RETINA WORLD CONGRESS

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RETINA WORLD CONGRESS

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RETINA WORLD CONGRESS

METHOD OF PARTICIPATION

This activity should take approximately 3 hours to complete. Participants should first read the objectives and other introductory CME/CE information and then proceed to the educational activity. To receive credit for this activity, participants must complete the post-test with a passing score of 80% and then complete the evaluation. Credit is provided through June 21, 2018. No credit will be given after this date. There is no fee to participate in this activity.

HARDWARE/SOFTWARE NEEDED TO PARTICIPATE

High speed internet access.

CONTENT SOURCE

This continuing education (CE) activity captures content from Retina World Congress (RWC). RWC gathers leaders in retina to discuss the latest hot topics and cases in retina; the congress is led by the RWC Board of Directors.

ACTIVITY DESCRIPTION

As more effective therapeutic interventions continue to develop around the globe, ophthalmologists and ophthalmic specialists require comprehensive updates on results from clinical trials and practical guidance. In addition, sharing of expertise from different regions with different challenges enables a collaborative approach to addressing unmet needs in the treatment of retinal diseases. Similarly, as new imaging technologies become available, and surgical instrumentation gets developed, their specialized features and utilization need to be communicated and demonstrated. RWC will be a forum permitting the exchange of ideas and innovative research focused on retinal diseases, highlighting the need for training and integration of these new practices on a global scale.

TARGET AUDIENCE

The Retina World Congress is for retina specialists, retina fellows, and healthcare professionals.

EDUCATIONAL OBJECTIVES

After completing this activity, the participant should be better able to:

- Review the latest clinical trial data and treatments in clinical trials
- Identify advantages and disadvantages of combination therapies for the treatment of neovascular age-related macular degeneration (AMD)
- Explain the mechanism of action, ongoing clinical trial designs, and advantages and disadvantages of new therapies being developed for the treatment of diabetic retinopathy (DR)
- Describe the latest clinical trial data, patient outcomes, and emerging treatments in clinical trials for diabetic macular edema (DME)
- Discuss novel management strategies in treating patients with diabetic retinopathy
- Recall the latest clinical trial data and management of retinal vein occlusion
- Identify new technologies that may reduce treatment burden for patients with retinal vascular disease
- Recognize side effects of commonly used uveitis treatments, and optimize management of patients who develop these side effects
- Summarize key clinical study findings for new treatment options being developed for the treatment of uveitis
- Apply new imaging technologies to improve disease detection and better assess patient responses to therapy

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- Retinal Detachment with Macular Hole – *Marco de Smet, MD*
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SESSION 6: IMAGING

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SESSION 8: DIABETIC VITRECTOMY

- Anti-VEGF Injection and Diabetic Vitrectomy: When and Why? – *J. Fernando Arevalo, MD, FACS*
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- Intra-arterial Chemotherapy versus Intravenous Chemotherapy for Unilateral Retinoblastoma. Who Wins? – *Carol L. Shields, MD*
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- New Therapies for Retinopathy of Prematurity (ROP) – *Paola Dorta, MD*
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SESSION 13: MEDICAL RETINA: DIABETIC MACULAR EDEMA (DME) AND DIABETIC RETINOPATHY (DR)

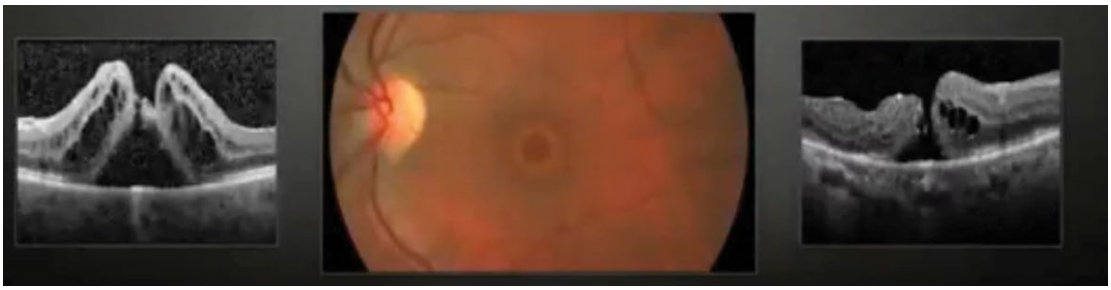
- RG7716—A Novel Bispecific Anti-VEGF/Anti-Angiopoietin-2 Monoclonal Antibody for Neovascular Age-related Macular Degeneration and Diabetic Macular Edema – *Pravin U. Dugel, MD*
- Characteristics of Patients with Diabetic Macular Edema Treated with Anti-VEGF Agents According to the Vitreomacular Interface – *Marcio B. Nehemy, MD*
- New Insights into Imaging DME and DR: Where Are We, and Where Are We Going? – *Richard B. Rosen, MD, DSc(Hon)*
- OCT Angiography for DME—Does It Give Us a New Understanding of Pathophysiology and Facilitate Outcomes? – *Nadia K. Waheed, MD, MPH*

Session 1:

MACULAR SURGERY

Recurrent Macular Hole – *Tarek Hassan, MD*

Macular hole closure rates have improved significantly since 1991 due to better training and experience as well as improved tools and visualization techniques. Results have been largely stable for the last 10 years.



Dr. Hassan presented here the first series looking at recurrent macular holes treated entirely with small gauge vitrectomy. It is not yet known how small-gauge vitrectomy will impact macular hole repair. It is slightly less invasive so may cause less inflammation and less postoperative cystoid macular edema, which may lead to a better closure rate. So far, the anatomic rates are about the same in terms of the closure of the macular hole.

Macular hole closures fail because of epiretinal membrane, residual vitreous and internal limiting membrane remnants, cystoid macular edema, and traumatic events, but the impact of each of these things is unknown.

There are past series that document 70%-80% likelihood of epiretinal membrane causing recurrence, but it has not been shown to be causative. All eyes had some tissue removed, but ERM is an extension of postoperative healing, and some series show there may be no need for peeling the epiretinal membrane. Cystoid macular edema might also be an issue.

There is a high incidence of bilaterality in these patients. This indicates something is abnormal about the vitreomacular interface or internal limiting membrane.[1]

Overall, there is a high likelihood of successful closure of regular size macular holes with reoperation using only vitrectomy, membrane peeling, and fluid-gas exchange. The majority of them are associated with a macular hole in the other eye as well.

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1. Thompson JT, Sjaarda RN. Surgical treatment of macular holes with multiple recurrences. Ophthalmology. 2000 Jun;107(6):1073-7.

The Inverted ILM Flap Technique for Macular Hole – *Jerzy Nawrocki*

The purpose of developing an inverted ILM flap technique was to prevent postoperative appearance of flat open macular holes. In this technique, the macular hole is covered with an ILM flap from the temporal side. This technique achieves an approximate reformation of the fovea and photoreceptor layer in the fovea, which relates to improvement in visual acuity.

A number of papers confirm the efficacy of this technique in the repair of large macular holes.

Author and Date	Technique	Primary Indication	Number of Holes	Closure
Michalewska Z. 2010	Inverted Flap	Large Macular Holes	50	49 + 1 flat open
Sakurai T. 2014	Inverted Flap	Large Macular Holes	9	9
Michalewska Z. 2015	Inverted Flap	Large Macular Holes	43	43
Belyi YA. 2016	Inverted Flap	Large Macular Holes	19	8 + 11 partially closed
Chen Z. 2016	Inverted Flap	Large Macular Holes	8	8
Michalewska Z. 2015	Inverted Flap	Large Macular Holes	44	44
Andrew NA. 2016	Inverted Flap	Large Macular Holes	24	24
Chakrabarti M. 2016	Inverted Flap	Large Macular Holes	26	26
Abou Shousha MA. 2016	Inverted Flap	Large Macular Holes	12	12

The same results were obtained as with previous techniques, but with less surgical trauma. In these cases no nerve fiber layer defects are observed between the optic nerve and the fovea.

When the technique was used in myopic macular hole, during at least 12 months follow-up, there was a decrease in photoreceptor defects and external limiting membrane defects, which correlates with improvement in mean visual acuity. Papers have also been published that confirm the efficacy in this indication.[1,2]

This technique can also be used in macular hole with advanced soft drusen and posttraumatic macular hole with subretinal fibrosis.

Macular hole in proliferative diabetic retinopathy is rare, but this procedure may be used for this as well. However, in this group of patients, even if the macular hole is closed, it may be wise to wait several months for reabsorption of the fluid in the subretinal area.

In rare cases where persistent macular hole occurs after successful rhegmatogenous retinal detachment surgery, this technique seems to be very useful.

Recurrence of macular hole doesn't often occur with this technique, but when it does it's because the flap has moved away from the macular hole. If the flap remains stable, there is a good chance for anatomic and functional recovery. The

results of reoperations show significant improvement; however, the results are not as good as in primary successes.

1. Mete M, Alfano A, Guerriero M, Prigione G, Sartore M, Polito A, Pertile G. Inverted internal limiting membrane flap technique versus complete internal limiting membrane removal in myopic macular hole surgery: A Comparative Study. Retina. 2017 Jan 6. doi: 10.1097/IAE.0000000000001446. [Epub ahead of print]

2. Oleñik A, Rios J, Mateo C. Inverted internal limiting membrane flap technique for macular holes in high myopia with axial length ≥30 mm. Retina. 2016 Sep;36(9):1688-93. doi: 10.1097/IAE.0000000000001010.

Epiretinal Membranes with Very Good Vision: Should One Operate? – *Andre V. Gomes*

Patients with epiretinal membrane (ERM) can be asymptomatic for years, then progressively lose vision over time with or without metamorphopsia. Prediction of the visual outcome is essential for counseling patients and for weighing the risks and benefits of surgery. Surgical indications aren't standardized, and therefore clinical outcomes vary.

The classic approach is to wait and observe, but that approach may go on too long. Currently, surgery is usually considered when a patient's vision is around 20/60 or 20/70 unless a metamorphopsia occurs or the patient is very symptomatic.

For patients with no metamorphopsia and visual acuity greater than 20/30, observation may be the best choice. But for patients 20/30 or worse, a determination must be made of when to offer surgery.

Surgery can be offered with greater confidence now than in the past due to better instrumentation and dyes. Severe foveal dystopia can lead to capillary leakage and possible damage to the RPE and photoreceptors. The extent of tractional dystopia correlates with decreased visual acuity. Cases with extreme degrees of foveal dystopia may benefit from early intervention to prevent irreversible structural and functional changes.

When surgery is performed, a decision must be made of whether to peel the internal limiting membrane (ILM). There may be some cases where it's better not to. Some cells may remain behind after ERM peeling, and recurrence rates can be up to 21%. If the ILM is removed, there is no more scaffold for cellular proliferation. Both recurrence and incomplete recovery of visual acuity are thought to be related to incomplete removal of the ERM.

There are many predictors for ERM surgery, but the main three are preoperative visual acuity, integrity of the photoreceptor layers, and severity of metamorphopsia. These all relate to the duration of the symptoms.

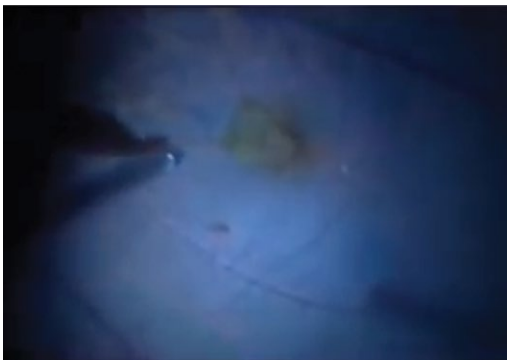
To maximize outcomes

- Consider operating earlier. Only observe patients who are 20/25 or better with no metamorphopsia
- Avoid long periods of preoperative leakage as this can generate anatomic damage
- Try not to leave tissue behind
- Minimize tissue stretching
- Be aware of toxicity that might come from the light pipe or dyes
- Consider not peeling the ILM in every case.

Even though visual acuity in patients with ERM may decrease slowly, surgery usually improves final visual acuity. There is enough evidence to show waiting too long may favor a worse outcome. Therefore, offering surgery much earlier in the process should be considered.

Epiretinal Membrane with Lamellar Hole: When to Operate?
– Fumiji Okamoto MD, PhD

Lamellar macular holes (LMHs) are defined morphologically as having a concave foveal contour that dips lower and wider than normal foveal depression, as seen on OCT. It should be noted that most LMHs accompany epiretinal membrane.



In the natural history of an LMH, visual acuity and foveal thickness do not change. However, in some cases visual acuity worsens, there is an increase in metamorphopsia, and there can be development into a full thickness macular hole. The indication for vitrectomy for LMH remains controversial.

Surgical outcomes for LMH are similar to those for ERM procedures, and these outcomes are generally good. Visual acuity improves, and almost normal foveal contour is restored.

LMHs can be divided into two types, depending on whether lamellar hole-associated epiretinal proliferation (LHEP) is present. LHEP appears on SD-OCT as a thick homogenous layer of material with medium reflectivity on the epiretinal surface. So an LMH case without LHEP means only a typical ERM exists on the epiretinal surface. Some cases without LHEP can develop the condition over the course of the disease. The thickness of LHEP can also increase as the disease progresses.

Eyes with LMHs with LHEP are associated with poorer visual acuity, larger diameters, thinner retinal thickness, and a higher instance of ellipsoid zone disruption than eyes without LHEP. Additionally, patients with LMHs with LHEP are less likely to demonstrate improved visual acuity after surgery. Thus, visual benefit cannot be expected from traditional vitreous surgery in LMH patients with LHEP.

Shiraga and colleagues performed a modified vitreous surgery for LMH with LHEP containing macular pigment.1 In a representative case of the modified surgery, visual acuity improved from 20/80 to 20/25 two weeks after the operation and to 20/20 after three months, and foveal contour was restored to almost normal.

With this in mind, it can be determined what criteria are important for deciding when to operate on an LMH. Surgery is not indicated immediately. The patient can be observed using OCT for 6 to 12 months. If the patient does not have LHEP, surgery can be considered if visual acuity decreases, if the ELM or ellipsoid zone become disrupted, or if there is an increase in metamorphopsia. In a patient who does have LHEP, a modified vitrectomy is appropriate if visual acuity worsens, the ELM or ellipsoid zone begin to be disrupted, metamorphopsia increases, or there is a thickening of the LHEP.

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1. Shiraga F, Takasu I, Fukuda K, Fujita T, Yamashita A, Hirooka K, Shirakata Y, Morizane Y, Fujiwara A. Modified vitreous surgery for symptomatic lamellar macular hole with epiretinal membrane containing macular pigment. Retina. 2013 Jun;33(6):1263-9. doi: 10.1097/IAE.0b013e31828bcb61.

Session 2:

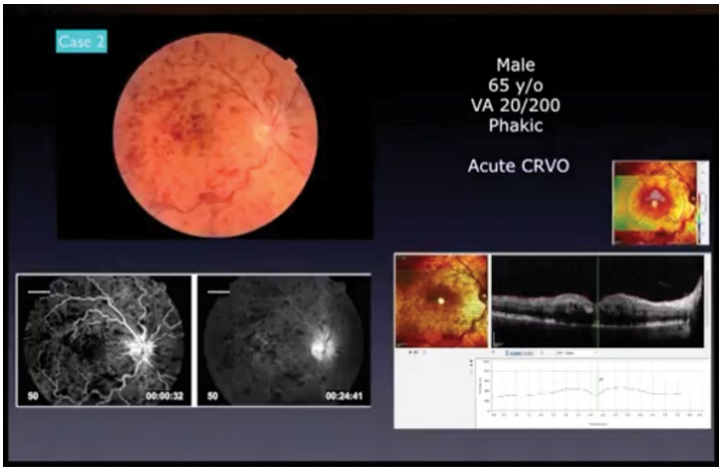
MEDICAL RETINA: RETINAL VEIN OCCLUSION (RVO)

When to Use Steroids for RVO: Early, Late, Never – *Marcelo Zas, MD, PhD*

Retinal vein occlusion (RVO) is the second most common retinal vascular disorder. It is estimated 16 million people worldwide are affected in one or both eyes, with more being affected every year.

If chronic macular edema accompanies RVO, prompt treatment is warranted to avoid permanent retinal damage and irreversible vision loss. Four treatment options currently exist: observation, laser photocoagulation therapy, pharmacological therapy, and surgery.

If a decision is made to go with pharmacological therapy, there is a choice between anti-VEGF agents and steroids. Steroids have three mechanisms of action, which is an advantage over anti-VEGF agents. In addition to the reduction of inflammatory mediators, steroids also offer stabilization of the blood-retina barrier and decreased vascular permeability.



