%;  $p < .001$ ). Similarly, multivariable logistic regression demonstrated that glaucoma increased the likelihood of nondipper status (odds ratio, 1.96;  $p = .003$ ).

Mechanisms for the low variability of circadian BP in patients with

glaucoma may relate to death of the intrinsically photosensitive retinal ganglion cells. Research indicates that the light exposure received by these cells, especially short-wavelength light, is a key contributor to circadian biological rhythm. Furthermore, it is possible that high epinephrine and low melatonin levels could induce circadian misalignment. Nuclear cataracts also have been implicated.

The authors acknowledged that large longitudinal studies are needed to refine potential relationships between nocturnal BP and the severity and progression of glaucoma.

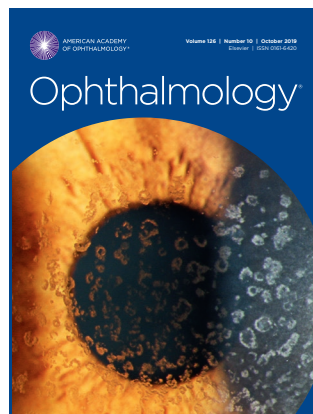
### Viability of Autologous Retinal Transplant for Refractory Macular Holes

October 2019

In 2016, Grewal et al. described use of the autologous neurosensory retinal free flap to close myopic macular holes (MHs) associated with foveoschisis. Since then, the technique has been adopted for various other indications. In a new study, these authors looked at structural and functional outcomes for patients with large refractory MHs that were closed with this procedure. In this initial experience, the technique was safe and successful in most patients.

The multicenter, retrospective, consecutive series included 41 patients (41 eyes) who had a full-thickness MH that persisted after vitrectomy with internal limiting membrane (ILM) peel and tamponade. The subsequent treatment included pars plana vitrectomy, autologous neurosensory retinal transplantation with gas, and tamponade with silicone oil or short-term perfluoro-n-octane heavy liquid. All patients had follow-up for at least six months. Main outcome measures were anatomic closure of the hole, ellipsoid zone (EZ) changes and external limiting membrane (ELM) defects noted on optical coherence tomography (OCT), recovery of visual acuity (VA), and surgical complications. The mean number of previous surgeries in the study group was 1.5 (range, 1-3).

The mean follow-up period after retinal transplantation was 11.1 months (range, 6-36 months). Per OCT findings,



complete anatomic closure of the MH was achieved in 36 eyes (87.8%). Mean corrected VA (logMAR units) improved from 1.11 to 1.03 ( $p = .03$ ) by the last postoperative visit. VA improved in 15 eyes (36.6%), was stable in 17 (41.5%), and declined in nine (21.9%). Of the 36 eyes with anatomic closure, VA improved in 52.3% and worsened in 13.8%. Among the other five eyes, VA worsened in two and improved in none.

Before transplantation, the mean largest basal diameter was 1,468.1  $\mu\text{m}$  (range, 621-2,600  $\mu\text{m}$ ), and the mean inner-opening diameter was 825  $\mu\text{m}$  (range, 336-1,649  $\mu\text{m}$ ). The mean diameter of the EZ defect was reduced from 1,777.3  $\mu\text{m}$  preoperatively (range, 963-2,808  $\mu\text{m}$ ) to 1,370  $\mu\text{m}$  (range, 288-2,000  $\mu\text{m}$ ) by the final follow-up exam ( $p = .007$ ). The mean preoperative ELM defect diameter was 1,681.5  $\mu\text{m}$  (range, 1,172-2,606  $\mu\text{m}$ ), which decreased to 1,408.5  $\mu\text{m}$  (range, 200-2,000  $\mu\text{m}$ ) by the final follow-up ( $p = .017$ ). The major postoperative complications were retinal detachment ( $n = 1$ ) and vitreous hemorrhage ( $n = 1$ ). There were no cases of proliferative vitreoretinopathy, endophthalmitis, suprachoroidal hemorrhage, or choroidal neovascularization.

