

Journal Highlights

NEW FINDINGS FROM *OPHTHALMOLOGY*, *AJO* AND *ARCHIVES*

Ophthalmology

24-Hour Assessment of IOP in Glaucoma Patients

May's *Ophthalmology*

In the first study to evaluate optic disc appearance in relation to 24-hour IOP, Deokule et al. found that untreated glaucoma patients with a generalized cup enlargement (or concentric optic disc enlargement) demonstrated higher mean IOP and a greater number of IOP peaks in the nocturnal period than those with focal ischemic, myopic glaucomatous or senile sclerotic (nonconcentric) optic disc appearance.

This study involved 75 eyes of 45 patients with primary open-angle glaucoma whose IOP was assessed for 24 hours in a sleep laboratory. The mean nocturnal IOP was significantly greater in the concentric group compared with the nonconcentric group. The majority of IOP peaks in patients with the concentric optic disc appearance occurred overnight compared with the diurnal period of patients with the nonconcentric optic disc appearance.

The authors conclude that measuring IOP only during office hours may lead to an underestimation of IOP.



Corneal Epithelial Homeostasis and Limbal Epithelial Stem Cells

May's *Ophthalmology*

In this case series, Dua et al. present evidence that raises questions about the role of the limbus in normal corneal epithelial homeostasis. They examined five patients (eight eyes) with clinically diagnosed total limbal stem cell deficiency in one or both eyes with a central area of normal corneal epithelial cells. Clinical slit-

lamp examination and in vivo confocal microscopy over a mean of 60 months revealed the existence and survival of a healthy sheet of corneal epithelial cells in the presence of a clinically apparent total limbal stem cell deficiency.

The authors conclude that these findings support the hypothesis that physio-

logical corneal epithelial homeostasis can be maintained in the absence of detectable limbal epithelial stem cells.

Angiotensin II Receptor Expression in Giant Cell Arteritis

May's *Ophthalmology*

Giant cell arteritis (GCA), a granulomatous form of vasculitis, produces a variety of symptoms, including blindness, jaw claudication, headaches, stroke and aortic arch

syndrome. The disease is treated with corticosteroids or immunomodulating agents.

Seeking a noncorticosteroid treatment alternative, Dimitrijevic et al. focused a study on angiotensin II, a vasoactive peptide involved in vessel inflammation during atherosclerosis. Angiotensin II receptor inhibitors have proven effective in preventing atherosclerosis. The authors conducted an immunohistochemical study of temporal arteries using archival tissue of 10 patients with GCA and 10 control patients clinically suspected of having GCA but not diagnosed. Their results show that angiotensin II type 1 receptors may play a role in the development of GCA. High levels of this receptor expression were found in the vascular smooth muscle cells and inflammatory cells in the temporal arteries of patients with GCA.

They conclude that inhibiting the renin-angiotensin system may serve as a noncorticosteroid alternative for the treatment of GCA inflammation.

FL-41 Tint in Benign Essential Blepharospasm

May's *Ophthalmology*

Blackburn et al. found that FL-41 lenses provide a benefit to patients with benign essential blepharospasm (BEB). The FL-41 is a tint that blocks light at the green-to-blue end of the spectrum.

The authors conducted two studies. The first was a crossover study comparing the perceived improvement in light sensitivity and activities of daily living provided by FL-41 lenses in 30 patients with BEB. The second study used surface electromyography to evaluate the effects of FL-41 on blink frequency, duration and force in 26 patients with BEB and 26 controls. Most participants observed improvement with both FL-41 and gray-tinted lenses. However, FL-41 lenses provided superior improvement in reading, fluorescent light sensitivity, overall light sensitivity, blepharospasm frequency and blepharospasm severity. In addition, FL-41 lenses reduced mean blink rate compared with both rose- and gray-tinted lenses, and reduced eyelid-contraction force compared with rose-tinted lenses.

The authors conclude that FL-41-tinted spectacles represent a viable option to help patients improve BEB symptoms.

American Journal of Ophthalmology

Inaccuracy of Laser Spot Size During PDT

May's *AJO*

In an observational case series, **Ranchod et al.** measured the laser spot diameter on the retina as generated by two FDA-approved lasers (Coherent Opal and Carl Zeiss Visulas) during photodynamic therapy.