Three steroids are available. Dexamethasone has US FDA approval and is approved for use in other parts of the world as well. Triamcinolone is less expensive and can be used off-label, but the optimal dose to use is unknown, and fluocinolone is FDA-approved only for chronic infectious uveitis and DME, not for RVO.

Dexamethasone leads to significant improvement in best-corrected visual acuity in patients with macular edema associated with RVO, and there is little difference in that improvement between patients with central RVO and branch RVO. Earlier treatment with dexamethasone is associated with a better visual acuity outcome. It is well tolerated and does a good job controlling intraocular pressure.

The goal of RVO management is to improve vision and quality of life for the patient while reducing retinal complications. Therefore, licensed pharmacotherapy, using dexamethasone on-label, can be considered for first-line treatment for macular edema following both branch and central RVO. Dexamethasone allows a lower rate of injections than an anti-VEGF agent and has multiple mechanisms of action.

How to Use Combination Therapy for RVO Effectively – *Lihteh Wu, MD*

Current management of retinal vein occlusion (RVO) includes intravitreal monotherapy of steroids or anti-VEGF agents. Some eyes, however, do not respond despite multiple continuous injections.

Studies such as SCORE, CRUISE, COPERNICUS, and PACORES show that a percentage of patients with central retinal vein occlusion (CRVO) have lost a significant amount of vision despite treatment with an anti-VEGF agent or the steroid triamcinolone, and some have a residual cystoid macular edema. Combination therapy can be considered in treatment of CRVO to improve outcomes, to decrease the burden of injections, and to avoid side effects.

A study by Wang et al1 compared treatment with intravitreal bevacizumab plus triamcinolone to intravitreal bevacizumab alone. The authors found that the combination was not better than monotherapy for visual outcome, resolution of macular edema, or frequency of retreatment. Singer et al2 injected an anti-VEGF agent and followed that two weeks later with an Ozurdex implant. The mean reinjection interval was 135 days, and they reported a peak chance in best-corrected visual acuity of almost 14 letters, with 48% of patients having a gain of more than three lines. This is a noncomparative study, however, with no controls to compare to. Other studies have been done looking at the possibility of combination treatment, but they have been small, short term, and retrospective.

No evidence has been found that supports combination therapy as primary treatment for cystic macular edema secondary to CRVO, thus intravitreal monotherapy remains the treatment of choice for that condition. Combination therapy should be considered in eyes that do not respond to intravitreal monotherapy, but there is no evidence to guide the treatment; the ideal combination remains unknown.

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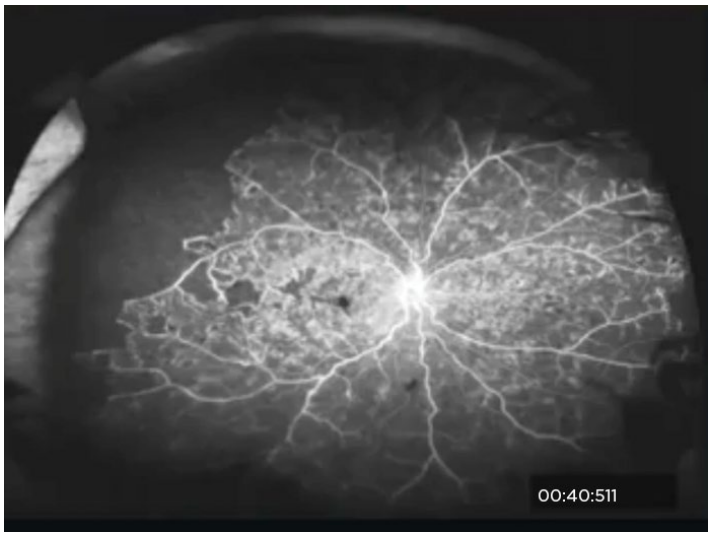
1. Wang HY, Li X, Wang YS, Zhang ZF, Li MH, Su XN, Zhu JT. Intravitreal injection of bevacizumab alone or with triamcinolone acetonide for treatment of macular edema caused by central retinal vein occlusion. Int J Ophthalmol. 2011;4(1):89-94. doi: 10.3980/j.issn.2222-3959.2011.01.21. Epub 2011 Feb 18.

2. Singer MA, Jansen ME, Tyler L, Woods P, Ansari F, Jain U, Singer J, Bell D, Krambeer C. Long-term results of combination therapy using anti-VEGF agents and dexamethasone intravitreal implant for retinal vein occlusion: an investigational case series. Clin Ophthalmol. 2016 Dec 19;11:31-38. doi: 10.2147/OPTH.S119373. eCollection 2017.

Management of Ischemia in RVO: A Modern View of Treatment Options Before and After Neovascularization is Seen – *Jay K. Chhablani, MD*

Neovascularization occurs in 33% of eyes with nonischemic CRVO during 12 to 15 months follow up, and in 20% of eyes with ischemic CRVO at around 8 to 9 months. The most serious complication, neovascular glaucoma, occurred in 23% to 60% of eyes with ischemic CRVO. In eyes with branch RVO (BRVO), neovascularization occurs in 22% to 29%, but none of these eyes had neovascular glaucoma.

Ischemic CRVO is defined as having poor visual acuity (less than 6/60) and greater than 10 disc areas of retinal capillary nonperfusion, as seen with fluorescein angiography. However, both 5 field photography and 7 field photography can miss a significant amount of ischemia. Widefield imaging allows visualization of the areas the other methods cannot see. There is now also the ischemic index, for use in CRVO. This is the ratio of the area of nonperfusion over the total fundus area, with neovascularization being associated with eyes that have a ratio greater than 45%.



Management of ischemia includes anti-VEGF injections, laser photocoagulation, aspirin for medical management, and surgical approaches. There is poor evidence for use of the medical approach.

Anti-VEGF injection has become the standard of care for these cases. The chance of neovascularization still exists with this treatment, but occurrence is delayed significantly. In patients with ischemic eyes who are receiving anti-VEGF treatment, neovascularization happens later than in non-ischemic eyes, but does still occur.

Using laser in the periphery for treatment of ischemia does not prevent neovascularization. Targeted or conventional laser treatment can reduce the VEGF load, and there is a role for laser after neovascularization has occurred.

For surgical approaches, with laser-induced chorioretinal venous anastomosis vascularization and capillary flow occur, but this technique is not usually used anymore. In radial optic neurotomy a non-muscular vein is compressed into a tight compartment, to raise the pressure, to improve optic nerve blood flow. With vitrectomy in treatment of CRVO removal of vitreo-papillary or epi-papillary adhesions may improve blood circulation.

At this point in time anti-VEGF in combination with laser therapy may be an effective treatment.

Yellow Micropulse Laser Therapy (577 nm) on Central Serous Chorioretinopathy – *Munir Escaf, MD*

With use of conventional laser, there is absorption of luminous energy, which causes increasing heat and protein denaturalization, resulting in a retinal burn. A number of complications can occur in use of conventional, continuous laser, including RPE cell destruction, pain, macular edema, decreased visual acuity, bleeding, disruption of contrast perception and visual fields, and what might be the biggest concern in treating central serous chorioretinopathy (CSC), the progressive extension of the retinal scar. With micropulse laser, the shorter pulses allow for less tissue damage because there is thermal relaxation with each pulse, so there is no scar.

A retrospective study was performed to evaluate the clinical and anatomical outcomes of patients with a diagnosis of chronic CSC, treated with yellow micropulse laser (577 nm). In all study participants, no prior treatment had been done, and CSC had not resolved after 4 months of observation. Parameters evaluated include best-corrected visual acuity (BCVA), central macular thickness and thickest macular point prior to laser and 4 weeks after.

The results showed mean improvement in BCVA of 2.1 lines with a Log/MAR visual acuity mean of 0.2. There was improvement in 87% of patients between 20/40 and 20/20. The mean initial central macular thickness was 347 µm, the mean reduction was 97 µm, the mean initial thickest macular point was 397 µm, and the mean reduction was 96 µm. Resolution occurred in 80% of patients, 30% underwent retreatment, one of those showed no positive results.

These results are comparable to any type of previous study. Reduction or disappearance of subretinal fluid occurred in more than 70% of treated patients. There was a decrease in central macular thickness, improvement in visual acuity, and no evident damage of the RPE. Using yellow laser resulted in an excellent response; clinical and anatomical resolution occurred in more than 80% of cases.

Although more studies are required to prove long-term outcomes, it is believed therapy with yellow micropulse laser is very useful and safe in the treatment of patients with chronic CSC, especially if leakage points near the fovea eliminate the use of other therapies.

Session 3:

TRAUMA AND PROLIFERATIVE VITREORETINOPATHY (PVR) SURGERY

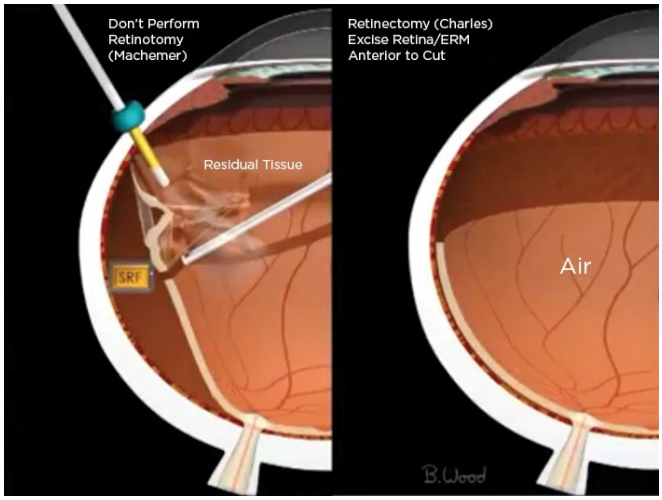
Retinectomy: When and Where? – *Steve Charles, MD, FACS, FICS*

Retinectomy (removing everything anterior to a circumferential cut) was developed almost 40 years ago. The technique discussed here is doing a retinectomy with air instead of perfluorooctane (PFO).

The reattachment sequence in this method involves removing frontal plane vitreous traction (confluence of anterior and posterior vitreous cortex), and anterior loop traction (radial fibers), and peeling the ERM with ILM forceps. Any significant subretinal bands should be removed using "punch-through retinotomy." Internal drainage of subretinal fluid is then done through the preexisting retinal break, and the fluid-air exchange is begun when the retina begins to move back. As the retina moves back further, if it attaches, laser is used and oil added, and the procedure is finished.

However, if the retina starts going back, but "hangs" instead of going all the way or some air gets beneath the retina, this indicates residual traction that needs to be removed. Rather than using PFO or starting over, a vitrectomy can be done under air (interface vitrectomy). Venturi pumps must be used; peristaltic pumps will not work for this. If no further traction is found but, as the retina unfolds and gets closer, there is a starfold that needs to be peeled or another band needs to be removed, these can also be done under air.

If after all of this the retina still won't go back all the way, a retinectomy is required. Under air, an incremental retinectomy can be performed until the retina reattaches. When retinectomy is performed under infusion fluid, there is no way to know how much to do. When done under air, the presence of the air sealing off the breaks will show how much retinectomy is really needed. If 270 degrees is reached, it should be extended all the way to 360 degrees.



Retinectomy is better than retinotomy, and it's best done under air. There is no use of PFO so there is never PFO under the fovea that needs to be removed, and it reduces cost. It also contains bleeding, the vessels can be lasered as necessary, and better outcomes will be achieved.

Pharmaceutical Management of PVR – *Demetrios G. Vavvas, MD, PhD*

It is well established how to determine whether proliferative vitreoretinopathy (PVR) is mild, medium, or severe. Risk factors for PVR include inflammation, large or multiple tears, hemorrhage, choroidals, aphakia, and multiple prior intraocular surgeries. The greater the occurrence of any of these, the greater the likelihood PVR will occur. Formulas have been developed to calculate the risk.

There are multiple cytokines involved, and multiple cells involved in the development and pathogenesis of PVR. Different pharmacotherapy approaches have been tried, such as steroids for inflammation and antiproliferatives for proliferation. There are also molecular targets, but there have not been enough clinical trials on specific targets for these to be an effective approach.

Researchers have tried different treatments, but none have shown great results. PVR forms over 8 to 12 weeks, with multiple factors involved. Most of the studies that have been done have used a single dose of a single agent, which is expected to last over time.

A study has been performed of long-term repetitive injections of methotrexate, which can inhibit both inflammation and proliferation. Of 20 test subjects, only three developed subretinal fluid requiring reoperation (one of those three declined another procedure). Another study has shown that methotrexate can be used safely in the treatment of PVR.[1]

A lot of circular reasoning has been done in research so far. Something works in an animal model, but not in humans, so that avenue goes nowhere. In the future, more complex approaches will be needed, looking more closely at molecular biology. It is known that TNF, TGF, VEGF, and PDGF may be involved, so specific molecular targets may be found. More appropriate dosing and timing are needed, with more long-term treatment and possibly a combination of agents. It should also be remembered that PVR involves intraretinal changes such as stiffness and shortening, not just epiretinal and subretinal membrane formation.

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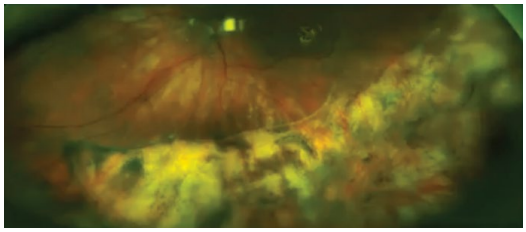
1. Sadaka A, Sisk RA, Osher JM, Toygar O, Duncan MK, Riemann CD. Intravitreal methotrexate infusion for proliferative vitreoretinopathy. Clin Ophthalmol. 2016 Sep 19;10:1811-1817. eCollection 2016.

Is Scleral Buckling Necessary? – *Carl D. Regillo, MD, FACS*

Much has been published over the years about techniques used for repairing retinal detachment, but nothing is definitive about optimal management. What is known, however, is that for primary retinal detachment repair, the overall results for scleral buckling to vitrectomy are comparable, and are comparably good in both approaches. Some studies have favored vitrectomy, with better visual outcomes in pseudophakic eyes.

The vitrectomy arms in these studies were vitrectomy with or without scleral buckling in combination. So, it must be asked, for primary retinal detachment, how does vitrectomy compare to scleral buckle with vitrectomy (buckle-vit)? Groups have

looked at this, and no real difference has been identified. Even in today's environment of small incision vitrectomy, no change is found from similar studies of years ago, there is no real difference in the results of these two approaches.



There is one study, however, that shows possibly better outcomes with combined buckle-vit.1 This study looked at cases that were high risk for PVR, which was defined as retinal detachment in 2 or more quadrants, retinal tear greater than one clock hour, preoperative PVR, or vitreous hemorrhage. The results slightly favored buckle-vit over vitrectomy alone for reattachment rates; however, this was a very small study.

In cases of retinal detachment complicated by PVR, nothing has been shown that suggests better outcomes will be achieved by adding scleral buckling to vitrectomy in this setting. For vitrectomy with retinectomy and silicone oil for established PVR detachments, there is nothing to suggest that adding scleral buckling provides any advantage.

The presenter's approach toward treating primary retinal detachment is to choose between scleral buckling and vitrectomy, not use a combination of the two. The basic decision criteria is to use scleral buckling for retinal detachment without PVD or flap tear, and vitrectomy if those conditions are present, and since most retinal detachments are associated with those, the majority of cases are done with vitrectomy alone.

Scleral buckling is still a useful technique for repair of retinal detachment and should remain as a potential treatment, but it should be used selectively. For most primary detachments, vitrectomy without buckling will be used, and the literature supports the lack of any real benefit in adding scleral buckling to the vitrectomy.

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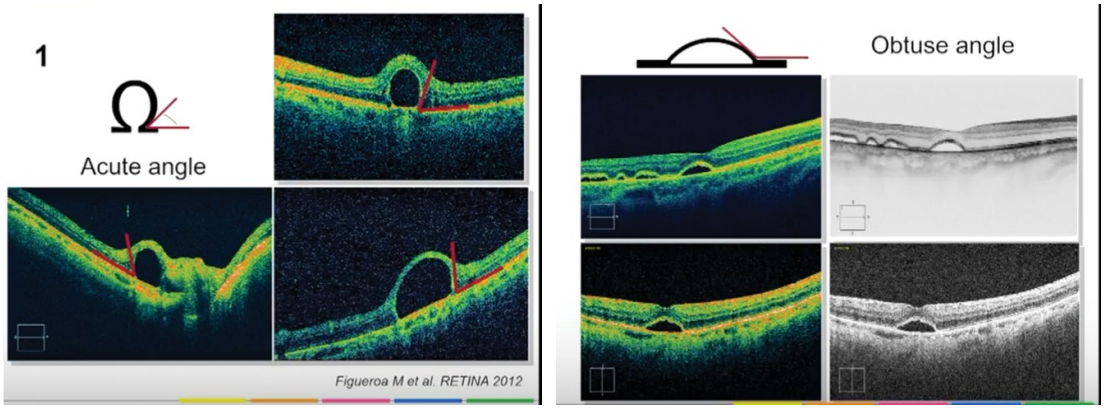
1. Storey P, Alshareef R, Khuthaila M, London N, Leiby B, DeCroos C, Kaiser R; Wills PVR Study Group. Pars plana vitrectomy and scleral buckle versus pars plana vitrectomy alone for patients with rhegmatogenous retinal detachment at high risk for proliferative vitreoretinopathy. Retina. 2014 Oct;34(10):1945-51. doi: 10.1097/IAE.0000000000000216.

