NOTES FROM THE 47TH ANNUAL ARDS MEETING

The list of retina specialists who have delivered the Taylor Smith and Victor Curtin Lecture at the Aspen Retinal Detachment Society (ARDS) meeting reads like a who's who of giants in the field. This year, Yale L. Fisher, MD, presented this named lecture and focused on advances in diagnostic ultrasonography. As expected, he delivered a robust history lesson that informed contemporary use of ultrasound technology coupled with pearls for modern imaging that ARDS members can apply in their clinics.

Hugo Quiroz-Mercado, MD, shared with meeting attendees his experience using anti-VEGF therapy for infants presenting with retinopathy of prematurity. Dr. Quiroz-Mercado's presentation reminds us that our work is not limited to adults with retinal disease, and that the stakes of treatment in infants are high, demanding great attention to detail.

Luis A. Gonzalez, MD, MPH, has prepared summaries of both of these lectures. His work and the work of his fellow ARDS meeting scribes, Ru-Ik Chee, MD, and Nimesh A. Patel, MD, help to ensure that the 2019 meeting will be transcribed for posterity. The meeting organizers owe these fellows a debt of gratitude.

The upcoming 2020 ARDS meeting will be held February 29 to March 4 in Snowmass, Colorado. Expect scientific discussion paired with hot chocolate during après-ski. Go to MedConfs.com to register.

—Timothy G. Murray, MD, MBA

THE ESSENCE OF DIAGNOSTIC ULTRASONOGRAPHY

Yale L. Fisher, MD, delivered the Taylor Smith and Victor Curtin Lecture at ARDS.

By Luis A. Gonzalez, MD, MPH

Yale L. Fisher, MD, delivered the Taylor Smith and Victor Curtin as the guest of honor at the 2019 ARDS meeting. This article presents a summary of portions of his talk.

UNDERSTANDING THE TECHNOLOGY

Dr. Fisher explained that ultrasound devices have changed significantly since they were first developed. To begin, we can review the different types of sonification by employing schlieren optics, a laboratory technique capable of visualizing sound waves. There are two forms of ultrasound sonification commonly used in diagnostic work: continuous wave (CW) and pulse/echo technology. For our purposes, pulse/echo is the form utilized in diagnostic ultrasound. It is part of a broader category of instruments called *distance measuring equipment*, platforms in which an energy pulse is timed from initial creation to return. In diagnostic ultrasound, sound pulses are weakly focused with sonic lenses to improve lateral resolution.

By moving the transducer in an arc-like motion, multiple areas can be exposed to sonic pulsed energy and their returning signals can be collected. Returning echoes are displayed as A-scans (time-amplitude) or B-scans (intensity-modulated). The images created are evaluated for artifact and stored as stills or movie segments. An understanding of both displays is critical to pattern recognition and diagnostic interpretation. Over the past half century, hardware and software have revolutionized this noninvasive, safe diagnostic technique for both opaque and clear media. Innovation and portability improvements continue.

The resolution of ultrasound depends on probe design and frequency. For posterior pole imaging probes, use 10 to 20 MHz frequencies, and resolution varies. Posterior segment images utilizing commercially available instruments are approximately 100 µm axially by 200 µm laterally for 10 to 12 MHz probes. Higher frequencies are capable of 85 µm by 120 µm in some situations. Anterior segment probes use higher frequencies (35 to 50 MHz), with resolution approximately 23 µm by 35 µm. Unfortunately, higher frequencies offer less penetration, so there are depth limits of approximately 5 to 6 mm. Older techniques for

Resource for Ophthalmic Ultrasonography

Challenges in the teaching of ophthalmic ultrasonography persist, including limited physician exposure and a small population of technicians who perform the scans for physicians in large institutions. Additionally, no formal training exists at many small institutions. Courses that teach ophthalmic ultrasound are limited in time and scope.