Fundus photographs were taken of one eye of 10 subjects with the Ophthalmic Imaging Systems (OIS) WinStation 4000 fundus photography system. Disc size was calculated using the OIS software. Slit-lamp photographs were taken of the PDT laser spot that was focused on the retina adjacent to the optic disc. Spot size at the retina was determined by measuring the ratio of disc diameter to spot diameter in Adobe Photoshop and applying this ratio to the OIS disc measurements. Spot size at the retina averaged 87 percent of expected spot size for the Coherent Opal laser and 104 percent of expected spot size for the Carl Zeiss

Visulas laser. Multivariate analysis demonstrated that the percentage of the expected spot size decreased with larger spot diameter.

The authors conclude that PDT spot size at the retina was consistently smaller than expected for the Coherent laser while the spot size was consistently within 10 percent of expected size for the Carl Zeiss laser. The clinical implications are not clear.

Corneal Confocal Microscopy After Crosslinking

May's *AJO*

Kymionis et al. investigated corneal tissue alterations after corneal collagen crosslinking in patients with post-LASIK keratectasia and in patients with keratoconus.

Five patients (five eyes) with iatrogenic keratectasia after LASIK and five patients (five eyes) with progressive keratoconus were included. All eyes underwent corneal crosslinking and were assessed by corneal in vivo confocal microscopy. Three healthy corneas and three corneas without post-LASIK ectasia served as controls.

All corneas revealed normal epithelial thickness before and after surgery.

Images of eyes with keratoconic or post-LASIK corneal ectasia revealed similar morphologic alterations: the subepithelial nerve plexus was absent immediately after treatment, while regeneration of nerves was evident after the third postoperative month. Keratocytes were also absent from the anterior 300 μm of the stroma in the first three months, while the posterior stromal density of keratocytes was increased. Corneal collagen fibers in the anterior stroma were distributed unevenly in a netlike formation. Full-thickness keratocyte repopulation in the anterior and midcorneal stroma was detected six months after treatment. The corneal endothelium did not undergo any significant changes.

The authors also observed keratocyte nuclei apoptosis in the anterior and intermediate corneal stroma during the first three postcorneal crosslinking months. Gradual keratocyte

repopulation was demonstrated over the following months.

Age-Related Choroidal Atrophy

May's *AJO*

Richard Spaide reported the clinical characteristics of a possible new entity of age-related choroidal atrophy.

The choroidal thickness was measured in images obtained by positioning a spectral-domain OCT device close enough to the eye to acquire an inverted image. Seven sections each comprising 100 averaged scans were obtained within a 5 x 15-degree or larger rectangle in order to encompass the macula and temporal juxtapapillary retina. Choroidal thicknesses of less than 125 μm were included. Patients were excluded if they had any previous photodynamic therapy, intravitreal corticosteroid injection, myopia of more than 6 D, trauma, tapetoretinal dystrophy, uveitis or ionizing radiation. The patients were evaluated for visual acuity, macular appearance and the presence of glaucoma.

There were 28 eligible eyes of 17 patients (mean age of 80.6 years). All eyes had a tessellated fundus appearance. The mean subfoveal choroidal thickness was 69.8 μm and became even more attenuated nasally.

Eighteen of the eyes had no evidence of late age-related macular degeneration, and mean visual acuity was 20/40. These eyes had pigmentary changes in the macula that arose in part from a rarefaction of the choroidal vessels under the macula, potentially mimicking early AMD. Concurrent late AMD was found in the 10 remaining eyes. Glaucoma was present in six patients (35 percent), all of whom had peripapillary atrophy.

Excimer Laser Surface Ablation and Thin Corneas

May's *AJO*

In a retrospective study, **Benito-Llopis et al.** evaluated the long-term outcomes of excimer laser surface ablation performed on thin corneas.

The study included 75 eyes (49 patients) with a preoperative central corneal thickness thinner than 500 μm . All the eyes had undergone surface ablation to correct their myopia and had been followed for at least 10 years. The authors evaluated the stability of visual acuity and refraction, as well as several other parameters, at various time intervals after surgery.