Management of Subretinal Perfluorocarbon Liquid – *Marta S. Figueroa, MD, PhD*

Microincisional vitrectomy is the treatment of choice for many rhegmatogenous retinal detachments. (RRDs). In a prospective series of 133 eyes operated with 23g vitrectomy without scleral buckling, the primary anatomical success rate was 96%, and there was a significant improvement in vision.1 There were few complications related to this procedure, the most common being an increase in intraocular pressure. A surprising finding in the series, though, was the high incidence of subretinal perfluorocarbon liquid (PFCL). This complication has been mostly described in eyes where large retinotomies were performed, but all the cases in this series were primary retinal detachments with no evidence of PVR, and no retinotomies were performed.

Looking for the cause of the high incidence of this complication, it could be that the slower fluid-air exchange with small gauge instruments may facilitate the slippage of PFCL under the retina, through the retinal tears. There are ways to avoid this complication, but even if those are done, small droplets may appear under the retina, and it may be unclear whether the droplets are PFCL or persistent subretinal fluid. OCT can be very useful in determining which of those two it is.

There are 4 characteristics of PFCL that can be seen on OCT. The first is that the retinal shape over PFCL resembles the Greek letter omega (Ω), due to the high surface tension of PFCL. The angle between the RPE and the neurosensory retina at the base of the PFCL is always an acute angle. In contrast, the shape of the retina over persistent retinal fluid looks like a hat, with an obtuse angle between the RPE and the neurosensory retina at the base of the PFCL.



The second sign is that retinal layers over PFCL are not visible, but they are visible over persistent retinal fluid. The third is elevation of the RPE hyperreflective band, which is seen beneath the PFCL, but not seen over persistent fluid. And the last finding, which can occasionally be seen on high resolution OCT, is a hyperreflective shadow beneath PFCL, which does not appear over persistent subretinal fluid.

It is well known that subfoveal PFCL causes visual acuity loss and an absolute scotoma. Several reports have shown that vision improved after PFCL was removed. The two main approaches for removal of subfoveal PFCL are direct removal through the retina, and inferior displacement of the PFCL following macular and inferior retinal detachment with subretinal injection of balanced salt solution (BSS), placing the patient in a vertical position.

The incidence of subretinal PFCL may increase following microincisional vitrectomy for primary retinal detachment. Use of OCT can assist in diagnosis of subretinal PFCL and to differentiate it from persistent subretinal fluid. Surgery can achieve good anatomical and functional outcomes and is indicated when PFCL affects the fovea or progresses toward the foveal vascular zone.

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1. Figueroa MS, Contreras I, Noval S; PACORES Study Group. Anatomic and visual outcomes of 23-G vitrectomy without scleral buckling for primary rhegmatogenous retinal detachment. Eur J Ophthalmol. 2013 May-Jun;23(3):417-22. doi: 10.5301/ejo.5000234. Epub 2013 Mar 6.

Session 4:

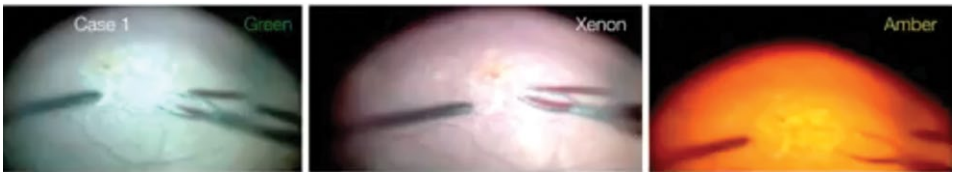
SURGICAL TECHNOLOGY

Advances in Illumination – *David R. Chow, MD, FRCS(C)*

There are four things to look for in a light source

1. Power – is it bright enough?
2. Safety – will it damage tissue?
3. Color – does it allow for enhanced tissue visualization?
4. Delivery – how is it delivered to enhance the surgeon's view?

The use of chandelier lighting has grown over the years. At the 2017 Retina Fellows Forum, 75% of retina fellows indicated they are using a chandelier for complicated retinal detachments or tractional retinal detachments. The value of chandeliers is also quite noticeable in safety calculation, allowing a surgeon much more time to work than previously possible, while the lighting remains safe. One obvious advantage of chandelier lighting is that it allows surgeons to become true bimanual surgeons, independent of assistance from others.



Adding color filters to the light source makes a difference. Early studies (2005) found that adding a yellow filter improves safety and provides an overall good viewing environment, while a green filter seemed to enhance visualization of the ILM but did not increase safety. In 2010, testing of new light sources showed that a mercury vapor light source provided the highest safety calculations, if all other factors were equivalent, and an improvement to a xenon light source provided an exponential increase in theoretic working time from the previous model, based on the safety curves. Reports of light-induced phototoxicity caused by lighting sources have decreased over time.

A survey of retina surgeons showed that green tint is preferred for macular surgery, and an amber filter, which provides a large increase in work time based on safety calculations, is not well liked for most operating situations. Exceptions to this are air-fluid exchange and macular surgery with Brilliant Blue dye. For North American surgeons using ICG, the use of a light filter can reduce the production of cytotoxic compounds, which may be where phototoxicity originates.

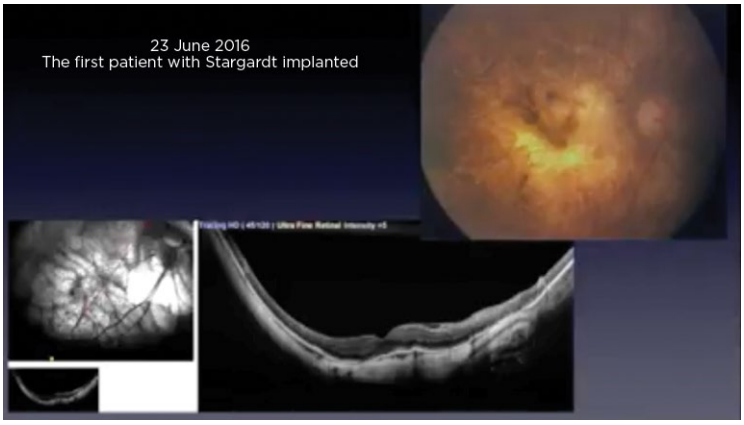
There are now LED light sources, one of which is a titratable color light source, with 20 step gradations to progressively yellow, which provides exponential increases in safety times. There is also a digitally assisted vitrectomy system, which opens up a new world of visualization opportunities. That system's High Dynamic Range

camera allows for lighting to be reduced, greatly increasing safety times. There will be a number of tissue visualization opportunities with this system by manipulating settings to enhance vision.

Artificial Vision: Everything You Need to Know – *Stanislao Rizzo, MD*

The principle underlying all retinal implants is the replacement of photoreceptor function in patients with outer retinal degeneration. Only two epiretinal prosthesis systems are commercially available currently (Second Sight and Pixium).

The Argus II from Second Sight is composed of a pair of glasses with a camera, which is connected by a cable to a computer, which sends information forward to a coil. The coil is connected by a cable to the heart of the system, which has an electrode array connected to the macula. The next generation will include a more powerful video processing unit and improved aesthetics, patient comfort, and usability.



The target for this technology is retinitis pigmentosa. It is currently being used in a study looking at potential use in treating dry AMD[1], and it may be useful in Stargardt disease as well.[2]

A patient survey at the end of Rizzo et al showed a satisfaction score of approximately 7, on a scale of 1 to 10, with 10 being best, and 75% of the patients said they would do it again. Of the patients that said they would not do it again, the reasons were that they expected more, and the rehabilitation is too demanding. The surgery is considered safe; there were only 4 severe complications in this series of 30 patients (13.3%), and the results are very encouraging, but the selection and motivation of patients are important. This technology should be used in patients who have barely light perception.

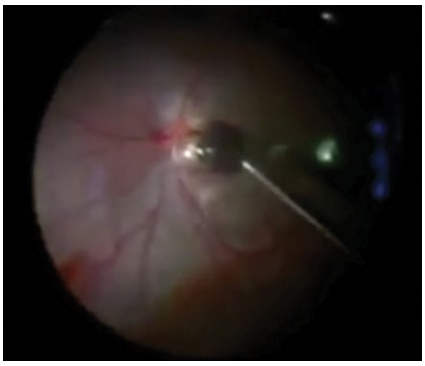
1. Argus II Retinal Prosthesis System Dry AMD Feasibility Study Protocol
ClinicalTrials.gov Identifier:NCT02227498
https://clinicaltrials.gov/ct2/show/NCT02227498

2. Rizzo S, Belting C, Cinelli L, Allegrini L, Genovesi-Ebert F, Barca F, di Bartolo E. The Argus II Retinal Prosthesis: 12-month outcomes from a single-study center. Am J Ophthalmol. 2014 Jun;157(6):1282-90. doi: 10.1016/j.ajo.2014.02.039. Epub 2014 Feb 19.

Eye Injuries with Intraocular Foreign Bodies Removal Techniques
– Mohamed Tarek Moustafa MD, FRCS

Ocular trauma associated with intraocular foreign bodies (IOFBs) is one of the main causes of vision loss, especially in young patients. IOFBs are found in up to 41% of open-globe ocular trauma, and time factor is crucial in their management. Early intervention with appropriate management can lead to a favorable visual outcome.

IOFBs should be suspected in all traumas related to firearms, hammering, and explosions. Signs to watch for are a small self-sealing would, iris holes, and focal cataract. CT scans are valuable in detecting IOFBs, with axial and coronal cuts done with a cut-to-cut distance of 1.5 mm or less. MRI should be avoided in any case where a metallic IOFB is suspected, and ultrasonography can be used, but must be done gently.



Complications can include the mechanical effect of the IOFB itself, endophthalmitis, a reaction to the IOFB (siderosis or chalcosis bulbi), and post-traumatic uveitis including sympathetic ophthalmitis.

Three techniques for removing IOFBs are being used at Minia University in Egypt.

1. Handshake technique
2. Shake magnet technique
3. Direct delivery technique

The handshake technique includes removal of the cataract if present, with anterior vitrectomy, to visualize the IOFB, followed by freeing the IOFB from the underlying structure into which it had impacted. The IOFB is then transferred to another hand, holding another forceps, through the pupil, and the foreign body is extracted through the corneal wound. The case is then continued as usual, with laser and air-fluid exchange.

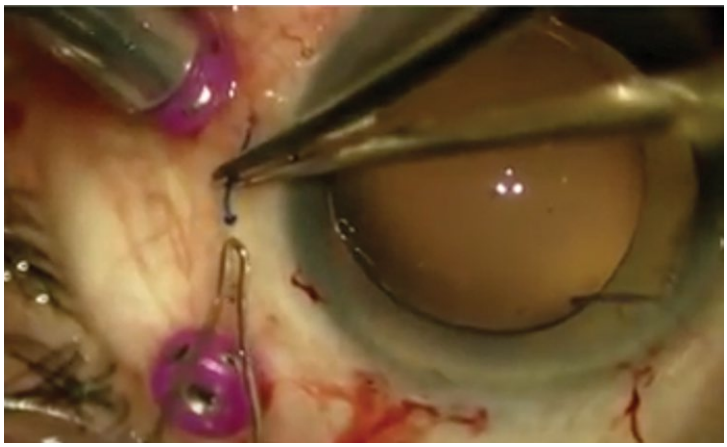
For the shake magnet technique, in the historical method of doing this, AP and lateral view X-rays are obtained, cryotherapy is used, then a sclerotomy done, and with an extender magnet the IOFB can be removed. In the current technique described here, the other hand is holding an intraocular magnet, and again the IOFB is removed through the corneal wound. The case is completed with PVD induction and air-fluid exchange.

The direct delivery technique, for a nonmagnetic IOFB, is done with endoscopy, diathermy, and a knife to open the choroid. Under visualization with endoscopy, the IOFB can be removed. For a case of a larger foreign body, Colibri forceps can be used to remove the IOFB through the sclerotomy side, with one suture to seal it after removal, and then the case can be continued as usual.

The choice of which technique to use depends on the size, nature, and site of the IOFB, as well as the status of the lens.

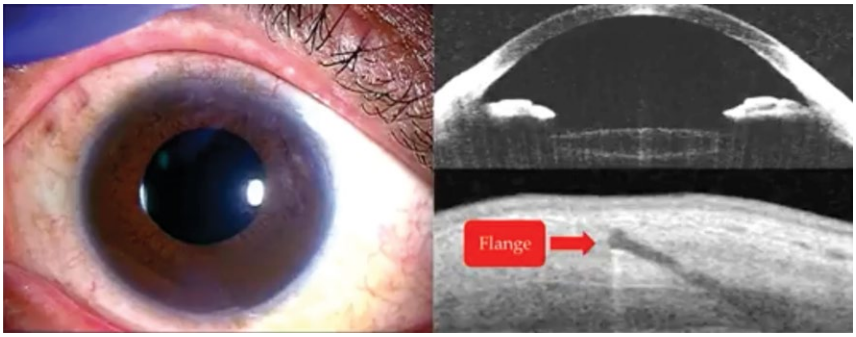
Flanged Intraocular Lens Fixation – *Shin Yamane, MD*

There is a new technique for transconjunctival intrascleral fixation of an intraocular lens (IOL), which involves creating a flange on the end of the IOLs haptics.



After marking, and a 27- or 25-gauge vitrectomy, a 3-piece IOL is injected into the anterior chamber, and a sclerotomy is done using a 30-gauge thin wall needle. The leading haptic is inserted into the lumen of a 30g needle, and the trailing haptic inserted into the lumen of a second 30g needle. The haptics are then externalized using the needles. Because the diameter of the haptics of a 3-piece IOL is 0.15 mm, these can be inserted into a 27g needle. However, the outer diameter of the 27g needle is too large, which is why the 30g needle is ideal.

The haptics are then cauterized to create a flange, or bulb, at the end of the haptic. The flange is pushed back and fixed into the scleral tunnel.



Picture and OCT show six months post-op. The IOL is well fixed and there is no sign of inflammation.

A study presented in this talk of 100 eyes treated in this way shows visual acuity was improved at 6, 12, 24, and 36 months postoperatively. Four models of IOLs were used in the study. The mean reflective difference from the predicted value was -0.21 diopters, and the mean IOL tilt was 3.44 degrees. Complications of the study included vitreous hemorrhage, hypotony, IOP elevation, and corneal edema early, and, later, iris capture of the IOL, cystoid macular edema, and IOP elevation. There were no cases with IOL dislocation after surgery.

This flanged IOL fixation technique is simple and minimally invasive, and it provides good IOL fixation with firm haptic fixation.

Session 5:

RETINAL DETACHMENT SURGERY

Advances in Suprachoroidal Buckling – *Flavio A. Rezende, MD, PhD*

Suprachoroidal buckling is useful for a surgeon to know how to do for specific cases. It is not meant to replace standard buckles or vitrectomy. El Rayes and Oshima1 described this procedure, using either Restylane or Healon5, cryotherapy, no drainage of retinal fluid, no preplaced suture, a chandelier, and indirect laser if cryotherapy was not used. They used either a catheter developed by El Rayes or an olive-tip cannula.

Many vitreoretinal surgeons are not comfortable attempting techniques involving approaches in the suprachoroidal space, but it's being explored more. The University of Montreal has adapted the previously described technique, using a noncontact wide-angle system; one 25-gauge valved trocar; an illuminated laser probe to avoid problems encountered with the chandelier; and a 26g needle on a 3 cc syringe without the plunger, to drain the subretinal fluid. Or, if the fluid is not drained, an AC tap must be done with a 30g needle, and either the I-Track catheter or the olive-tip cannula is used, and importantly, Healon5 (2 vials).

It is not a problem to work in a vitreous cavity filled with vitreous when the instruments are small as with the illuminated laser probe.

For the fluid removal method, a 26g needle was inserted into the subretinal space to drain the fluid. Complete fluid resolution is recommended, especially if there is difficulty visualizing the RPE. A small amount of Healon5 was injected to separate the choroid from the sclera, and then the catheter was migrated to the suprachoroidal space. There were several difficulties and complications with this fluid removal method.