A tremendous online resource created by Yale L. Fisher, MD, for the sole purpose of facilitating ultrasound education is available for free at www.ophthalmicedge.org. (Dr. Fisher stated that he has no financial interests in the website.)

anterior segment ultrasound utilized cumbersome, makeshift water baths as "stand-offs" for diagnostic evaluations. Commercial development of water-filled, sterile cups fitted over the ultrasound transducer probe permit rapid, easy scanning without difficulty. Interchange between posterior, contact scanning and anterior, water-bath probes for anterior scanning is now much easier.

Anterior segment ultrasound examination is performed directly on the cornea and anterior conjunctiva. The eyelids are held gently separated and the water-filled cup of the anterior segment probe is applied to the cornea. Posterior segment examination does not require direct contact and is usually performed through the lids.

In diagnostic ultrasonography, three concepts are fundamental: (1) Examinations are done in real time, which means there is movement; (2) the display is in gray scale, indicating intensity; and (3) users must generate 3D images based on 2D cross-sections.

"This final point is by far the hardest concept to master," Dr. Fisher said. "An experienced ultrasonographer should feel comfortable drawing an architectural map of the interior of the globe based on an ultrasound exam alone."

COMMON ERRORS

Some common pitfalls and mistakes encountered in performing ultrasound diagnostics include the following:

- **Performing examination through the patient's lens or IOL.** These lens systems create too many artifacts. Quick fix: Place the probe anywhere else. Use transverse or radial scans.
- **Screen image registration.** Be aware of how the probe is oriented. The screen does not change, but the probe does. The mark on the probe indicates what is registered at the top of the screen. The left side of the screen always shows what is closest to the probe and the right side farthest. It seems simple, but one must practice to master it.
- **Forgetting movement.** Intraocular abnormalities often have peculiar diagnostic motions when the globe is voluntarily moved. Ask the patient to look in different directions while imaging.
- **Jumping to a diagnosis.** Instantaneous diagnoses may be wrong. It is recommended to finish the scan first in an orderly

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TABLE 1. PEARLS OF WISDOM FOR POSTERIOR ULTRASOUND EXAMS

On technique and the machine	Know your settings and probe positioning. Know your probe orientation.
On measuring choroidal tumor or nevus	The time-gain control is used to improve image quality. It does so by increasing weaker signals. For precise measurements, *turn off* the time gain control.
On artifacts	Do not shoot through the lens; this will help prevent artifacts. Always do real-time imaging; ask the patient to move the eye around.
On choroidal hemorrhage	Always do real-time to differentiate choroidal hemorrhage from tumor. Follow up with series of ultrasound images to determine when a choroidal hemorrhage is liquid enough to drain.
On flashes and floaters	You can use real-time ultrasound along with simultaneous scleral depression to localize tears. Try to draw from ultrasound alone. Practice really helps.
On retinal detachments	Do real-time ultrasound to assess the extent and presence of cysts and chronicity.
On persistent fetal vasculature	Especially in patients with nystagmus, ultrasound is really helpful.
On calcified masses	Calcium is highly reflective and fairly easily detected with ultrasound.
On eyes with silicone oil	Silicone oil slows down the beam, and therefore the speed of sound must be appropriately adjusted. Imaging is much more difficult and sometimes not possible.
On residual PFO or silicone oil	Pay attention to patterns and changes in eye length. When silicone oil is present, the eye will look longer and distorted vertically (because sound travels slower). When oil has been removed, you can use ultrasound to search for residual oil bubbles. Residual PFO is also detectable, usually seen as comet-like changes.
On choroidal melanoma	You can see it on A-scan and B-scan. In real time you can detect movement of intratumor vessels.
On vitreous hemorrhage	Check for areas of traction or pulling; you might detect small retinal detachments or tears.

Abbreviation: PFO, perfluro-n-octane.

manner and ponder all findings before rendering a diagnosis.
- **Still images versus movie segments.** Be cognizant of the type of images you are interpreting. Movie segments are better. Stills show no motion.