Preoperative central corneal thickness averaged 481.54 μm and preoperative spherical equivalent averaged -6.12 D. Best-corrected visual acuity significantly improved during the follow-up. The uncorrected visual acuity also showed significant improvement in all visits when compared with the three-month postoperative visit. Both the sphere and cylinder showed a slight but significant regression between three-month and 10-year follow-up visits.

Ten years after the surgery, 40 percent of the eyes were within 0.5 D and 57 percent were within 1 D of emmetropia. Moreover, the safety index improved over the 10-year period and was always higher than 0.9, while the efficacy index remained stable at around 0.8.

Archives of Ophthalmology

Combined Approach for Repair of Orbital Wall Fractures

March's Archives

Lee et al. described the combined transcaruncular and transconjunctival approach in isolated large medial orbital wall fractures and examined the implications of uncorrected posterior orbital volume on postoperative enophthalmos.

The authors performed a medical record review of 23 consecutive patients who underwent reduction surgery for isolated large medial orbital wall fractures using the combined transcaruncular and transconjunctival approach. The unaffected contralateral orbital volume was assumed to represent the pretrauma volume of the affected orbit, and the uncorrected posterior orbital volume after reduc-

tion was determined using a software program.

The mean volume of the affected orbit changed from 26 cm^3 to 24.08 cm^3 after reduction, which was still larger than the contralateral unaffected orbit by 1.48 cm^3 . Despite the uncorrected volume in the most posterior portion of the medial wall, the mean postoperative enophthalmos measured only 0.17 mm (using Hertel exophthalmometry at a mean follow-up of 8.5 months).

The authors conclude that the combined transconjunctival and transcaruncular approach resulted in excellent outcomes in terms of prevention of postoperative enophthalmos of the large medial wall fracture without substantial complications. The uncorrected volume of far posterior orbit may not contribute significantly to the development of posttraumatic enophthalmos.

Effect of Triamcinolone Acetonide on CNV

March's Archives

Tatar et al. performed a histopathological examination of choroidal neovascularization (CNV) membranes in an attempt to evaluate the effect of intravitreal triamcinolone acetonide.

They examined CNV membranes from 29 patients for different markers related to proliferation and inflammatory process. Fourteen patients had not undergone previous therapy, five had undergone treatment with triamcinolone acetonide alone, four had undergone photodynamic therapy alone and six had undergone PDT in combination with triamcinolone acetonide.

The study revealed that CNV membranes treated with triamcinolone acetonide alone or in combination with photodynamic therapy was characterized by macrophagic infiltration and a high expression of vascular endothelial growth factor. Proliferative activity and leukocytic infiltration were also lower. The authors postulate that triamcinolone acetonide had no inhibitory effect on macrophage infiltration

or ICAM-1, Thy-1 or VEGF expression in early term.

They conclude that the clinical benefits observed with the use of triamcinolone acetonide are probably not based on pure anti-inflammatory or VEGF-suppressing mechanisms. A combination with anti-VEGF agents may therefore converge opposite routes and provide synergism.

Retinoblastoma Regression Patterns

March's Archives

Shields et al. conducted a retrospective study on 557 retinoblastomas to assess regression patterns following chemoreduction. Regression patterns were categorized as type 0 (no remnant), type I (calcified remnant), type II (noncalcified remnant), type III (partially-calcified remnant) and type IV (atrophic flat scar).

Small tumors of thickness less than 3 mm most often regressed to type IV, medium tumors of 3 to 8 mm in thickness regressed to type III or IV most often and large tumors over 8 mm in thickness regressed most often to type I or III. Factors predictive of type I regression included large tumor base and macular location. Factors predictive of type III regression were similar. Factors predictive of type IV regression included smaller tumor base and greater distance from the foveola.

The authors note that it is important to understand regression patterns following chemoreduction so that the clinician can judge whether or not a tumor has responded appropriately and to judge further consolidation therapy.

Eye Care Utilization in the United States

March's Archives

Using data from the National Health Interview Survey, Lee et al. documented the prevalence of eye care utilization over the course of the previous 12 months.

Data from nearly 290,000 adult participants were analyzed. Multi-variable analyses in racial/ethnic and

age category subgroups indicated that reported visual impairment, lack of health insurance, male sex and low education were not associated with low rates of eye care utilization. Gaps in insurance coverage in the previous 12 months were associated with lower eye care utilization rates relative to partici-

pants with consistent coverage.