Using a commercially available olive-tip cannula resulted in an 85% single surgery success rate, and a 100% final success rate, in the first 59 cases performed by this group. When using the olive-tip cannula, there must be an extension used rather than being directly attached to the Healon5, which requires an assistant to inject. Current indications for this technique are young phakic high myopes with inferior RD with atrophic holes in the same quadrant, prior refractive surgery, retinal dialysis, retinoschisis-related RD, and phakic flap tears with inferior RD with complete PVD.

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1. El Rayes EN, Oshima Y. Suprachoroidal buckling for retinal detachment. Retina. 2013 May;33(5):1073-5. doi: 10.1097/IAE.0b013e318287daa5.

Retinal Detachment with Macular Hole
– Marco Mura, MD talk given by Marc de Smet, MD, PhD, for Dr. Mura

In myopic patients, there is a fairly high prevalence (9%-10%) of macular schisis, and this in the presence of vitreomacular traction can lead to foveal detachment. If there is tangential traction, a macular hole may occur.

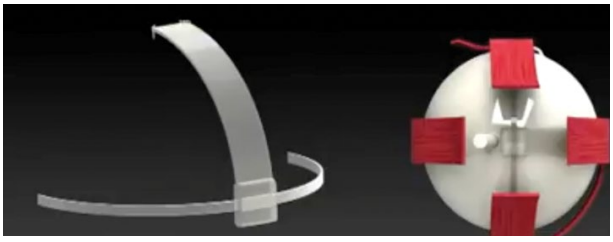
Myopic macular holes with no associated foveal detachment can be repaired with a standard pars plana vitrectomy, ILM peel, and gas, but when they are associated with a foveal detachment, there's a high failure rate if PPV is used alone. Historically, the usual approach was to use a buckle procedure, which was quite successful, about 85% to 90%. In the early 1980s, PPV was introduced as an alternative, but the success rate is lower. This is because retinal traction cannot completely be eliminated in many of the cases, especially in younger patients.

Options for treatment are PPV with ERM and ILM peeling, macular buckling, or a combination of these procedures. Using just PPV may get success, but the surgical and visual outcomes are limited. Macular hole closure has a success rate of 10% to 66% with PPV; retinal reattachment is much better, 43% to 100%, but even when success is achieved, there often is no improvement in postoperative visual acuity.

Poor prognostic factors for myopic macular hole and detachments include high myopia (axial length >30mm), posterior staphyloma, longstanding macular hole, younger age due to incomplete posterior vitreous separation, and the presence of chorioretinal atrophy.

A retrospective study was performed of 21 patients, 11 with macular hole and macular detachment, 5 with associated macular schisis, and 5 without schisis. Primary outcome was complete closure of the retinal hole and reattachment of the retina. Half of the patients had prior surgery involving PPV, peel, and silicone oil but failed, and were then operated with a macular buckle, and in a few cases oil was removed. The remainder of the patients had a primary macular buckle with a PPV about half of them with gas or oil. The choice of one or the other depended on the anatomy more than anything else. The macular hole closure rate was 90.5% (2 patients failed). Retinal reattachment rate was 100%. There was some improvement in vision in 71.4% of patients; some were significant and some were limited. There were no significant adverse complications, and 1 patient had diplopia.

Another approach is the ando plombe, in which a hard silicone band is placed under the macula, but it causes significant indentation, which may cause complications. Comparing this external compression procedure to the current technique, we see the new technique is more adjustable intraoperatively, causing less bulging and a good anatomical outcome. Advantages of this system are that there is no posterior suturing, no muscle disinsertion, and the ability to adjust the height of the buckle under visualization. Potential complications are diplopia and possible extrusion of the buckle, and subretinal hemorrhage and choroidal hemorrhage can occur if the buckle is placed on top of the vortex vein, so this must be avoided.



Treatment of macular holes due to high myopia can be challenging and lead to disappointing results. Pars plana vitrectomy combined with macular buckling appears to increase the success rates and is probably the preferred procedure rather than PPV alone for best result in terms of both repair and visual outcome.

ILM Peeling During Retinal Detachment Surgery: Is It Necessary?
– Stanislao Rizzo, MD

Peeling of the internal limiting membrane (ILM) is primarily performed in patients suffering from macular hole, but it also is considered for other indications, such as chronic diabetic macular edema not responding to intravitreal anti-VEGF or steroid therapy; the presence of epiretinal membrane in the macular region; and chronic or recurrent retinal detachments that have inner retinal wrinkling, retinal stiffness, or apparent intrinsic contraction. But is ILM peeling always necessary in primary macular hole-induced retinal detachment (MHRD), or rhegmatogenous retinal detachment (RRD)?

The important causative factors of MHRD might be related to tangential traction caused by a premacular membrane, or fibrosis, and the inverse traction caused by posterior staphyloma. It has been proposed that removing the ILM ensures the complete removal of any overlying ERM adjacent to the macular hole and the vitreous traction on the retina. There is still a debate, however, about whether and when to peel the ILM in MHRD.

A meta-analysis of published studies was performed to assess existing evidence about efficacy and safety of vitrectomy with ILM peeling, vs vitrectomy with no peeling, for MHRD.[1] Of 417 studies, only 6 were included due to determined exclusion criteria. The study group included 92 eyes with ILM peeling and 89 eyes without.

The anatomic reattachment success rate was around 90% for the ILM peeled group and about 50% in the nonpeeled group. The primary macular hole closure rate for the ILM peeled group was 96% and in the nonpeeled group was about 57%. The conclusion was that peeling of the ILM in MHRD is mandatory.

For RRD, the occurrence of macular pucker can affect visual acuity after repair of retinal detachment. Epiretinal membrane in RD differs from idiopathic cases because they are full of myofibroblasts and RPE, with a tendency to contract.

Two groups were compared following vitrectomy-based primary RRD repair: one group without ILM peeling, and the other with triamcinolone assisted ILM peeling. In the group with no peeling, 34% had an incidence of macular pucker, and in the group with peeling, only 3% had macular pucker. Regarding best-corrected visual acuity and central macular thickness, the group with ILM peeling had the best visual acuity and lower central macular thickness.

ILM peeling was significantly associated with the prevention of ERM growth. The preventive effect of ILM peeling is attributed to removal of cellular components on the ILM surface that might develop into ERM and removal of the scaffold that promotes cellular differentiation. Evaluation of the visual prognosis revealed that ILM peeling did not influence the final BCVA significantly.

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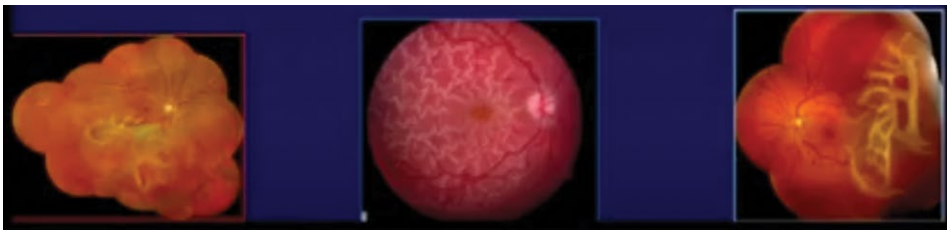
1. Su J, Liu X, Zheng L, Cui H. Vitrectomy with internal limiting membrane peeling vs no peeling for Macular Hole-induced Retinal Detachment (MHRD): a meta-analysis. BMC Ophthalmol. 2015 Jun 20;15:62. doi: 10.1186/s12886-015-0048-5.

Natural History and Management of Degenerative Retinoschisis and Associated Retinal Detachment – *Gaurav K. Shah, MD*

Retinoschisis (RS) can be broken down into types:

1. Posterior extension of RS without a break
    - Extremely rare to involve the fovea
    - Asymptomatic
2. Schisis detachment
    - Outer with or without inner wall breaks
    - Subretinal fluid at the edge of RS
    - Asymptomatic
3. Retina detachment complicating retinoschisis (RDRS)
    - Rare, 0.05% of RS patients
    - RD and RS morphology
    - Symptomatic, progressive



There isn't much in the literature about surgical experience with RDRS. What does exist says don't resect the schisis cavity, and most of these patients receive vitrectomy with or without scleral buckle, but typically not scleral buckle alone.

A review of the population of RS patients at the presenter's institution was performed, and natural history and considerations in management were considered. This covered a 15-year period in a tertiary retina practice, retrospectively. Over that period, 2.4% of 587 cases had the complication of RDRS. Previously estimated incidence was 0.05% of RS cases, but the current series is the largest, with longest follow up, so far. It includes multiple physicians and done in a tertiary retina-only practice.

There were 67 cases (11.4%) with outer wall breaks, 35 cases with outer wall breaks observed, 10 of which (28.6%) progressed to symptomatic RDRS. Factors associated with RDRS are presence of symptoms, and posterior extension to the arcades and macula. It is unclear whether treatment with laser or cryotherapy prevents progressive RDRS, and treatment is with these is not recommended in asymptomatic eyes. Surgery for progressive and symptomatic eyes is recommended; 86% in this series had single procedure success.

It's important to observe asymptomatic cases to watch for progression. Multimodality imaging can be used, including widefield infrared imaging.

Session 6:

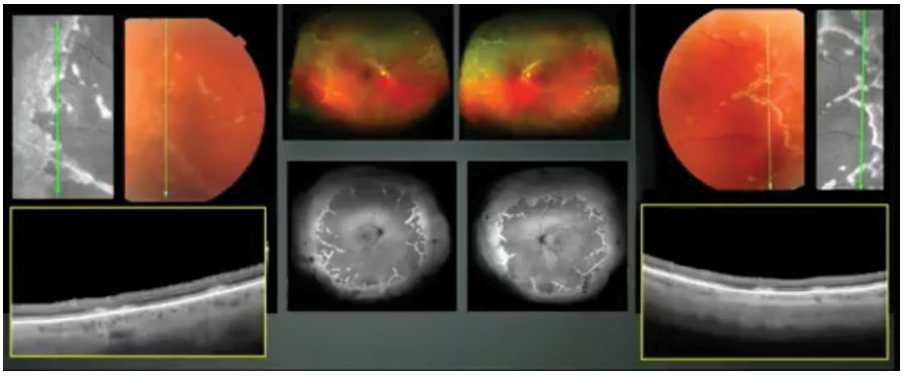
IMAGING

It's a Big Broad World in There: Widefield Imaging and Optical Coherence Tomography (OCT) – *Netan Choudhry, MD, FRCS(C)*

Researchers in this group have done previous work in ultra-widefield steering-based OCT for the periphery. Those efforts were focused on the macula and some element of the posterior pole for OCT. Using an OCT with a steering arm, it was possible to move to different fields of view, extending out into the periphery.

But what if a steering arm is not available, and instead swept-source OCT (SS-OCT) is used? The objective of a new study was to describe the qualitative features of a variety of retinal diseases using a novel navigated imaging technique, using SS-OCT.

Rather than repositioning the laser head, or the patient, an internal fixation light was used to navigate toward the periphery and toward areas of interest that had been seen on clinical exam. The OCT scans were taken in a 12mm fashion, and in many cases were montaged into a single image.



A model was developed to find how far out into the periphery imaging could be done using this stable approach. In various cases and patients, different degrees of the periphery could be reached, on average about 130 degrees. In the previous study where the OCT could be navigated, imaging of about 230 degrees was possible. Limitations in the stable approach include the extent to which the internal fixation light can be moved out to the periphery, poor dilation, patient fixation, and patient comfort.

The SS-OCT montaged technique is reproducible and gives high quality images with excellent anatomic detail, and the SS-OCT images correlate well with published histopathologic findings. It can enhance understanding of pathophysiology of these retinal lesions in the periphery and the extent to which systemic diseases affect the periphery, and it can show early changes in conditions.

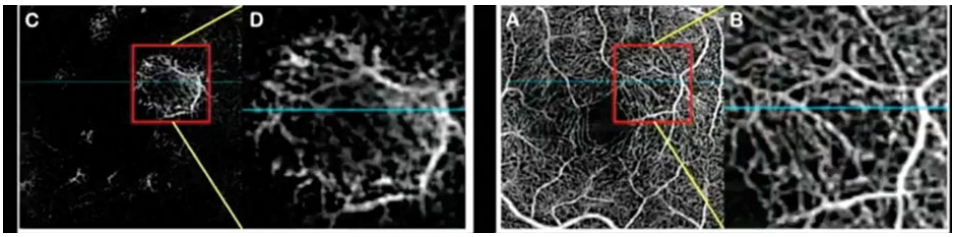
The study concluded that widefield images of the retina can be obtained using internal fixation only with a currently available SS-OCT device; a maximum of 169 degrees was achieved but on average 130 degrees could be reached, detailed imaging of normal and pathologic peripheral retinal findings can be done in patients who are well dilated, and understanding of normal and pathologic peripheral retinal findings can be enhanced.

OCT Angiography Artifacts and Findings: Sometimes Dots and Doodles Mean Something (And Sometimes They Don't!) – *Andre Romano, MD*

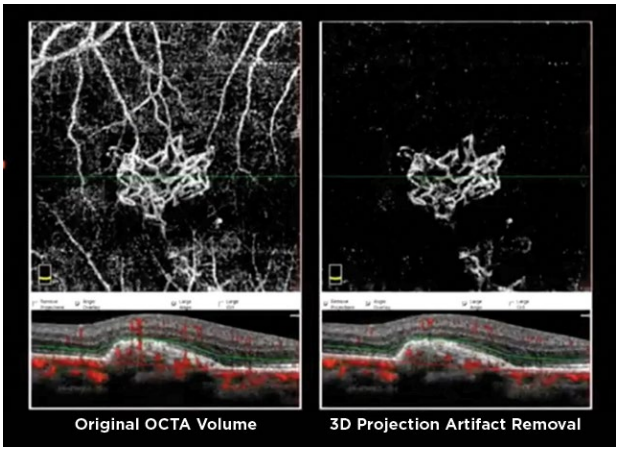
OCT angiography (OCT-A) has evolved over the years, but one of the biggest challenges remaining is motion artifacts. To understand why these are formed, it's important to understand how OCT-A works. In OCT-A, motion of red blood cells is detected by sequential OCT-B scans, repeated at the same location. Using the light reflected from blood cells, motion is detected and vessels with blood flow can be identified. There are different methods for calculating flow, using phase and amplitude, but all use the comparison of repeated scans.

The primary cause of motion artifacts is segmentation algorithm failure. It's directly associated with ocular motion, including such things as vessels doubling, and stretching defects. A lot of data is acquired in a small amount of time, which is especially a problem with patients who have a hard time fixating, such as patients with geographic atrophy or wet AMD. Eye motion limits data size and acquisition time. So poor fixation and blinking may lead to a lot of artifacts. Vessel doubling is associated with the software attempting to correct eye motion, and two copies of each blood cell are created. The algorithm will also cause the stretching defect, where blood vessels seem to be stretched in a nonuniform way.

Another important concept is projection artifacts, which is very common. This is due to the images being constructed in an en face manner, so the images from the superficial capillary plexus are projected into all the other plexus. Therefore, care must be used with automatic segmentation, to be sure what you are seeing is not the superficial plexus projected over another area.



The greatest challenge for the OCT companies is to create a projection artifact removal algorithm. One approach to this is to use intelligent algorithms, such as a machine-learning algorithm using artificial intelligence. This type of algorithm will remove projected artifacts to clean up the images.



Fundus Autofluorescence: Where and When Can I Use It Most Effectively? – *Sophie J. Bakri, MD*

Fundus autofluorescence is an imaging modality that allows mapping of lipofuscin distribution in the retinal pigment epithelium (RPE) and other fluorophores in the outer retina and subretinal space.

There are three different camera types used for autofluorescence:

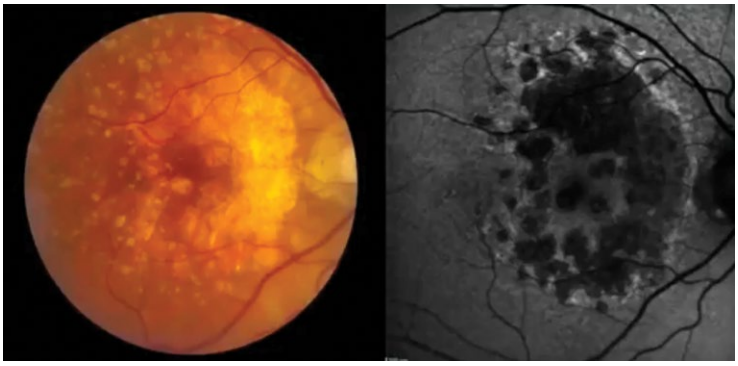
1. cSLO
2. Fundus camera
3. Widefield cSLO

Lipofuscin buildup is caused by incomplete degradation of RP outer segment discs, with incomplete release of the degraded material. It is a hallmark of aging in neurons, cardiac muscle cells, and RPE cells.