Dr. Fisher also added a number of pearls, which are listed in Table 1.

OTHER APPLICATIONS

Current ultrasound machines can be easily switched to perform ultrahigh-frequency ultrasound of the anterior segment. Although this is similar to posterior segment examination, there are key differences. First, conjunctival or corneal direct contact is needed, as described above. Second, screen registration is different in this mode. The image is displayed as if the patient is supine. The top of the screen displays objects closest to the probe and the bottom displays those furthest away. The left side of the screen corresponds to the white mark on the probe, and the right side is the end of the transducer arc movement. These changes may be confusing initially but are rapidly learned in most cases.

Anterior ultrahigh-frequency ultrasound allows examination of the cornea, iris, and iridolenticular interaction. With pupillary constriction (lights on) and dilation (lights off), the contact of the iris with the lens can easily be assessed. The most common problem is finding where the probe is placed. In trauma or postoperative cases, anterior segment ultrasound can be quite complicated, requiring significant experience in techniques and interpretation.

Other uses of anterior segment ultrasound include finding slipped or dislocated IOLs. With ultrasound, finding the location of the lens within the vitreous cavity is easy. Transverse view can be also used to count ciliary processes and anticipate potential problems with IOP. Finally, ultrasound can be of great help in vitreous taps to increase the chances of performing a successful tap.

WHAT'S COMING UP?

Further innovations in ophthalmic ultrasound will allow moveable focus and faster imaging. Recently introduced annular transducers are different from previous single-element transducers in that they provide dynamic focus. Use of an annular array along with ultrafast imaging can result in incredible image quality. Dr. Fisher estimated that advances in a new field called *ultrafast ultrasound* will allow us to acquire 3D images in real time, probably within the next 5 years.

WHAT HAVE WE LEARNED ABOUT ANTI-VEGF THERAPY IN ROP?

Hugo Quiroz-Mercado, MD, recounted lessons learned at his pioneering center in Mexico City.

By Luis A. Gonzalez, MD, MPH

At the 2019 ARDS meeting, Hugo Quiroz-Mercado, MD, presented a summary of recent findings regarding the use of anti-VEGF therapy in patients with retinopathy of prematurity (ROP). Dr. Quiroz-Mercado and Maria Ana Martinez-Castellanos, MD, both of whom practice at the Asociación para Evitar la Ceguera en México (APEC-México), have been pioneers in the development of an algorithm for use of anti-VEGF agents in patients with ROP.

This summary of Dr. Quiroz-Mercado's talk includes a discussion of risk factors for ROP, a review of potential systemic and local complications of anti-VEGF therapy, and an overview of the treatment algorithm in use at the APEC-México.

A BRIEF REVIEW OF ROP

The high oxygen demand of the retina is thought to significantly contribute to the vulnerability of retinal tissue to vascular disease. The most important part of ROP screening is identifying vascular tortuosity. A full clinical examination of premature infants is mandatory, whether by dilated fundus exam or photography.

Identification of infants with pre-plus and plus disease is paramount to determine proper follow-up and treatment. Premature infants with plus disease are known to have arterial and venous engorgement, iris vascular engorgement, pupillary rigidity, or vitreous haze. Pre-plus disease is defined as vascular abnormalities of the posterior pole that are insufficient for the diagnosis of plus disease but that demonstrate more arteriolar tortuosity and more venular dilation than normal.

Patients with plus disease can rapidly evolve to retinal detachment and therefore require close follow-up and, if necessary, treatment. Pre-plus disease early in the course of ROP is strongly associated with development of severe ROP that requires treatment. Therefore, very close follow-up in patients with pre-plus disease is mandatory.

Aggressive posterior ROP, or *APROP*, is a progressive, severe form of ROP. It is mainly characterized by its posterior location, presence of plus disease, and a very ill-defined natural history, which usually progresses to stage 5 if untreated. This rapid progression has also been called *rush disease*. It is important to identify and treat patients with APROP early. One key feature in these eyes is that they do not usually have the classic demarcation line.