The authors conclude that interventions designed to increase eye care utilization rates in select sociodemographic subgroups are needed and that progress toward increasing the number of Americans with health care coverage will also enhance rates of eye care

utilization.

Ophthalmology summaries are written by Lori Baker Schena and edited by John Kerison, MD. American Journal of Ophthalmology summaries are edited by Thomas J. Liesegang, MD. Archives of Ophthalmology summaries are written by the lead authors.

ROUNDUP OF OTHER JOURNALS

Mechanosensitive Transcriptional Mechanism Linked to Angiogenesis

Nature

2009;457:1103–1109

Most of the angiogenesis inhibitors approved by the FDA target the oxygen-sensitive vascular endothelial growth factor. However, according to Mammota et al., other microenvironmental signals control neovascularization, including mechanical forces conveyed by extracellular matrix.

The authors demonstrated that the Rho inhibitor, p190RhoGAP, also controls VEGFR2 expression, as well as angiogenesis in vitro and in vivo. It accomplishes this by altering the balance between two mutually antagonistic transcription factors, TFII-1 and GATA2. The investigators also showed that mechanical signals conveyed by variations in extracellular matrix elasticity regulate p190RhoGAP and this downstream transcriptional control mechanism.

Frequent Somatic Mutations of GNAQ in Uveal Melanoma

Nature

2009;457:599–603

Although uveal melanoma only accounts for approximately 5 percent of all melanomas, it constitutes the most common intraocular malignancy in the United States. Once this highly aggressive cancer metastasizes, no effective treatment options are available.

In a letter, Van Raamsdonk et al. present their study that identified

signaling components downstream of the heterotrimeric G protein alpha-subunit, GNAQ, as potential targets in uveal melanoma.

The investigators point out that most nevi and melanomas demonstrate oncogenic mutations in signaling components of the mitogen-activated protein kinase pathway, specifically BRAF and NRAS. Yet a subset of melanocytic neoplasms does not show BRAF and NRAS mutations. In this study, the investigators found frequent somatic mutations in GNAQ in both blue nevi (83 percent) and ocular melanoma of the uvea (46 percent). They occurred only in codon 209 in the Ras-like domain and resulted in constitutive activation—turning GNAQ into a dominant-acting oncogene.

IOP and Systemic Blood Pressure During Exercise

Investigative Ophthalmology & Visual Science

2009;50:760–764

Bakke et al. have found that IOP increases in parallel with the transient, continuous changes in systemic blood pressure during isometric exercise.

Six healthy men and three healthy women who were all nonmedicated, normotensive nonsmokers participated in the study. Their systemic blood pressure, heart rate and IOP were recorded continuously for 30 seconds before, two minutes during and 30 seconds after a two-minute period of isometric exercise that involved a custom-made handgrip unit. The participants exerted a force corresponding to

40 percent of the maximum voluntary contraction of their forearm.

During the two-minute isometric exercise, systolic and diastolic arterial blood pressure increased from 125 ± 6 to 169 ± 8 mmHg and from 65 ± 3 to 96 ± 5 mmHg, respectively. IOP increased from 15 ± 1 mmHg at rest to 19 ± 2 mmHg at the end of the isometric exercise.

Variants in the SERPING1 Gene and AMD

The Lancet

2009;373:461–462

In a letter, Kralovicova and Vorechovsky provide insight into a previous investigation that demonstrates an association between the SERPING1 gene (located on chromosome 11) and age-related macular degeneration.

The two authors explored which biological mechanisms are affected by the population variability in SERPING1 and which variants play a major role in a genetic disposition to AMD. They inspected gene sequences associated with the newly identified variants and found that one of them, rs2511988, appeared highly likely to possess functional consequences. Specifically, a single-nucleotide substitution is located 20 base pairs upstream of the 3' splice site of exon 7 and is much closer to the SERPING1 coding sequence than the rs2511989 variant initially discovered. The rs2511988 variant sits adjacent to a branch point sequence.

Roundup of Other Journals is written by Lori Baker Schena and edited by Deepak P. Edward, MD.