In normal autofluorescence, the optic nerve, retinal vessels, and fovea appear dark, and slightly less dark is the parafoveal area. There are many possible causes of hyper-autofluorescence, generally corresponding to an increase of lipofuscin in the RPE, or an increase in subretinal autofluorescent material. Window defects can be a cause, and there are other reasons such as optic disc drusen, and astrocytic hamartomas.

Autofluorescence is decreased when there is a decrease in lipofuscin, as may occur in RPE atrophy, and when there is blockage from pigment and scars.

In macular degeneration, autofluorescent patterns can be very variable. In drusen they can be increased or decreased depending on the type and size of drusen. In geographic atrophy, autofluorescence is decreased within the atrophy, but increased, or absent, at the margins. In PEDs, it is increased over the PED, and decreased at the margins.



Autofluorescence shows hyper-autofluorescent rim

The junctional zone is a hyper-autofluorescent rim, with RPE cells full of lipofuscin. The increased autofluorescence is from outer segment phagocytosis and engulfment of spent RPE cells, and it precedes cell death.

The autofluorescence types in geographic atrophy have been classified as none, focal, banded, patchy, and diffuse. Each type corresponds to a particular rate of progression. Banded and diffuse patterns have a higher rate of GA than those with focal, or no autofluorescence.

Color photography and autofluorescence have been found to correspond, but in general the lesion size is smaller with color photography.

Autofluorescence can be used in macular degeneration to measure atrophy size and symmetry, to assess the rate of progression, and to assess the risk of progression by looking carefully at the junctional zone. This will become increasingly important in deciding who to treat with new medications that are coming available and in assessing response to treatment. It is also very important to use autofluorescence in the differential diagnosis of AMD. It can also be used to look for medication toxicity, and to distinguish choroidal nevi from melanoma.

Intraoperative OCT: Is It Ready for Prime Time? – *Justis P. Ehlers, MD*

OCT has transformed the clinic, and a question now being asked is if it's ready for use in the operating room. There are now three FDA-cleared microscope-integrated OCT systems, and the current technology can provide immediate feedback to surgeons. Functionality is improving and there are new capabilities such as Z-tracking and automatic signal detection technology, and there are studies that suggest the promise of this technology.

There have been multiple studies looking at the validation of microscope integration. Microscope-integrated OCT systems have demonstrated a strong correlation to portable SD-OCT systems. The microscope integration allowed for visualization of surgical maneuvers without needing to stop surgery. It has also been shown that utilizing intraoperative OCT during surgery may reduce the need for intraoperative dye staining.

Intraoperative OCT provides a unique opportunity for intraoperative visualization including extended range systems and heads-up displays to actually see surgical maneuvers while still in the eye.

The Cleveland Clinic is looking at the potential utility and surgical decision-making afforded by intraoperative OCT in the DISCOVER study, a large prospective intraoperative OCT study examining multiple platforms. At 36 months, over 800 eyes are enrolled in the study. For membrane peeling, when the surgeon thought they were finished, but then looked with an OCT, in 22% of cases they went back and peeled more. Conversely, when they thought they needed to do more, after using the OCT they realized they had reached their surgical objectives in 15% of cases.

Intraoperative OCT can also be used in the retinal periphery, and can be helpful in evaluating retinal breaks, defining peripheral anomalies, and identifying the specific location of pathology.

Current systems provide for potential real-time and rapid static feedback on retinal anatomy during surgery. In select cases, this information can impact surgical decision-making and surgical maneuvers. And microscope-integration has enhanced efficiency and workflow, for the utilization of intraoperative OCT.

Still needed however, are enhancements to make image acquisition more rapid and efficient. The quality and consistency of images needs to be improved. There should be automated tracking to areas of interest and potentially back to the surgical instruments, and there need to be better software packages. There also needs to be improvement in the way the surgeon interacts with the technology, and there needs to be further validation of outcomes and value. Finally, a reimbursement model will need to be developed.

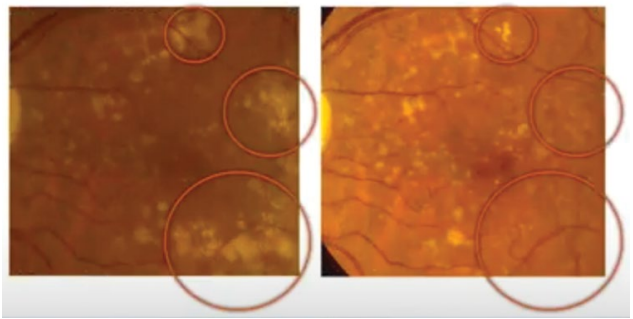
Session 7:

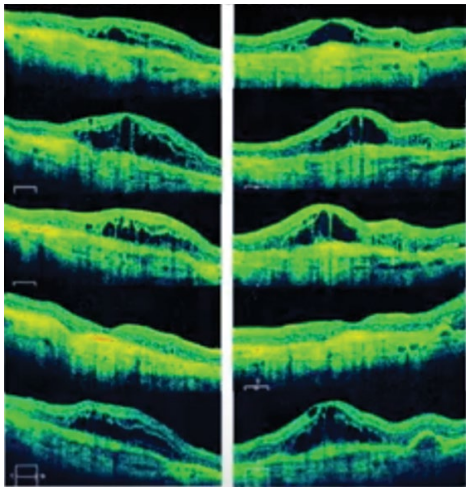
AGE-RELATED MACULAR DEGENERATION (AMD)

Emerging Therapies for Dry AMD – *David S. Boyer, MD*

There are currently trials going on for treatment of geographic atrophy (GA), and a number of therapeutic options have failed.

One problem is that there is no good model for testing drugs. Neuroprotection has been tried with ciliary neurotrophic factor, intravitreal brimonidine tartrate, topical tandospirone and topical OT-551, but these have all failed.





However, intravitreal brimonidine tartrate is moving forward. Intravitreal brimonidine has been shown to be protective of retinal ganglion cells, bipolar cells and photoreceptors. It has been effective in a number of insults, including ischemia, ocular hypertension, phototoxicity, and partial optic nerve crush. The results of the first phase 2 trial were encouraging and showed that there is some biological effect.1

Reduction of byproduct accumulation has also been looked at. Intravenous RN6G (an anti-amyloid beta antibody) failed, while subcutaneous glatiramer acetate appears to reduce amyloid-induced retinal microglial cytotoxicity and allow a neuroprotective phenotype of microglia to form.

Visual cycle modulators have been tried. Oral fenretinide failed, oral ACU-4429 failed but will be tested for Stargardt disease.

Other possible mechanisms include increasing circulation, using an aldehyde trap, or doxycycline.

MacuCLEAR (MC-1101) is a topically administered eye drop that works by increasing ocular blood flow in the choroid vessels, preventing the rupture of Bruch's membrane. There has been proof of concept that it can do this, and there are ongoing studies.

Tetracyclines at low dose are active against many molecular pathways suspected to be important in the pathogenesis of GA and AMD, including reactive oxygen species, matrix metalloproteinases, caspase activation, cytokine production, and complement activation. Minocycline has been shown to protect RPE cells against

oxidative damage, and attenuate photoreceptor degeneration.

Doxycycline reduces neovascularization and lesion volume in a murine laser model of CNV. The TOGA study should soon have results testing this approach.

Complement inhibition is another approach of interest and several compounds are being looked at. Photomodulation is the use of light to reduce GA, and there are some preliminary results that show an effect.

The last approach is inflammasomes, which are found in immune cells and are activated by Alu RNA molecules. There is a theory that high levels of uncut Alu RNA in RPE cells (which can result from low levels of the protein DICER) causes tissue destruction in GA.

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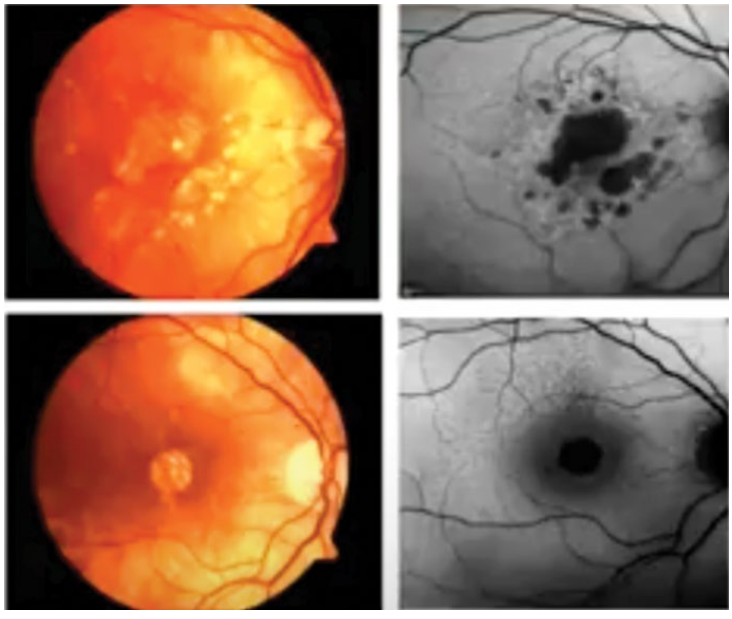
1. Freeman WR. Intravitreal brimonidine drug delivery system (brimonidine DDS) in patients with geographic atrophy: A phase 2 study. Presented at: American Academy of Ophthalmology annual meeting; Oct. 14-18, 2016; Chicago.

Biomarkers in Retina – *Anne Fung, MD*

The NIH Biomarkers Definitions Working Group has defined a biomarker as "a characteristic that is objectively measured and evaluated as an indicator of normal biologic or pathogenic process or pharmacological response to a therapeutic intervention."

Many retina characteristics have potential as biomarkers. They need to be objective and repeatable in measurements, representative of a biologic process, and need to be continually evaluated for objectivity and relationship to disease. This can range from a functional test, to a biological sample such as aqueous, vitreous, blood, or tissue, to an imaging test.

A biomarker is prognostic if it identifies patients at an increased risk for disease progression, and predictive if it indicates the likelihood of response to a specific therapy. It can also be both.



Without proper patient selection, a potentially efficacious therapy could be missed in a clinical trial. Individualizing treatment for patients is going to be increasingly

important. In retina, there have be multiple well-powered studies of genetic risk, identifying approximately 35 risk loci. But studies to identify the genetic factors that affect the rate of disease progression and response to treatment have been fewer and more modestly sized. More and larger studies are needed in that direction.

There has been progress in prognostic imaging biomarkers. Color fundus photography can be used to predict the rate of progression of geographic atrophy. Eyes with multifocal lesions progress faster than eyes with a single lesion. Using SD-OCT, it can be seen that microstructural alterations of the deep layers have also been associated with faster rates of GA enlargement. A banded or diffuse trickling pattern seen on fundus autofluorescence also predicts a faster rate of GA progression. OCT-angiography will also hopefully reveal some characteristics that can be associated with faster progression, or certain characteristics of diseases.

It's important that there is consensus and collaboration within the retina community when identifying and prospectively testing new biomarkers. To validate and evaluate biomarkers, the first step is to validate the methodology. Protocols should be developed to make measurements as objective and reproducible as possible. Then the clinical correlations with biologic processes need to be demonstrated. Looking at a retrospective data set can be helpful to develop a hypothetical relationship between what can be seen, and the outcome. Then collaboration is needed to develop prospective data to test the hypothesis to see if it's true. Continued evaluation of new data can then reconfirm that relationship.

Patient-, Caregiver-, and Healthcare Provider–Reported Burden of Geographic Atrophy – *Sunil S. Patel, MD*

A study was undertaken to understand the burden of geographic atrophy from the perspectives of patients, caregivers, and healthcare providers. It was intended to identify key factors that should be included for assessment in future studies designed to collect GA-specific data. Interviews were conducted with 8 patients with symptomatic GA, 6 caregivers of participating GA patients, and 5 healthcare providers (3 retina specialists and two optometrists) involved in the care of GA patients across the United States.

The interviews were tailored for each participating group to evaluate:

1. Understanding of disease
2. Costs and burden of illness
3. Use of vision aids and services
4. Impact on emotional and psychological well-being
5. Impact on activities of daily living

The major concerns patients had included cooking, reading, driving, health, and banking. They also had concerns with outdoor hobbies, household chores, and the emotional impact, such as anxiety about personal hygiene and appearance.

Regarding the burden of the disease, patients paid out of pocket for vitamins and for flashlights, and other visual aids such as magnifiers, lights, and electronic reading machines.

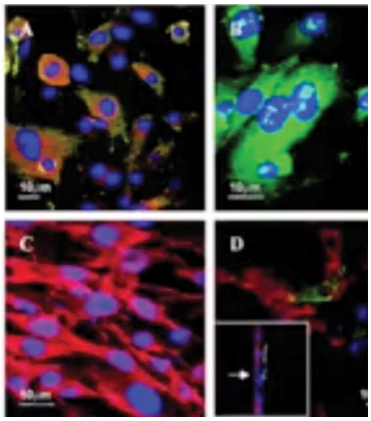
The caregivers' concerns about the burden of the disease and the wellbeing of the patient included modifying their schedule to be able to provide care, the demands on their time, frustration over the inability to improve the patient's health, and providing transportation for medical visits.

Healthcare provider concerns were the emotional impact of vision loss on the patient (depression or other mental concerns), in rural settings travel is difficult for the patients, having low vision aids and education available was a concern, accidents and injuries to the patients that are attributable to GA, and the frequency of patient visits. For the accidents and injuries, it is difficult to know if they were directly related to GA, or perhaps a result of unstable gait and the like, but there is likely some association with GA.

The study findings highlight the negative impact of GA on the patients' quality of life, emotional status, social functioning, indirect resource use, and patient out-of-pocket costs. More research is needed on patient wellbeing (especially regarding mental health), and on accidents and injuries directly attributable to GA. The burden of illness on GA patients and their caregivers needs to be further characterized.

Gene Expression Can Be Modified by Anti-VEGF Drugs in Retinal Muller Cells in Vitro – *Javier Caceres-del-Carpio, MD*

It is well known that increased expression of VEGF plays a role in cancer, during hypoxic conditions, and in the pathogenesis of macular degeneration, diabetic macular edema, diabetic retinopathy, and retinal vein occlusion.



However, VEGF is useful in many ways as well. It has an important role in embryogenesis and fetal development, and it promotes cell survival. In normal adult physiology, it is also important in wound healing and the female reproductive cycle.

In the last decade, anti-VEGF drugs have revolutionized ophthalmology. However, recent studies have shown that anti-VEGF drugs may increase the size of geographic atrophy in patients with AMD1,2, and possibly worsen macular ischemia in patients with DME.3

To understand why this happens, a traditional approach can be used to identify

the effects of drugs on cells and tissues, beginning with cell culture experiments, looking particularly at retinal Muller cells. These are the most important glial cells in the retina, with very important functions such as retinal neuroprotection, wound healing, and retinal regeneration.

For the study discussed here, the hypothesis was that anti-VEGF drugs can affect nonangiogenesis pathways related to oxidative stress and apoptosis. Cells were treated for 24 hours with an anti-VEGF drug (ranibizumab, bevacizumab, aflibercept, or ziv-aflibercept) in 1x or 2x the clinical concentration. The study looked at angiogenesis with VEGF-A or placental growth factor (PGF), antioxidant enzymes SOD2 and GPX3, and apoptosis genes BCL2L13 and BAX.

The gene expression levels were measured using Q-PCR, which allows for comparing folds between treated and nontreated tissue. Higher fold values indicate increased production of RNA and gene expression, and lower fold values indicate a decrease in production.

In VEGF-A, results showed that ranibizumab, bevacizumab, and aflibercept significantly decreased gene expression, and ziv-aflibercept appeared to be less efficient. For PGF, aflibercept had an important increase in expression. Bevacizumab also showed an increase in expression, and there was a slight increase in expression with ranibizumab in the higher concentration dose.

In the enzyme SOD2, it was found that all of these drugs decreased expression. This enzyme has an important role in metabolizing hydrogen peroxide inside the cell, and it protects the cell from oxidative stress.

Regarding the proapoptotic genes, bevacizumab and aflibercept increased gene expression, and ranibizumab decreased the expression.

The study concluded that anti-VEGF drugs induce changes in the expression of genes involved in key pathways in angiogenesis, antioxidant enzymes, and proapoptotic enzymes. Interestingly, ziv-aflibercept, despite the fact it is supposed to be the same molecule as aflibercept, has different behavior. This is likely due to the different formulation with higher osmolality and lower pH.