CLASSIFICATION, TREATMENT

The Early Treatment for Retinopathy of Prematurity (ETROP) study was instrumental in the definition and classification of ROP.[1] The

objective of ETROP was to determine whether early treatment with ablation of the avascular retina in high-risk ROP resulted in improved VA and structural outcomes compared with conventional treatment.[1] The study concluded that early treatment of high-risk prethreshold ROP significantly reduced unfavorable outcomes to a clinically important degree.[1]

For treatment purposes, ROP as defined by the ETROP can be classified as shown in Table 2.[1]

Well-established treatment alternatives for ROP include cryotherapy and laser. Both work well and have permanent effects on the ischemic retina.[2] These therapies allow less frequent follow-up after treatment.

Recently, intravitreal anti-VEGF therapy has been used to treat patients with ROP. The incidence of retreatment after anti-VEGF therapy is only 4%, compared with 11% in patients treated with laser.[2] Moreover, anti-VEGF therapy results in no visual field reduction, myopia, or difficulty with dark adaptation.[2] An additional advantage over laser treatment is that anti-VEGF therapy does not require the additional expertise and efficiency necessary with laser to reduce anesthesia time.

To understand why anti-VEGF therapy works in patients with ROP, Dr. Quiroz-Mercado and colleagues studied the proliferative membranes of eyes undergoing vitrectomy in advanced ROP.[3] In this study, proliferative membranes of ROP eyes were harvested and sent for testing including polymerase chain reaction, in situ hybridization, and Western blot analysis.[3] They observed the expression of 16 kDa prolactin, a protein hormone related to the VEGF family, supporting the hypothesis that ROP is a VEGF-driven disease.[3] Other studies have also supported this hypothesis, demonstrating increased levels of VEGF and hepatocyte growth factor in the subretinal fluid of eyes with advanced ROP.[4] Anti-VEGF therapy should therefore in theory have a role in treating eyes with ROP.

CLINICAL EXPERIENCE, RISKS

The first pediatric patient treated with intravitreal anti-VEGF injection at the APEC-México was a premature baby undergoing multiple brain, abdominal, and other surgeries in whom a vitreous hemorrhage impeded a fundus view. The decision was made to treat the infant with an anti-VEGF injection, after which the vitreous hemorrhage started to clear and the view was much improved. After this case, the Mexico City team started treating selected patients with ROP using anti-VEGF intravitreal injections.[5]

Multiple studies have since compared laser panretinal photocoagulation (PRP) versus anti-VEGF therapy in patients with ROP.[6,7] In summary, both intravitreal bevacizumab (Avastin, Genentech) and laser are effective, but the incidence of recurrences after treatment remains controversial. The BEAT-ROP study showed a higher recurrence after PRP than after bevacizumab therapy overall (22% vs 4%) and for zone 1 ROP (35% vs 3.2%).[7] Hwang and colleagues reported a recurrence rate of 14% in their bevacizumab group compared to only 3% in their PRP group.[6] In a retrospective study, Mintz-Hittner et al found a recurrence incidence of 8.3% in infants with type 1 ROP in zone 1 or zone 2 treated with intravitreal bevacizumab monotherapy.[8] The risks factors for recurrence in this study included APROP appearance, extended hospitalization, and lower birth weight.[8]

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Additionally, differences in response between anti-VEGF agents have been observed. Bevacizumab seems to last longer than ranibizumab (Lucentis, Genentech). At APEC- México, Dr. Quiroz-Mercado reported, reactivation of ROP occurs in approximately 3% of patients receiving intravitreal bevacizumab (approximately 400 cases in 9 years) versus a reactivation rate of 15% in those receiving intravitreal ranibizumab.