Despite the large thick retinal flap, displacement of the flap was the most common complication intraoperatively and immediately afterward (with silicone or gas tamponade). The authors noted that further refinement of the surgical techniques should help sustain the flap's position. (*Also see related commentary by Michael J. Koss, MD, in the same issue.*)

## U.S. Versus International Costs of Ophthalmic Drugs

October 2019

Health expenditures in the United States are expected to grow to 20% of the gross domestic product by 2025. As prescription drugs represent the health care category with the largest increase in real per-capita spending in the past four decades, Gong et al. conducted an observational study to compare the costs of common ophthalmic drugs in the United States and other countries.

They found that costs are substantially higher in United States, especially for topical medications. They also noted large price variations between the countries studied as well as between brand and generic products.

The study focused on 25 commonly prescribed ophthalmic medications (22 topical and three intravitreal). Third-quarter 2017 data were obtained, including U.S. average wholesale price, drug-acquisition costs, and consumer pricing. Data sources included U.S. government health insurance plans (Veterans Affairs [VA], Medicaid, Medicare Parts B and D), commercial drug plans (CVS Caremark and Navitus Health Solutions), Costco (for online pricing without insurance), and government-sponsored health plans in Canada, Japan, Italy, Spain, and Turkey. Currencies were converted to U.S. dollars.

The authors found that aflibercept and ranibizumab were priced similarly in the United States, and each was more expensive than dexamethasone. Aflibercept and ranibizumab were less expensive in Italy, Spain, Turkey, Canada, and Japan than in the United States—by as much as 84.3%. The price of topical medications in the United States varied significantly by drug class and according to whether the drug was generic or branded. In general, ophthalmic drugs were less expensive if obtained through VA and Medicaid plans instead of the other U.S. sources, but the lowest costs were attained through hospital-employee drug insurance plans.

As a partial solution to these drug pricing issues, the authors recommended developing an easy-access online database that shows true out-of-pocket costs for patients with each type of insurance.

—Summaries by Lynda Seminara

## Ophthalmology Glaucoma

Selected by Henry D. Jampel, MD, MHS

### Dark Adaptation Survey and Screening for POAG

September/October 2019

Ramsey et al. set out to study the extent to which patients with primary open-

angle glaucoma (POAG) have trouble with dark adaptation (DA) and with seeing in low-light conditions. In addition, they correlated these findings with disease severity. The results showed that problems with DA and vision under low luminance are common in patients with POAG and that patients' subjective self-assessment scores correlated with disease severity.

For this pilot study, the researchers developed a questionnaire that was presented to patients with POAG during routine examinations in a hospital-based eye clinic. The questionnaire included such statements as "I have trouble reading the menu in a dimly lit restaurant" and "After looking at my cell phone, tablet, or computer screen in a dim room, I find it difficult to recognize objects when I look away from the screen."

All told, 85 patients with POAG and 127 control participants completed the questionnaire. All were 40 years of age or older and had a visual acuity of 20/50 or better. The researchers then extracted data related to the patients' ocular health and degree of glaucoma severity from their medical records. A multiple regression analysis was performed to create a predictive model for POAG.

The results confirmed that vision problems in low light and issues with DA are common in patients with glaucoma. And although these problems become more prominent as the disease progresses, patients with POAG report more subjective visual dysfunction in the early stages of the disease than do healthy controls. With regard to the questionnaire's ability to serve as a predictive tool, the DA survey score—when combined with cup-to-disc ratio and family history of glaucoma—showed an accuracy, sensitivity, and specificity of 96.7%, 92.9%, and 99.2%, respectively.

The authors noted that patients with glaucoma are not always queried about DA problems and similar challenges during routine glaucoma care. A questionnaire such as this one, when paired with family history and structural assessment of the optic nerve, might serve as a screening tool, they concluded.