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1. Comparison of Age-related Macular Degeneration Treatments Trials (CATT) Research Group, Martin DF, Maguire MG, Fine SL, Ying GS, Jaffe GJ, Grunwald JE, Toth C, Redford M, Ferris FL 3rd. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. Ophthalmology. 2012 Jul;119(7):1388-98. doi: 10.1016/j.ophtha.2012.03.053. Epub 2012 May 1.

2. Grunwald JE, Daniel E, Huang J, Ying GS, Maguire MG, Toth CA, Jaffe GJ, Fine SL, Blodi B, Klein ML, Martin AA, Hagstrom SA, Martin DF; CATT Research Group. Risk of geographic atrophy in the comparison of age-related macular degeneration treatments trials.

Ophthalmology. 2014 Jan;121(1):150-61. doi: 10.1016/j.ophtha.2013.08.015. Epub 2013 Sep 29.

3. Manousaridis K, Talks J. Macular ischaemia: a contraindication for anti-VEGF treatment in retinal vascular disease? Br J Ophthalmol. 2012 Feb;96(2):179-84. doi: 10.1136/bjophthalmol-2011-301087.

Session 8:

DIABETIC VITRECTOMY

Anti-VEGF Injection and Diabetic Vitrectomy: When and Why?
– J. Fernando Arevalo, MD, FACS

Tractional retinal detachment (TRD) following preoperative intravitreal bevacizumab (IVB) in severe proliferative diabetic retinopathy (PDR) was first described in 2008.1 The authors of the study determined the prevalence of the complication of TRD after injection of IVB was 5.2%.

These authors have now done a study to report the development or progression of TRD following IVB as an adjuvant to vitrectomy for the management of severe PDR with a larger series of patients, and to determine risk factors that may help in future studies.

The new study is a retrospective multicenter study of eyes with TRD that had undergone IVB before vitrectomy, for the management of PDR. The authors identified 25 eyes out of 698 IVB injections that developed or had progression of TRD, a prevalence of 3.2%.

All patients had a PRP at least 2 months before bevacizumab injection, and all eyes had PDR refractory to PRP. Eighteen patients had diabetes type 1 with more than 15 years from diagnosis, seven patients had diabetes type 2, and all patients had uncontrolled diabetes, with a mean HbA1c level of 9.2%.

The first risk factor found is that time from injection to TRD had a mean of 13 days. Duration of diabetes is also a risk factor. Visual acuity decreased significantly with TRD, and after vitrectomy 50% improved, 25% remained stable, and 25% lost vision, compared to baseline BCVA.

The development of progression of TRD in PDR following IVB could have happened by natural history, or rapid NV involution with accelerated fibrosis and posterior hyaloidal contraction as a response to decreased levels of VEGF. The short time between the injection and TRD (mean time 13 days) suggests a cause and effect relationship. 81.8% of TRDs developed or progressed 5 days or more after the injection.

In cases at risk for progression of TRD that might involve the central macular region, timely surgery should be anticipated. Diabetic eyes may be very sensitive to IVB2, so use of lower doses is prudent in eyes with pre-existing significant traction.

There are however advantages of using IVB in these cases. It may reduce the risk of intraoperative bleeding, facilitating the removal of fibrovascular membranes, better visibility leads to less likelihood of creating an iatrogenic retinal break, and the chances of postoperative complications such as rebleeding or fibrinoid syndrome may be decreased. These advantages may allow more eyes to be saved by using preoperative IVB, regardless of increased traction in some severe cases of PDR.

The authors concluded that TRD in PDR may occur or progress after IVB used as an adjuvant to vitrectomy. Surgery should be performed 4 days after IVB. Most patients had poorly controlled diabetes associated with elevated HbA1c, insulin administration, PDR refractory to PRP, and longer time between IVB and vitrectomy.

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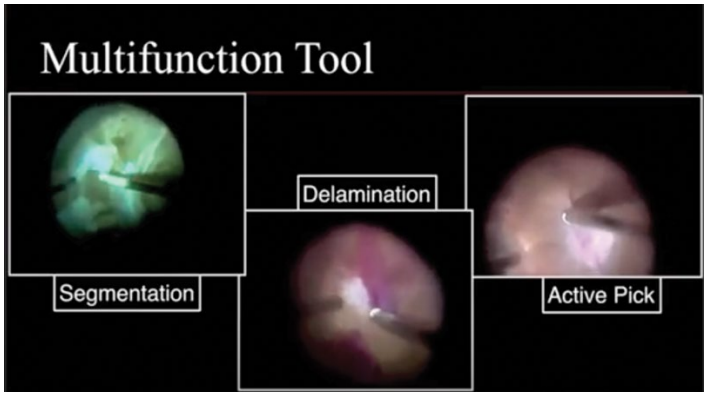
Advances in Traction Detachment Surgery: 27 Gauge – *Christopher D. Riemann, MD*

27-gauge diabetic vitrectomy is evolving into a new best practice to handle more challenging surgical patients. 27g vitrectomy is all about a brand new surgical paradigm of ultrahigh cut rates, excellent duty cycle, high vacuums, and small 27g vitrectomy port size, which provides the concept of a reduced sphere of influence.

The sphere of influence is the ability of the cutter to draw things in, and it is proportional to port size, vacuum or flow, and duty cycle, and inversely proportional to the cut rate. The smaller gauges have less attraction, or less sphere of influence. That means that the cutter itself becomes a multifunction tool. It can be used for segmentation with a level of precision not usually obtained with a 25g or 23g cutter, which will reach out and pull in retina. The 27g cutter will only pull in what is actually at the tip of the port. Delamination can be done right on the surface of the retina, actively vacuuming up fibrovascular tissue without worrying much about pulling in retina. The cutter can also be used as an active pick, by engaging gel, letting it fill the cutter port, and lifting the neovascularization of the disc off of the optic nerve head.



Taking that further, these cutters, at high cut rates with good duty cycles, are very capable of pulverizing whatever gets into the cutter tip. So lensectomies are not completely unheard of. Some ILM peels can be done using nothing but aspiration

from a 27g cutter. This is not a typical way to do this, but it shows how much precision the surgeon has on the retinal surface. If you put a haptic into the mouth of the cutter, with the cutter turned off, you can aspirate at high vacuum and create enough holding force to lift an IOL.

The concept is that the reduced sphere of influence of 27g vitrectomy limits the cutter's effect to the immediate area around the cutter tip, which increases precision and control, allowing the cutter to become a multifunction tool on the surface of the retina. The high cut rate and excellent duty cycle of modern vitrectomy cutters means that tiny little port is hyper-efficient at pulverizing, holding, and removing whatever is in the cutter port.

The downside of these small cutters is that there is a learning curve. These cutters only work if you put the cutter in the gel. It is very efficient at removing the gel once it is in the gel. Also, while the 27g cutter is more flexible than current 25g instruments, today's 27g instruments are much better, and stiffer, than first-generation 25g instruments.

A broad array of 27g devices is available in oil infusion, subretinal injection cannulas, and next generation "side flo" dual bore cannulas.

Another advantage of 27g is operated eyes look very quiet and clean from day 1 post-op; they're not as inflamed. Subconjunctival anesthesia can be used in anticoagulated patients.

But what really matters is the reduced sphere of influence of these 27g cutters, which provide increased precision and control and make 27g diabetic vitrectomy potentially the procedure of choice.

Bimanual Dissection in Traction/Rhegmatogenous Detachment (TRD/RRD): Pearls and Tricks – *Maria H. Berrocal, MD*

Traction and rhegmatogenous retinal detachments (TRD/RRD) are the most challenging diabetic pathologies. They are usually seen in younger diabetics who are poorly controlled with many years of diabetes, and usually there is a concave tractional detachment, then the increased traction pulls on the fibrovascular tissue, and the very ischemic and thin retina tears. It converts from a concave appearance to convex, and the retina is floppy, which is what causes the difficulty. This is mainly because there is no counter traction on the retina. This increases the difficulty of dissecting tissue because there is no force behind, and the space between the fibrovascular tissue and the retina is reduced so it's very hard to get instruments in between. It is imperative in these cases to remove all of the fibrovascular tissue, unlike in a TRD. Perioperative bleeding can be a problem and can impede the efficient completion of the case.

There are many useful techniques for this:

1. Viscodissection
2. VEGF-inhibitors before the surgery

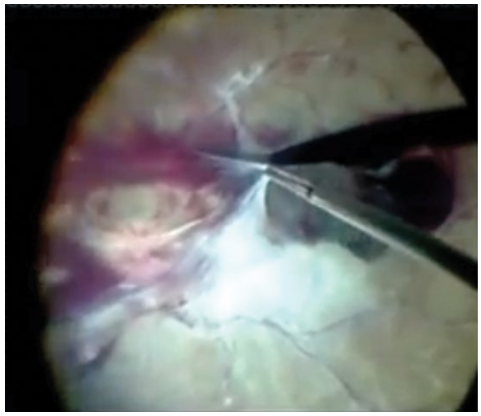
3. Perfluorocarbon liquids
4. 27g instrumentation
5. Wide angle viewing systems
6. 3D vitrectomy with magnified view and enhanced depth protection
7. En-bloc dissection
8. Bimanual techniques with chandelier illumination

The last one, bimanual techniques with chandelier illumination, is probably the best technique for some of the more difficult cases. It is particularly useful in peripheral proliferation, since the thinner retina is much more prone to tears and it is difficult to access.

The most important tool for this is a chandelier to provide adequate illumination. Usually placement is at 12 o'clock, and ideally it will be 90 to 180 degrees from most of the pathology. You can change the location by changing wherever you put it in the trocars. An assistant to direct the light can be helpful. You can override the light output of the machine if you need more light, and sometimes you can use transillumination through the sclera as a low-cost option.

The surgical sequence for these cases is:

1. Remove all the vitreous behind the lens
2. Use scleral depression to remove vitreous in the peripheral retina. It's important to remove all the vitreous 360 degrees to prevent traction
3. Find a dissection plane to begin. If there is fibrovascular tissue that is very adherent everywhere, you can start in the posterior pole and start lifting things there. Sometimes diathermy can be used to create an opening. A vitrector can be used to blunt dissect tissue bimanually, which is sometimes very useful in diabetics.



4. Usually the forceps is used in the nondominant hand and the scissors or probe is used in the dominant hand. The advantage of the small gauge platforms is that you can usually use the probe as scissors and as forceps and make the operation more efficient, and require fewer instruments.

A combination of techniques usually works best for these cases, such as bimanual, segmentation, and shaving, because the goal is to remove all traction.

ILM Peeling During Diabetic Vitrectomy: When and Why?
– *Timothy G. Murray, MD, MBA, FACS*

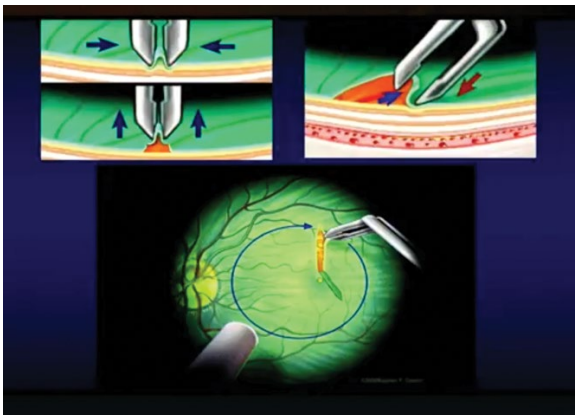
There has been significant evolution over the last decade in the approach to treating diseases affecting the macula. This has represented two converging technologies, advances in surgical ability to manipulate the macula safely, and significant improvement in the ability to image the macula preoperatively and now intraoperatively, and postoperatively. The understanding of pathophysiology and a comfort level of surgical manipulations have allowed surgeons to move to earlier surgical interventions with better expectations for both anatomic and visual improvements.

The goal for pars plana vitrectomy in diabetic macular edema (DME) is to always remove the posterior hyaloid and to consider the implications of removing the internal limiting membrane (ILM) for macular surgery, which will be discussed here. Important parts of that discussion are the approach to and the importance of how to manage the ILM. Media opacities are removed, endolaser can be applied in the setting of proliferative retinopathy, and intravitreal triamcinolone acetonide can be used off-label to suppress postsurgical inflammation in these patients.

The major advances include high-speed instrumentation with cut rates now between 7,500 and 10,000 cuts per minute, controlled fluidics with valved cannulas, smaller gauge surgery evolving from 23g to 27g, and excellent widefield imaging systems.

Surgical management of the ILM has benefitted from improvements in instrumentation, especially the ability to image and visualize the ILM. In the United States, ICG is used, and outside of the U.S., membrane blue or membrane blue-dual is used for staining. All of these staining elements are outstanding, and toxicity issues that are shown in the laboratory may not translate into clinical impact on our patients.

Approaches can include “pinch and peel”, in which you pinch, release, and peel, and also the ability to use a scraper or a Flex Loop, to gently tease the ILM away from the retinal surface.



It’s critical to stain the ILM with ICG or membrane blue, then peel the ILM. The staining is often patchy because of concomitant membrane even after removal of the posterior hyaloid.

The algorithm for DME management is intravitreal pharmacotherapy first, surgical management second, and then long-term follow up. The patients must be managed aggressively after surgery; they have recurrent DME and require a targeted approach.

So, ILM peeling is beneficial, ILM staining is important, all of the macular traction should be removed, and the inflammatory response should be suppressed. Then provide excellent follow-up care with intravitreal treatment using SD-OCT guidance for the best anatomic and visual outcomes.

Session 9:

OCULAR ONCOLOGY

Using Imaging to Help Diagnose Ocular Tumors – *Prithvi Mruthyunjaya, MD*

Multimodal imaging in ocular oncology has become irreplaceable for the diagnosis, confirmation, and risk stratification of potentially malignant intraocular tumors.

There are four main imaging technologies used

1. Optical coherence tomography (OCT) – provides information about lesion thickness, the morphology, and surface features associated with choroidal tumors
2. Fundus autofluorescence – used to confirm high risk features such as lipofuscin, and helps confirm the status of the RPE
3. Ultrasound – the gold standard for determining and quantifying lesion thickness, and determining internal reflectivity
4. Fundus photography – very important to document the lesion and help understand the extent of the borders of the tumors.

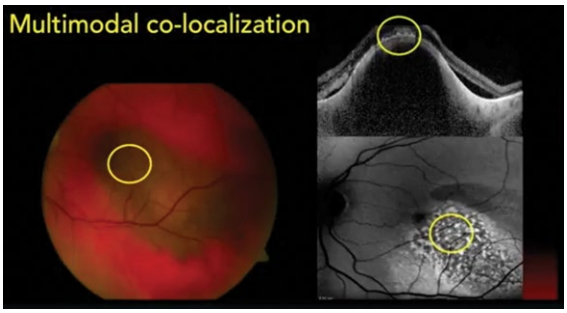
The information included here will focus on the first two imaging modalities.

Enhanced depth imaging OCT is very important, to allow deeper penetration of the signal to help better identify the full choroidal component of the lesion, as the scleral-choroidal junction can be seen better. Commercially available software tools within the systems can be used to manually measure the choroidal thickness of these tumors, and even the retinal component of the tumors. This can allow more accurate measurements of thinner tumors. There are some limitations, however. These measurements are not possible in tumors greater than approximately 2.5mm thick, there may be some inconsistency in imaging the scleral-choroidal junction in tumors, and OCT cannot be used to measure the base of the tumors.

OCT morphology helps in aiding diagnosis, and OCT can identify surface alterations that may lead to a higher or lower risk profile for a tumor. Intraretinal fluid collections, retinal thickening, and alterations in the RPE are important to identify, as are subretinal deposits, and subretinal fluid.

OCT angiography is developing in its role in ocular tumors, but so far there is not a lot of information. There are some patterns developing. Choroidal nevi and melanocytoma seem to show abnormal or absent flow in outer retinal layers, but relatively preserved choriocapillaris. Tumors like choroidal melanomas or choroidal osteomas show dense irregular networks in outer retinal layers and the choriocapillaris.

Fundus autofluorescence is important in helping to identify high risk hyper-autofluorescent components of tumors that would suggest the presence of high risk lipofuscin. Some tumors can have a mixed pattern that shows also low risk areas with hypo-fundus autofluorescence that can indicate chronic RPE atrophy, or fibrotic or even dead RPE.



Multimodal techniques can be used to colocalize the clinical appearance of lipofuscin on fundus autofluorescence and on OCT to help with diagnosis.

Also interesting is the use in clinically invisible retinoblastoma of hand-held OCT scanning at the time of examination, under anesthesia in children.

Multimodal imaging in ocular oncology can confirm and enhance clinical diagnosis, it's important in the accurate identification of high risk features, and it extends beyond the clinic to the OR.

Future Therapeutics for Ocular Oncology – *Arun D. Singh, MD*

Oncology overall is moving more toward targeted therapies, which are slightly different than chemotherapy. They are based upon the pathways that are involved in the pathogenesis, and targeting molecular mediators. In contrast to chemotherapy they are more cytostatic than cytotoxic. And it's basically looking at progression-free survival rather than overall survival.