The potential risks of anti-VEGF therapy in this group of patients is not well understood. As with any treatment in medicine, there are risks associated with the use of anti-VEGF therapy. Wood and colleagues have

TABLE 2. CLASSIFICATION OF ROP

Class	Definition	Recommendation
Mild ROP	Stage 1 or 2 in zone 2 without plus disease; or Any stage in zone 3 without plus disease	Observation recommended.
Type 1 ROP	Any stage in zone 1 with plus disease; Stage 2 in zone 1 without plus disease; or Stage 2 or 3 in zone 2 with plus disease	Treatment within 48 hours required.
Type 2 ROP	Stage 1 or 2 in zone 1 without plus disease; or Stage 3 in zone 2 without plus disease	Close observation with no immediate treatment required.

Abbreviation: ROP, retinopathy of prematurity.
Table adapted from: Good WV; Early Treatment for Retinopathy of Prematurity Cooperative Group. Final results of the Early Treatment for Retinopathy of Prematurity (ETROP) randomized trial. *Trans Am Ophthalmol Soc*. 2004;102:233-248; discussion 248-250.

described a *crunch phenomenon*, in which the injection of one eye with an anti-VEGF agent may evolve to tractional retinal detachment or to ROP progression in the fellow eye.[9]

APEC TREATMENT ALGORITHM

Based on the experience at APEC-México and current evidence, Drs. Martinez-Castellanos and Quiroz-Mercado developed an algorithm for ROP treatment (Table 3).[10] The dosages used are bevacizumab 0.625 mg/0.025 mL and ranibizumab 0.25mg/0.025 mL.

The main reason behind observation in patients with stage 5b or closed funnel, he said, is that even with successful anatomic reattachment of the retina, the tissues have such an advanced degree of atrophy that visual prognosis is generally poor.

Before anti-VEGF treatment for ROP is considered, assessing the patient as a whole is paramount. Premature babies with ROP are also affected by neurodevelopmental disorders. Dr. Quiroz-Mercado said that, in his experience, up to 50% of infants with ROP have some degree of neurodevelopmental delay, likely due to intraventricular hemorrhages. This association had been noted even before the anti-VEGF era.[11] Had these patients undergone intravitreal anti-VEGF injections, the anti-VEGF agent would likely have been condemned as a cause of the neurodevelopmental disorders. Fortunately, studies have shown that treatment with low-dose anti-VEGF therapy for a short period may actually help prevent intraventricular hemorrhages.[11] This is important in ROP because, unlike other vasoproliferative diseases that may fluctuate, ROP has a very short time window for treatment.

Although theoretically anti-VEGF therapy may help prevent intraventricular hemorrhages, the reality is that the true effect in premature babies is unknown. In real clinical scenarios, collaborative work with perinatology is strongly recommended to elucidate the potential effects of intraocular anti-VEGF therapy, Dr. Quiroz-Mercado said. He recommended using the smallest quantity of anti-VEGF agent possible.

TABLE 3. SUMMARY OF ROP TREATMENT ALGORITHM

Type 1 ROP and/or APROP	Immediate anti-VEGF injection with follow-up in 1 week (clinical or RetCam [Natus Medical])	- If NV regression, weekly observation until week 52; then monthly until age 6 months - If more NV, retreat with anti-VEGF, with or without laser
Type 2 ROP	Perform FA (widefield camera) and observe in 1 week	- If progression to type 1, see above - If regression, weekly observation until week 52; then monthly until age 6 months
Stage 4	Stage 4a - intravitreal anti-VEGF agent with PPV within 48 hours	
	Stage 4b - lens-sparing PPV	
Stage 5	Stage 5a "open funnel" by ultrasound - lensectomy plus PPV	
	Stage 5b "closed funnel" by ultrasound - observation plus visual rehabilitation	

Abbreviations: APROP, aggressive posterior retinopathy of prematurity; FA, fluorescein angiography; NV, neovascularization; PPV, pars plana vitrectomy; ROP, retinopathy of prematurity.
Table adapted from: Cernichiaro-Espinosa LA, Olguin-Manriquez FJ, Henaine-Berra A, Garcia-Aguirre G, Quiroz-Mercado H, Martinez-Castellanos MA. New insights in diagnosis and treatment for retinopathy of prematurity. *Int Ophthalmol*. 2016;36(5):751-760.