—Summary by Jean Shaw

### Nomenclature and Guidelines for Widefield Imaging

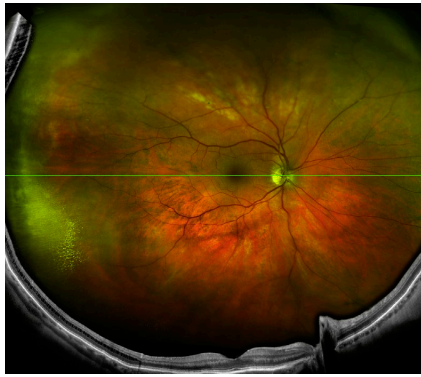
October 2019

The term widefield has been used inconsistently in the literature in describing retinal images. To address this problem, an international panel of 11 retina specialists was convened to evaluate the terminology for widefield images obtained with current retinal imaging methods. Choudhry et al. summarized the findings and recommendations of the panel, known as the International Widefield Imaging Study Group.

Before the consensus meeting, a set of seven images was circulated to panel members. The images were acquired with current approved and commonly used imaging methods, including swept-source optical coherence tomography (OCT) and fluorescein angiography. Both healthy and diseased eyes were represented in the image set.

In addition to evaluating the capabilities of the imaging methods, panel members also reviewed published studies and discussed the definitions of widefield and ultra-widefield imaging. Their recommendations include the following:

- The term *widefield* should be limited to images depicting retinal anatomic features beyond the posterior pole, but posterior to the vortex vein ampulla, in all four quadrants.
- *Ultra-widefield* images are those showing retinal anatomic features anterior to the vortex vein ampulla in all four quadrants.
- *Posterior pole* should continue to be defined as the area of retina within the major temporal vascular arcades and slightly just beyond, as captured in a 50-degree view with most devices.
- In discussing field of view (FOV) and its point of centration for fundus cameras and OCT devices, the panel agreed that the FOV should have the macula at its center.
- FOV boundaries should correspond to anatomic landmarks within the retina, and these landmarks should be incorporated into the nomenclature. For



**DEFINITIONS.** *The panel proposed that the term panretinal be used for a complete 360-degree ora-to-ora view of the retina. In lieu of a single capture method, the montage technique (shown here) is likely to remain popular.*

instance, they said, the term *midperiphery* should refer to the region of retina extending from the vascular arcades to the posterior edge of the vortex vein ampulla, which is captured at a range of 60 degrees to 100 degrees.

Finally, panel members proposed that this standardized nomenclature be used in future publications, and they noted that their findings will need to be updated in the future as imaging technology develops.

—Summary by Jean Shaw

## American Journal of Ophthalmology

Selected by Richard K. Parrish II, MD

### Race and Persistent Uveitis After Cataract Surgery

October 2019

Reddy et al. set out to identify risk factors for the occurrence of persistent anterior uveitis (PAU) secondary to uncomplicated cataract extraction in patients with no history of uveitis or autoimmune disease. The authors determined that African Americans are more likely than others to experience this postoperative condition and that PAU does not predict worse visual outcomes.

This study was a three-year, single-center retrospective series of patients who did not have autoimmune disease or previous uveitis. They had undergone cataract surgery by

phacoemulsification with implantation of an IOL. A total of 3,013 eyes (2,019 patients) were included in the study; of these, 61 eyes (48 patients) had post-op PAU. Cystoid macular edema (CME) also developed in 18 of these 61 eyes.

The authors calculated relative risk (RR) to determine whether certain characteristics were linked to the probability of PAU. These included age, sex, race/ethnicity (white, African American, Hispanic, or other), operating time, cumulative dissipated energy during phacoemulsification, visual acuity, intraocular pressure (IOP), anterior chamber cell grade, CME presence, and steroid use during follow-up.