Looking at uveal melanoma, there is 95% tumor control with radiation therapy. But vision loss is a very important consideration and is very common with radiation, occurring in more than 50% of cases, with the onset typically delayed.

There are many factors involved in vision loss. It can involve the loss of RPE, loss of choriocapillaries, loss of pericytes, loss of endothelial cells, leakage, etc. Overall it can be said that radiation retinopathy is untreatable, and even if there's some benefit with anti-VEGF agents and steroids it's short term and partial.

The best idea then is to avoid radiation retinopathy, which is one current challenge in oncology. The prescribed dose may be able to be reduced (typical dose is 86 Gy), as well as the scatter of radiation, by using some new designs, and it may be possible to reduce the radiation toxicity by use of steroids or other agents. There may also be development of alternatives to radiation therapy as treatment of primary tumor.

Regarding reducing the dose, a systematic review of data from multiple studies showed with a higher dose, near 100 Gy, the recurrence rate seems to be less than with a lower dose of around 65 Gy, but the difference was not statistically significant; the recurrence rate using the lower dose was not statistically higher. This may indicate that the standard dose of 85 Gy can be reduced, but it's still too early to know.

As for reducing scatter of the radiation, the COMS plaques currently being used were designed in 1985. There need to be improvements to this old design. One potential new idea is the Eye Physics Isoaid 917 plaque. Studies done on theoretical dosimetry show that in 17% to 20% of cases, the radiation dose to the disc and macula would be reduced with newly designed plaques.

Methods for reducing the radiation toxicity may include use of steroids or other agents, and clinical trials of these agents may be done using only at-risk patients.

An alternative to radiation therapy that is generating excitement is AU-011, a first-in-class targeted therapy that uses viral nanoparticles that bind selectively to melanoma, and then laser is used to activate them and help resolve the tumor. This has recently been approved by the FDA and trials will begin soon.

Looking toward a more systemic approach, which will be an adjuvant therapy for uveal melanoma (additional therapy on top of primary treatment), the logic for this is that over the years, the survival rate has not improved. Although eyes and vision are sometimes saved, justice hasn't really been done to the patient in terms of survival. Metastasis in uveal melanoma is an early event, preferentially to the liver. There are ways to predict which patients are at risk; there are prognostic tests available.

In a very broad sense, there are two types of uveal melanoma, nonmetastatic and metastatic, and the difference is really in metastatic, micrometastases converts into macrometastases, through mechanisms that are not yet understood. Some genetic alternations are starting to be understood in the pathways. Past studies included all patients, not just at-risk patients, so the fact that 50 percent of the patients in those studies did not have metastasis was simply because they weren't at risk to do so. Future studies can identify high risk patients and only include them, and pathways can be looked at to choose potential drugs for targeted use.

Intra-arterial Chemotherapy versus Intravenous Chemotherapy for Unilateral Retinoblastoma. Who wins? - *Carol L. Shields, MD*

This discussion will look only at unilateral retinoblastoma (RB), and two important therapies, intra-arterial chemotherapy (IAC) and intravenous chemotherapy (IVC).

The decision of which therapy is better is based on a balance of factors, including systemic safety, globe preservation, and visual potential. For years, the only approach was enucleation. In the 2000s, there was a choice between enucleation and IVC. In 2008 IAC became an alternative, which now is used without hesitation in some cases, and enucleation would not be considered unless it is a very advanced case with concerns for optic nerve invasion.

There are different ways to give chemotherapy for RB:

1. Intravenous – injection of vincristine, etoposide, and carboplatin into a peripheral vein
2. Subtenons – this is not used any more
3. Intra-arterial – injection of the "magic bullet" melphalan, sometimes combined

with topotecan, through the femoral artery

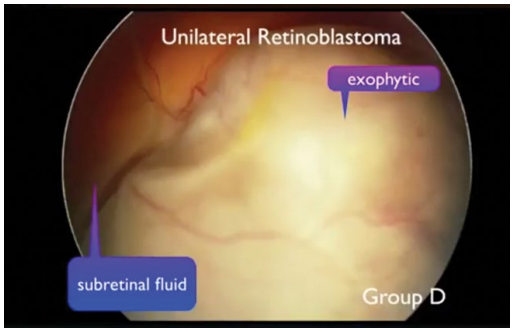
4. Intravitreous – injection is given directly into the eye with melphalan or topotecan

Generally, IVC is used for bilateral disease, and IAC for unilateral disease. Enucleation is still performed for very advanced eyes with no hope for vision, high-risk eyes, unreliable parents, or where chemotherapy is not available.

There is some agreement, and some disagreement, on treating RB. But huge progress has been made, and this is the most successfully treated pediatric cancer. And there is mostly agreement that IAC should be used for unilateral RB.

In a head–to-head comparison of IVC vs IAC for unilateral RB, a recently published report1 shows the IAC group had tumors that were significantly larger with greater base and thickness, more vitreous seeds, and total RD seen in significantly more eyes, than the IVC group. So these were more advanced eyes that were treated with IAC compared to those treated with IVC.

Overall, the results showed no difference in the treatments. But if you break it down into the categories of retinoblastoma, A, B, C, D, and E, there was double the success rate in group D, significantly more eyes saved in group D retinoblastoma. So the conclusion was there was significantly improved globe salvage with IAC for group D retinoblastoma, and control was significantly better for solid tumor, for subretinal seeds, and for vitreous seeds.



So IAC is better than IVC for unilateral retinoblastoma, because in 75% of cases unilateral retinoblastoma is group D or E. However serious complications have been reported, including metastatic disease, severe vasoconstriction, and even stroke, so caution needs to be exercised.

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1. Shields CL, Jorge R, Say EA, Magrath G, Alset A, Caywood E, Leahey AM, Jabbour P, Shields JA. Unilateral Retinoblastoma Managed With Intravenous Chemotherapy Versus Intra-Arterial Chemotherapy. Outcomes Based on the International Classification of Retinoblastoma. Asia Pac J Ophthalmol (Phila). 2016 Mar-Apr;5(2):97-103. doi: 10.1097/APO.0000000000000172.

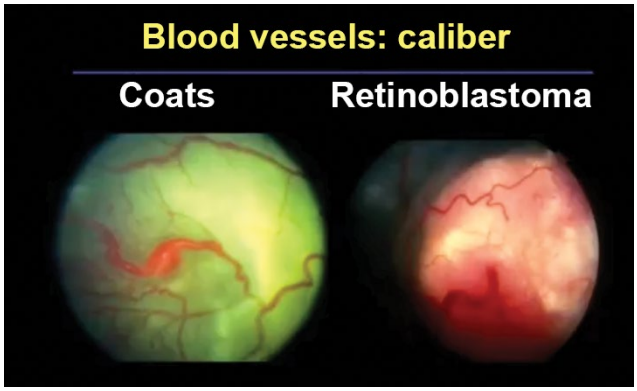
Ophthalmoscopic Differentiation of Coats' Disease from Retinoblastoma – *Jerry A. Shields, MD*

Coats' disease and retinoblastoma can be clinically similar, but the differentiation is very important to achieve better patient care, and avoid some of the medicolegal issues that have arisen from misdiagnosis of these cases. A study of 604 cases[1] of pseudoretinoblastomas found that 40% of the patients referred into the oncology service did have Coats' disease.

It is possible in many cases to differentiate Coat's disease from retinoblastoma by looking at clinical features. Possibly helpful in differentiation are the age, gender, family history, and laterality. These are not highly reliable, however. It's better to look at the following clinical findings:

1. Pupillary reflex – more yellow is typical of Coat's disease, more white is typical of RB
2. Findings in the anterior chamber – hyphema and neovascularization can be found in both conditions, but in Coats' disease when there's true anterior chamber involvement, the cholesterol can migrate into the anterior chamber. In RB, at least in the endophytic type, they get a white pseudohypopion, which is never seen with Coat's disease
3. Clarity of vitreous – in Coats' disease, looking with an ophthalmoscope, you'll usually see yellow material beneath the retina, and clefts of cholesterol. In RB you'll see the white reflex
4. Color of subretinal fluid – in Coats' disease, if you have a clear enough media, which is usually the case, you can see a yellow reflex called xanthocoria, and in RB of the exophytic type, you see more of a white-grey reflex behind
5. Caliber of retinal vessels – in Coats' disease the blood vessels have irregular dilations as you look across the retina, but in RB they dip back into the underlying tumor
6. Course of retinal vessels – in Coats' disease you can follow the vessels all the way out to the aura, whereas in RB they often stop and dip into the tumor
7. Macular appearance – Coats' disease patients have a macular reflex when they're referred in. But when you look at them it's a yellow material in the macular area, and no dilated feeder vessels. In RB, there is a white mass, with dilated feeder vessels that come and go

Ancillary studies are also well known and always done, such as ultrasonography and fluorescein angiography. A retinoblastoma on ultrasonography will often show a mass with flecks of calcification. And fluorescein angiography will show the telangectasias in Coats' disease, but not in RB.



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Session 10:

PEDIATRICS, PEDIATRIC SURGERY AND GENE THERAPY

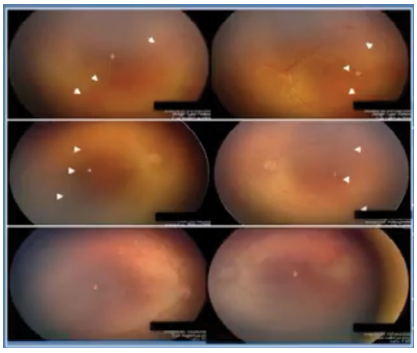
New Therapies for Retinopathy of Prematurity (ROP) – *Paola Dorta, MD*

Conventional laser photocoagulation is not effective in some cases of posterior ROP, and laser ablation of the vascular retina is sometimes too destructive. It was a logical choice to look at anti-VEGF therapy as a possible treatment.

In 2008 this group started using bevacizumab in a group of patients that had progression of the disease despite laser, and then in babies with posterior Zone 1 without macular development. The area where the macula should develop was not lasered, but instead bevacizumab was injected after photocoagulation.[1]

Subsequently, bevacizumab was used as a primary treatment, and the results of the study showed all eyes had regression of the disease with no need for further treatment. Vascularization of the retina following treatment showed a normal, though slower, pattern, and there was less destruction and better refractive outcomes than with laser.

There are important issues to be considered when using anti-VEGF therapy:



1. Local safety
    a. Anti-VEGF therapy appears to be safe locally, allowing the development of a vascular and functional retina.
2. Systemic safety
    a. Both bevacizumab and ranibizumab can migrate from the eye to the systemic circulation and reduce the serum level of VEGF in patients with ROP
    b. The safety of anti-VEGF agents in premature babies has not been established
3. Drug and dose
    a. Bevacizumab and ranibizumab have been used with good results; it's possible a lower dose or different drug could give the same local effect with less systemic risk

The issue of retreatment raises questions. The current series had a lower incidence of retreatment than some previous reports. One factor that may influence this is patient population, whether more immature with different evolution or more mature and sicker, different genotypes, etc. If there is progression of the disease after use of anti-VEGF, and vessels are already in Zone 2, laser should be applied.

Regarding anti-VEGF and ROP retinal detachment, there are two situations to look at. First is using the anti-VEGF agent as an adjunct in ROP retinal surgery, and the other is in ROP retinal detachments following the use of anti-VEGF drugs to treat type 1 ROP.

The presence of vascular activity is the major problem when operating ROP detachments. For the purpose of inducing regression of the neovascularization, anti-VEGF can be injected prior to the surgery.

There are two groups of retinal detachments after using an anti-VEGF agent to treat ROP:

Group 1: The detachment develops shortly after the injection due to a change from vascular to fibrous tissue that pulls on the retina and causes ROP crunch. A vitrectomy in the presence of fibrous tissue is very important.

Group 2: The detachment has a delayed onset, despite an initial regression. Patterns of regression and recurrence are not yet well known in patients treated with anti-VEGF. Therefore extended follow up after injections must be performed. If follow up is not possible, use of laser is advised.

Abnormal macular configuration present in preterm children, and laser-treated ROP, was also found in patients treated with anti-VEGF. Remarkably, by looking at the retina images it is not possible to determine the macular configuration of these eyes, thus OCT is necessary.

So in current management of ROP, consider the use of an anti-VEGF agent as primary treatment, depending on the zone of the disease, and as an adjunct in progressive cases.

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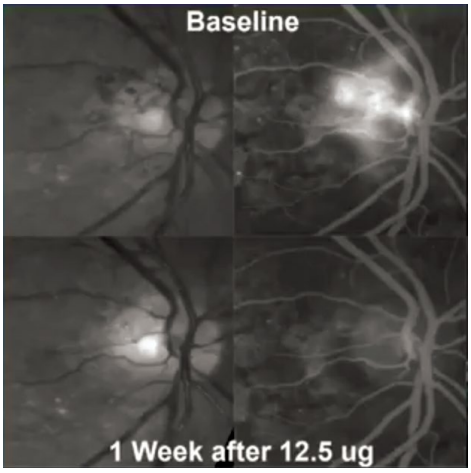
Are There Safety Concerns with Bevacizumab for ROP? – *Robert L. Avery, MD*

The BEAT ROP study[1] showed that bevacizumab can be quite useful in the treatment of ROP, but it underserved the systemic risk with statements saying things such as bevacizumab does not penetrate the full thickness retina. It had already been shown that it does penetrate the full thickness retina, and that bevacizumab and ranibizumab and aflibercept leech into the bloodstream in levels that can cause an inhibition of VEGF.[2,3] The systemic exposure is about 40- to 70-fold higher for bevacizumab than ranibizumab. It also reduces the free-VEGF in the bloodstream, more with bevacizumab and aflibercept than ranibizumab.



A study of bevacizumab pharmacokinetics in ROP babies found that it is present in the bloodstream for at least 60 days with a reduction in VEGF.[4] It also found that the serum maximum concentration was 9-fold higher than what had been seen in adults. Another study looked at bevacizumab vs ranibizumab for use in ROP for the effects on

VEGF and found what had been found in adults, that bevacizumab lowers systemic VEGF, but not so much with ranibizumab.[5]

Fellow eye effects had been noted in earlier research, which indicated the doses being used were much higher than what could create a change in the retinal neovascularization. So lower doses were studied and it was found that doses of 1/100th to 1/200th of a typical dose could cause regression of neovascularization.[6] This is a level similar to what has been found in ROP babies about 2 weeks after injection4. So it's no surprise that fellow eye effects are seen.

It appears that bevacizumab has a longer duration of effect in ROP treatment than ranibizumab. This is not what is seen in use in treating AMD or in diabetes. This may be because bevacizumab lingers in the bloodstream for 3 weeks, whereas ranibizumab clears in about 2 hours. It has also been seen in an animal model that an bevacizumab injection into one eye leeches across the bloodstream and affects the fellow eye.

ROP babies often have lung disease. VEGF inhibition mimics BPD in animals, and inhibits surfactant production. There are also things other than VEGF affected by bevacizumab injection. There is a reduction in a number of cytokines, which could affect lung development. Reduced cerebral blood flow has been reported after bevacizumab injection in ROP, and neurodevelopmental outcomes may also be affected with use of bevacizumab to treat ROP.

In summary:

1. Anti-VEGF therapy has been helpful in ROP
2. Injections get into the bloodstream and reduce VEGF (bevacizumab more than ranibizumab)
3. More pronounced in ROP than in adults, with Cmax 9 times higher (biologically relevant) and VEGF reduction>60 days after bevacizumab
4. This is evidenced by fellow eye effects
5. There is biologic plausibility for potential adverse effects on lung and neuronal development, with some inconclusive clinical trial data
6. Ranibizumab may be theoretically preferred over bevacizumab in ROP
7. Prospective clinical trials are indicated to evaluate these therapies

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2. Shahar J, Avery RL, Heilweil G, Barak A, Zemel E, Lewis GP, Johnson PT, Fisher SK, Perlman I, Loewenstein A. Electrophysiologic and retinal penetration studies following intravitreal injection of bevacizumab (Bevacizumab). Retina. 2006 Mar;26(3):262-9.

3. Avery RL, Castellarin AA, Steinle NC, Dhoot DS, Pieramici DJ, See R, Couvillion S, Nasir MA, Rabena MD, Le K, Maia M, Visich JE. Systemic pharmacokinetics following intravitreal injections of ranibizumab, bevacizumab or aflibercept in patients with neovascular AMD. Br J Ophthalmol. 2014 Dec;98(12):1636-41. doi: 10.1136/bjophthalmol-2014-305252. Epub 2014 Jul 7.