IMPROVING DIAGNOSIS AND TREATMENT

Dr. Quiroz-Mercado shared the experience at APEC-México in premature infants treated with anti-VEGF therapy who did not respond to treatment or who had a recurrence after initial treatment. In a study done at APEC-México, failure of treatment was defined as persistence of pathologic new vessels, elevation of the ridge in the demarcation line, worsening of plus disease, or retinal crunch in the first week after treatment. Recurrence was defined as the appearance of plus disease, an elevated ridge, or pathologic new vessels after an initial regression of ROP after treatment.

Investigators analyzed suspected cases of recurrence or failure of treatment with supplementary angiograms and in some cases with ultrasound to guide the therapeutic modality to be offered. Treatment consisted either of conservative management (ie, close monitoring with fluorescein angiography [FA], modification of oxygen supplementation) or interventional therapy (ie, second injection of anti-VEGF agent, switch to different anti-VEGF agent, laser, vitrectomy, or combined therapy). Of 672 patients initially treated with intravitreal anti-VEGF injection, 17 (2.5%) did not respond to treatment and 47 (6.8%) had a recurrence. (Of note, 37 patients were misdiagnosed as having an ROP recurrence and referred to APEC-México for treatment. On further testing, they were diagnosed as having proliferative retinopathy other than ROP.)

The findings of this study showed that failure of treatment can be associated with an initial misdiagnosis or with inadequate treatment. A thor-

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ough examination and differential diagnosis workup is mandatory to prevent misdiagnosis. The most common misdiagnoses include familial exudative retinopathy, proliferative retinopathy associated with congenital cardiopathy, and oxygen-induced retinopathy.

On the other hand, one of the most common mistakes that leads to inadequate treatment is an error in the preparation of the intravitreal injection. Priming the needle prior to injecting is important, especially when the injected volume is so minimal. If the needle is not primed prior to injecting, most of the injected volume will be air from the dead space in the syringe needle.

In special situations, an anti-VEGF injection may be given before vitreoretinal surgery. For example, in patients who have active vessels and traction, an anti-VEGF injection alone will likely result in retinal detachment; however, a combination of anti-VEGF injection followed by immediate pars plana vitrectomy seems to prevent progression of ROP and the crunch phenomenon.

New imaging technology can facilitate the examination and documentation of infants with ROP. Widefield fundus photos and FA are helpful in following patients with ROP. In those who cannot undergo FA, red-free fundus photography can capture good images of the blood vessels and retinal pigment epithelium atrophy.

Finally, oxygen-induced retinopathy is a devastating disease seen in many parts of the developing world. This entity is seen in preterm neonates with no high-risk characteristics for developing ROP who were exposed to high oxygen concentration.[12] The peripheral vascular abnormalities in these infants can be classified in areas of ischemia with arteriovenous shunting and proliferative disease at the boundary of perfused and nonperfused retina.[12] Oxygen-induced retinopathy changes are observed in babies older than 32 weeks gestational age and heavier than 1,500 g.[12] The pathophysiology of this entity remains to be elucidated. Close follow-up and possible treatment with laser and/or anti-VEGF therapy remains to be studied in these patients.

CONCLUSION

The use of anti-VEGF agents in the treatment of ROP is increasing. More studies are needed to determine the proper dosage and frequency and to determine which anti-VEGF agent is best for ROP management. More important, the safety of intravitreal anti-VEGF injections in premature babies, especially in those with neurodevelopmental disorders, must be cautiously pondered before treatment is considered. ■

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