Results showed that African Americans were much more likely than whites to have PAU after uncomplicated cataract extraction (RR, 11.3;  $p < .0001$ ). No other patient-level characteristic was identified as a risk factor for PAU. Three months postoperatively, the visual acuity of patients with and without PAU was comparable, but the mean IOP was slightly higher in those with PAU. Among patients with PAU, visual acuity and IOP results were similar for the various races.

The authors concluded that, after cataract surgery, African Americans have a high risk of PAU; however, this prolonged inflammation does not seem to affect long-term visual outcomes.

### Phakic IOLs for Myopia and Myopic Astigmatism

October 2019

Long-term data on the visual outcomes of implantable collamer lenses (ICLs) are minimal. Nakamura et al. conducted a 10-year retrospective study of patients who received Visian implantable collamer lenses to treat moderate to high myopia, with or without astigmatism. The authors found that ICL implantation produced good long-term outcomes for safety and efficacy as well as for predictability and stability.

For this observational case series, the researchers included 114 eyes (61 patients) that underwent ICL placement to correct myopia or myopic astigmatism. At the time of surgery, the patients were between the ages of 20 and 50.

The authors collected data from the pre-op visit and from follow-up visits that extended until 10 years following surgery. Safety and efficacy indices were calculated from corrected and uncorrected distance visual acuity (VA) using these equations: post-op CDVA/pre-op CDVA and post-op UDVA/pre-op CDVA, respectively.

The researchers implanted toric ICLs in 72 eyes and spheric ICLs in 42 eyes. At the 10-year mark, 70 eyes (38 patients) were examined. Of these, 71.4% were within 0.5 D of the attempted spherical equivalent correction, and 87.1% were within 1.0 D. The mean logMAR results were  $-0.01 \pm 0.24$  (UDVA) and  $-0.18 \pm 0.07$  (CDVA). The mean safety index was  $0.88 \pm 0.15$ , and the mean efficacy index was  $0.66 \pm 0.26$ . The intraocular pressure was unchanged during the observation period, and eyes lost an average of  $5.3\% \pm 12.3\%$  of their pre-op endothelial cell density.

Adverse events included anterior subcapsular cataract in 12 of the 114 eyes; four of these required ICL explantation and phacoemulsification. As cataract formation after ICL surgery is concerning, the authors emphasized that risk factors for this complication should be explored further.

Given these results, it appears that good 10-year outcomes are likely for eyes with myopia or myopic astigmatism that receive implantable toric or spheric ICLs. Knowledge of the longer-term postoperative course is crucial, the authors said.

—Summaries by Lynda Seminara

## JAMA Ophthalmology

Selected and reviewed by Neil M. Bressler, MD, and Deputy Editors

### Retinal Characteristics of Patients With Yellow Fever

September 2019

Two outbreaks of yellow fever (YF) occurred recently in Southeastern Brazil. To better understand the retinal changes that accompany this virus, **Brandão-de-Resende et al.** studied patient data collected during the outbreaks. Among patients with YF,

retinopathy was observed in 20%. The most common retinal findings were superficial hemorrhage, retinal nerve fiber layer (RNFL) infarct, and grayish outer retinal lesions. Systemic findings associated with retinopathy were low platelet counts and elevated levels of serum aspartate aminotransferase, total bilirubin, arterial lactate, and serum creatinine. Even though retinopathy is common in YF, the authors said, it may be overlooked, especially if virus severity precludes careful ophthalmoscopic examination.

This cross-sectional study was performed at a referral center for infectious diseases in Southeastern Brazil. Data were collected for 94 patients suspected of having YF, all of whom had undergone ophthalmic exams. Collected data included demographics, clinical findings, lab results, and the presence or absence of retinopathy.

Of the 94 participants, 64 were confirmed to have YF. Their mean age was 47 years (range, 38-56 years), and 12 patients (19%) were female. Twenty eyes (16%; 13 patients) had retinopathy at the time of yellow fever. The most common fundus changes in these 20 eyes were RNFL infarcts ( $n = 11$ ), superficial hemorrhage ( $n = 7$ ), and grayish deep lesions ( $n = 6$ ). The RNFL infarcts and superficial hemorrhages (but not the grayish lesions) resembled those of other flavivirus infections. Lab findings noted in these patients included aspartate aminotransferase  $>3,000$  U/L ( $p < .001$ ), total bilirubin  $>2.3$  mg/dL ( $p < .001$ ), serum creatinine  $>2.0$  mg/dL ( $p = .003$ ), arterial lactate  $>17.1$  mg/dL ( $p = .03$ ), and platelet count  $<94 \times 10^3/\mu\text{L}$  ( $p = .004$ ). Retinopathy was most common in patients whose YF was severe. Overall, it was not associated with arterial hypertension, diabetes, international normalized ratio, or death.

This study demonstrates the wide range of retinal changes that may occur with YF. Further research would be needed to determine whether the findings have clinical or prognostic relevance, said the authors, who stressed the importance of ophthalmic screening in patients with YF. (Also see related commentary by *Jessica G. Shantha, MD,*

*Steven Yeh, MD, and Nisha Acharya, MD, in the same issue.*)

### Ophthalmology Residency: Gender and Case Volume

September 2019

The number of male and female medical students who enter ophthalmology residency programs is roughly equivalent, but little is known about differences in surgical training between these men and women. According to the Accreditation Council for Graduate Medical Education, ophthalmology residents are required to perform a specific number of surgical procedures and must receive “equivalent [training] opportunities” by gender. Data from 1999 to 2002 showed that surgical efficiency improves as case volume increases—beyond the minimum number of required cataract operations for graduation (currently 86). Even after 160 cases, operating efficiency improves and complication rates decline. In a longitudinal study, **Gong et al.** reviewed case logs of residents to compare surgical volume between male and female students. They found that men performed substantially more cataract operations and total procedures. The gender disparity in case volume grew throughout the 12-year timeline.

For this retrospective study, the authors collected and analyzed 12 years of data (through June 2017) for 24 U.S. ophthalmology residency programs, reflecting the experience of 1,271 residents. Details of interest were gender, parental leave status, volume of cataract operations, and total number of surgical procedures.

The analyses showed that female gender correlated with fewer cataract operations and fewer total operations. Men performed a mean (standard deviation) of 176.7 (66.2) cataract operations, whereas women performed 161.7 (56.2) (mean difference,  $-15.0$ ;  $p < .001$ ). The mean number of total procedures was 509.4 (208.6) for men and 451.3 (158.8) for women (mean difference,  $-58.1$ ;  $p < .001$ ). Eighty-five (10.4%) of the 815 male residents and 71 (15.6%) of the 456 female residents took parental leave. On average, male

residents who took paternity leave performed a mean of 27.5 more cataract operations than the men who did not take leave ( $p < .001$ ). However, the case volume of female residents who took maternity leave was similar to that of women who did not (mean difference,  $-2.0$ ;  $p = .81$ ). From 2005 to 2017, the increase in total number of procedures was greater for men than for women ( $\beta = -8.0$ ;  $p = .008$ ).

Educators should be aware of this gender disparity, and further investigation is needed to ensure that training experiences truly are equivalent, the authors noted. (*Also see related commentary by Julia A. Haller, MD, and Qiang Zhang, PhD, in the same issue.*)

## OCT CST Results Do Not Reflect Visual Acuity Changes in DME

September 2019

Some research indicates that changes in central subfield thickness (CST) after anti-VEGF treatment of diabetic macular edema (DME) may correlate with changes in visual acuity (VA), while other studies do not support this finding. In a post hoc analysis of the DRCR Retina Network (DRCR.net) Protocol T randomized clinical trial, Bressler et al. looked at the relationship between these parameters and found that CST changes as noted on optical coherence tomography (OCT) account for very little of the entire variation in VA. Hence, the findings do not support OCT CST as a marker for VA changes in clinical trials of anti-VEGF therapy for DME or as a guide regarding potential changes in VA from such treatment.

For this study, VA and OCT CST changes were compared for 652 patients who had been treated with aflibercept, ranibizumab, or bevacizumab in the randomized trial. Each patient received six monthly intravitreal injections of the anti-VEGF agent, unless success was achieved before the six-month mark. Subsequent injection or focal/grid laser photocoagulation treatment was given if needed (per protocol) to achieve stability. The main outcome measure was the association between changes in VA letter score and

changes in OCT CST at weeks 12, 52, and 104 after randomization.

The mean age of participants was 61 years (range, 54-67 years). The correlations between OCT CST changes and VA changes were 0.24 at 12 weeks, 0.31 at 52 weeks, and 0.23 at 104 weeks. The correlation coefficients of change in VA versus change in OCT CST at these time points were 0.36, 0.36, and 0.33, respectively, and were similar for each treatment. For any given change in OCT CST from baseline, there was a broad range of changes in VA from baseline to each time point.

These results support those of laser photocoagulation studies of DME and anti-VEGF studies of other macular diseases, wherein, at best, only a moderate correlation was observed between VA changes and CST changes. The DRCR.net has not evaluated whether other OCT features—such as altered disorganization of the retinal inner layers—may correlate with changes in VA over time.

Clues to reasons for the weak correlation between CST and VA changes are beyond the scope of this study, said the authors. However, their findings do suggest that OCT CST changes should not be used in lieu of VA changes either as a main outcome in DME trials of anti-VEGF therapy or as an indicator of the VA changes to expect from such treatment. (*Also see related commentary by Sapna Gangaputra, MD, MPH, and Paul Sternberg Jr., MD, in the same issue.*) —Summaries by Lynda Seminara

## Other Journals

Selected by Deepak P. Edward, MD

### Machine Learning for Diagnosis in Automated Glaucoma Clinics

*Eye*

2019;33(7):1133-1139

The demand for global glaucoma services is growing rapidly, driven by factors such as longer life expectancy, earlier diagnosis, and the plethora of available treatments. Machine learning is a powerful tool for analyzing patient data, and various computer algorithms can distinguish between glaucomatous signs and neurological field defects. In

a glaucomatous population, Thomas et al. explored the utility of feed-forward back-propagation artificial neural networks (ANNs) for detecting field defects caused by pituitary disease. They found that by inspecting bilateral field representations, traditional ANNs are efficient in detecting chiasmal field defects. The findings suggest that machine learning may play a key “diagnostic oversight” role in the future.

For this study, the researchers obtained 24-2 Humphrey visual field reports for 121 patients with pituitary disease and 907 patients with glaucomatous findings, and they used optical character recognition to extract threshold values from the reports. For each patient, left- and right-eye visual fields were coupled in an array to create bilateral field representations. ANNs were created to detect chiasmal field defects. The authors then assessed the networks’ ability to identify a single pituitary field among the 907 glaucomatous distractors.

Results of the analyses showed that mean field thresholds in all locations were lower for the pituitary group (20.3 dB, standard deviation [SD] = 5.2 dB) than for the glaucoma group (24.4 dB, SD = 5.0 dB), suggesting that the degree of field loss is greater in patients with pituitary disease ( $p < .0001$ ). However, the substantial overlap in results implies that mean bilateral field loss alone is not a reliable indicator of etiology.

Overall, ANNs performed well in the discrimination task; sensitivity and specificity exceeded 95%. When a single pituitary field was hidden among 907 glaucomatous fields, it had one of the five top indexes of suspicion in 91% of the ANNs.

The advent of telemedicine means that better methods are needed to automatically identify not only glaucoma but also any accompanying pathology or masquerading conditions, the authors said. They added that ANNs such as theirs may have a role to play in the automated care of the future.

—Summary by Lynda Seminara



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