4. Kong L, Bhatt AR, Demny AB, Coats DK, Li A, Rahman EZ, Smith OE, Steinkuller PG. Pharmacokinetics of bevacizumab and its effects on serum VEGF and IGF-1 in infants with retinopathy of prematurity. Invest Ophthalmol Vis Sci. 2015 Jan 22;56(2):956-61. doi: 10.1167/iovs.14-15842.

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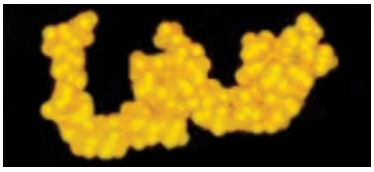
6. Avery RL, Pearlman J, Pieramici DJ, Rabena MD, Castellarin AA, Nasir MA, Giust MJ, Wendel R, Patel A. Intravitreal bevacizumab (Bevacizumab) in the treatment of proliferative diabetic retinopathy. Ophthalmology. 2006 Oct;113(10):1695.e1-15.

Genetic Testing for Inherited Retinal Diseases – *Byron L. Lam, MD*



There are many benefits to genetic testing

1. It leads to more accurate diagnosis and prognosis
    a. The same genotype can result in different clinical presentations
    b. It's important to use to rule out a suspected syndromic disease
2. It also helps to determine inheritance accurately
    a. This improves patient counseling
    b. It allows identification of affected or carrier family members
3. Essential for some clinical trial participation, especially gene therapy clinical trials

Before genetic testing, it is important to determine the clinical diagnosis as accurately as possible, using indicated testing, and also to obtain an accurate family history. It's also important to recognize that X-linked recessive inheritance may mimic recessive inheritance when only siblings are affected, and may mimic dominant inheritance if there are manifesting female carriers. Also remember that the key feature of autosomal dominant inheritance is male-to-male transmission.

Although the knowledge of different genotypes that are mapped and identified for hereditary retinal diseases has grown, not all genotypes are known. A negative genetic result does not necessarily exclude inherited retinal disease. An appropriately certified lab (CLIA or equivalent) should always be used for genetic testing. There will be some international barriers to such testing.

There are two strategies for genetic testing. One is specific genotypes and phenotypes to look for simpler hereditary retinal diseases such as achromatopsia

and choroidemia, and the other is panel-based sequencing for more complex disorders like retinitis pigmentosa, Leber congenital amaurosis, or Usher syndrome. Sometimes organizations can be found to help patients with the costs of this testing.

Genetic testing is not foolproof and is dependent on the careful interpretation of results by the lab. Disease-causing genotypes are determined from previously reported genotypes, or the effects of new genotypes predicted by type and change of protein structure and function (pathologic score). Now, with next generation sequencing (NGS) and whole exome sequencing (WES), variants of uncertain significance (VUS) will be found. This will affect patient counseling; for example, a patient who has a specific genotype that is responsible for a hereditary retinal disease may also be a carrier for other inherited retinal disease. It's important to tell the patient the certainty of the findings, explain the inheritance and implication for family members, and talk about the current and anticipated treatments and clinical trials.

Overall, genetic testing has become beneficial for inherited retinal diseases, and benefits patient care. Accurate early diagnosis and rapid genetic testing will become more important and routine in future practice with approval of treatments. For clinical trials, it is time to think about identifying patients with LCA, Stargardt disease, choroideremia, achromatopsia, X-linked retinoschisis, and Usher syndrome.

RPE65 Injection – *Adda Villanueva, MD*

This discussion about functional vision presented a case, with the objective of properly evaluating retina function during a pediatric retina clinic.

A mother brought in her daughter and said, "My child is not normal." She had spent 5 to 6 years seeing general practitioners, pediatricians, retina specialists, and neurologists, and had gotten a psychiatric referral. All ancillary tests, fundus pictures, ERG, OCT, were within normal limits. The only thing really noticeable was that her pupillary response showed "large hippus" followed by nystagmus and crying. The mother said the symptoms were most noticed around dawn (early in the morning) or dusk (around 6 or 7 pm). A molecular test was performed for RPE65 mutation.

The patient was approximately 6 years old when presenting to the clinic, and it took some months to get the RPE65 mutation. Six years later, the patient's vision deteriorated to hand motion at 10 cm. So an injection was done with AAV2-hRPE65v2 in both eyes. The results were functional vision and no pupil abnormality.

In the clinics, even with all the ancillary tests, it's very difficult to know whether something is RPE65, or which type of LCA or inherited retinal dystrophy it might be. Pupils, and the child's behavior, can be helpful. Listen to what the parents are saying. But then it must be decided if this is amaurosis, in a bigger diagnosis, or can it be narrowed down to which type of inherited retinal dystrophy it is. Genetic testing is vital; the Retina Genomics Institute of Mexico now tests for 238 genes.

Session 11:

RETINAL SURGERY

Autologous Retinal Transplant Updates – *Tamer Mahmoud, MD, PhD*

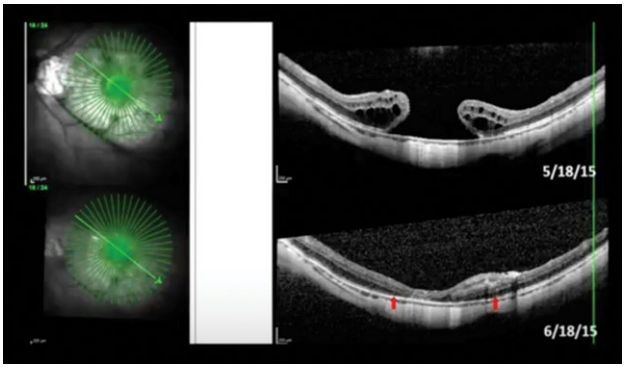
This talk focused on different techniques for autologous retinal transplants using case presentations.

The first case was a very high myopic patient who had had multiple prior surgeries for a detachment and a large macular hole. Oil was removed, she had a buckle, and she still had a persistent 1100-micron hole with eccentric fixation.

A free peripheral ILM flap to close the hole was planned. A problem that exists with a deep staphyloma is that any dye used will fill the staphyloma, and it's very difficult to get peripheral staining. Thinking that the retina was very thin, the surgeon decided to get a piece of the neurosensory retina and cover the hole to prevent a recurrent detachment.

Working bimanually, the surgeon moved to the center of the fovea, then with a dual bore cannula and PFC stretched the piece of retina over the area of the fovea. The eye was filled completely with PFC, and then a direct PFC-silicone oil exchange was done to keep it in place. It's tricky at the base of the staphyloma to be sure the transplant doesn't move from side to side at the end. The hole did not close, but the transplant closed it.1,2

The exciting part is that as the hole closed, the vision improved and the patient developed a central retina, and the transplant started thickening and developing outer layers, which was very unexpected. Colocalization with microperimetry showed increases not only on the adjacent retina but over the area of the transplant as well. The multifocal ERG corresponded in both eyes.



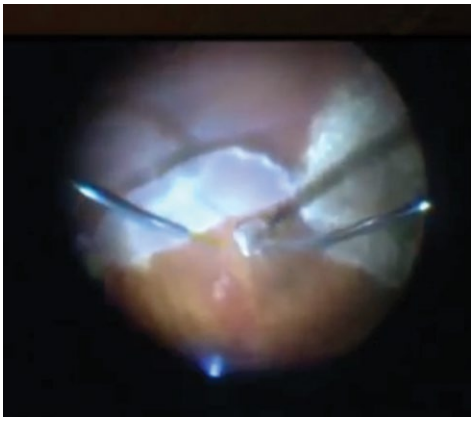
In another case, a patient with high myopia came in with a deep staphyloma. An inverted ILM flap was tried but the hole stayed open, so the surgeon decided to go in for a retina flap. This patient was not pseudophakic, this was an ICL, and it was difficult to work on the edge of the staphyloma. The technique here changed; instead of doing diathermy the surgeon did only laser, marked the area with a finesse loop, and only did diathermy at the point where the blood vessel is crossing, to then create a micro hole and go in with pneumatic scissors to cut all the way around. The field was much more stable in this case than in the one described above, working under PFC, less bleeding, and everything well controlled. You can work unimanually and move the transplant over the area of the hole. Because of the myopic degeneration, you

can see the pigmented edge of the transplant, you can adjust it and extend it and stretch it over the hole with the dual-bore cannula, then gradually add PFC and do a PFC-silicone oil exchange, and close. That patient is now 20/400 and will have the cataract removed.

A third, very complicated case demonstrates a different technique. The patient had light perception vision for more than one year because of urosepsis, and had had a renal transplant. He had multiple prior surgeries. The surgeon went in, removed the lens, and peeled all the membranes for the PVR. There was a very large hole, so the surgeon thought he could get remnants of the ILM and close the hole. The work was done under PFC because of the detachment. However, there weren't enough tissue remnants from the ILM or ERM to cover the hole. Since an inferior retinectomy was already planned, the surgeon decided to use a piece of the peripheral retina.

A lot of work has been done about peripheral Muller cells that can act as stem cells for photoreceptors. This is one of the main hypotheses of how this works. The surgeon marked the peripheral retinectomy and then decided he could get a piece of inferior retina instead of superior retina, for this case. He marked the inferior retinectomy edge, with diathermy cut it all the way around, and had already marked the peripheral island of retina that he wanted to use, larger than the size of the hole. That area of the flap must be protected, so you don't aspirate it, so use a very high cut rate and very slow suction.

After marking the peripheral retinectomy, you move to the fovea. One of the challenges encountered early when using this technique, especially for retinal detachment, was to keep the piece of retina in the preretinal space, exactly in the space. Instead of going preretina, you can go subretina, because you have a macular hole. So you reflect the retina all the way back, go in with the dual-bore and the forceps, reaching all the way to the hole. In many cases we cannot reach all the way to the hole, but you can reflect the retina and because you have a macular hole you can go with the dual-bore cannula through the hole, very slight suction. The transplant centralizes over the area of the hole. You already have the dual-bore so you can add PFC and a direct PFC-silicone oil exchange. The rest of the case was routine as usual for PVR. Post-op OCT showed two layers of retina, rather than the edge of the transplant being against the edge of the retina. But in post-op week 1 the two layers became one, and there was a nice foveal depression. The edge between the transplant and the host retina was seen, but then was almost gone at 1 month and 6 months. The patient had light perception for one year, 20/400, then gradually improved to 20/160. At one year the oil was removed, another retinotomy was performed because he had early PVR superiorly, added oil, and he's 20/100 at one year.



There are many hypotheses about these transplants, some can be classified into contexts. Like ectopic synaptogenesis at the edge of the transplant, others like Muller cells and growth factors, there is discussion about material transfer between stem cells and surrounding degenerated cells to help them survive. A key in the future is positioning the transplant, and where we get the graft, because of the wide spectrum of changes in morphology we have seen.

So autologous retinal transplant is not just a plug for macular holes, it is a true transplant, with morphological and functional changes. There is no need for immunosuppression, and there are many implications for macular diseases.

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1. Grewal DS, Mahmoud TH. Autologous Neurosensory Retinal Free Flap for Closure of Refractory Myopic Macular Holes. JAMA Ophthalmol. 2016 Feb;134(2):229-30. doi: 10.1001/jamaophthalmol.2015.5237.

2. Grewal DS, Fine HF, Mahmoud TH. Management of Challenging Macular Holes: Current Concepts and New Surgical Techniques. Ophthalmic Surg Lasers Imaging Retina. 2016 Jun 1;47(6):508-13. doi: 10.3928/23258160-20160601-01.

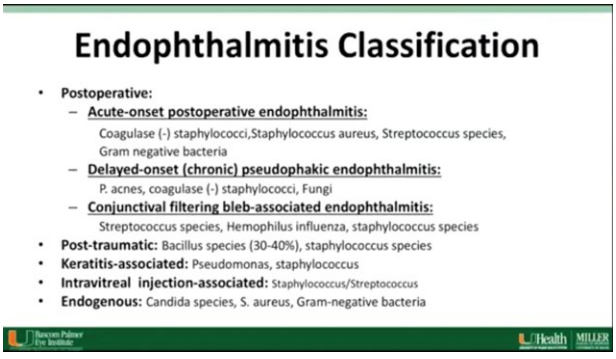
Vitrectomy in the Endophthalmitis Patient – *Harry W. Flynn, Jr., MD*

Vitreoretinal surgeons have become more involved in management of endophthalmitis. Presented here are techniques and outcomes of vitrectomy in endophthalmitis.

There are three main points in this presentation:

1. Use a 6mm infusion cannula to avoid suprachoroidal effusion
2. The uninvolved crystalline lens should be preserved during vitrectomy for endophthalmitis
3. EVS guidelines do not recommend against the use of vitrectomy for endophthalmitis cases with visual acuity better than light perception.

Vitrectomy can be used in a broad spectrum of cases, following filtering bleb surgeries, tube placement, routine cataract surgery or trauma, and in chronic endophthalmitis cases.



A classification scheme such as shown here can be useful in predicting the organism that may be involved in particular categories of endophthalmitis.

Vitrectomy is often reserved for the more advanced disease cases, or cases that have recurrence of endophthalmitis. There are benefits and disadvantages to using it.

Benefits of PPV

1. Reduces microbial load and toxins they produce
2. Removal of vitreous membranes and vitreous opacities
3. Allow for obtaining an abundant specimen for achieving a positive culture
4. Improved visualization during follow up to assess posterior segment disease and treatment response

Disadvantages of PPV

1. Need specialized equipment and support staff
2. Done in an operating room setting
3. Anesthesia-related risks

Regarding current PPV options in management, there has been an evolution toward smaller gauge surgery. The key element is making sure that the 6mm infusion cannula penetrates into the vitreous cavity. Use of silicone oil can be reserved for only the most severe cases, and beware of the "boggy conjunctiva."

The presenter prefers to aspirate the initial specimen into a syringe so it can be handed off to a microbiologist for a smear and culture. The remaining specimen is then collected into the cassette, and then finally antibiotics are injected through the cannula at the end of the procedure.

Bascom Palmer, with other centers around the U.S., recently published a study that shows that in delayed vitrectomy for late sequelae of endophthalmitis, the indication for vitrectomy is vitreous opacities, epiretinal membrane, and retinal detachment.[1] Rates of improvement were low but some very bad cases were salvaged.

The microbiologic outcomes have also been reported.[2] The multicenter series showed positive cultures with vitrectomy in about 80%, the most common organism was streptococcus in this series, visual acuity was generally poor but 27% achieved 20/400 or better at last follow up, and the rate of enucleation was low (4.3%).

Regarding the crystalline lens, Drs. Townsend and Flynn presented a series of cases in which the lens was uninvolved.[3] These often were cases of bleb-associated endophthalmitis, or trauma, or endogenous endophthalmitis.

The Endophthalmitis Vitrectomy Study (EVS), conducted from 1990-1994, utilized 20g vitrectomy, which is rarely done. But the study was important because it was a randomized prospective clinical trial involving 420 patients with acute onset endophthalmitis within six weeks of cataract surgery or secondary IOL implantation. The goal of vitrectomy in the study was to remove at least 50% of the foreign vitreous; there was no peripheral shaving or dissection of ERM. The study evaluated vitrectomy vs vitreous tap as initial treatment, and it also evaluated systemic antibiotics vs no systemic antibiotics.

The results showed that for eyes that were hand motion or better, there was no difference in the vitrectomy group vs the tap and inject group, in this selected series

of patients. However, if patients had light perception vision, vitrectomy was clearly better, with a 3x increased chance of 20/40 or better, a 2x increased chance of 20/100 or better, and a 50% decrease in chance of being worse than 5/200. So, the study did not conclude that vitrectomy is contraindicated in this group of patients. Dr. Flynn frequently uses vitrectomy in eyes with hand motion or better visual acuity.

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1. Thomas BJ, Mehta N, Yonekawa Y, Sridhar J, Kuriyan AE, Relhan N, Liang MC, Woodward MA, Witkin AJ, Shah C, Flynn HW Jr, Garg SJ, Wolfe JD. Pars plana vitrectomy for late vitreoretinal sequelae of infectious endophthalmitis: Surgical management and uutcomes. Retina. 2017 Apr;37(4):651-656. doi: 10.1097/IAE.0000000000001208.

2. Sridhar J, Yonekawa Y, Kuriyan AE, Joseph A, Thomas BJ, Liang MC, Rayess N, Relhan N, Wolfe JD, Shah CP, Witkin AJ, Flynn HW Jr, Garg SJ. Microbiologic spectrum and visual outcomes of acute-onset endophthalmitis undergoing therapeutic pars plana vitrectomy. Retina. 2016 Oct 21. [Epub ahead of print]

3. Townsend J, Pathengay A, Flynn HW Jr, Miller D. Management of endophthalmitis while preserving the uninvolved crystalline lens. Clin Ophthalmol. 2012; 6:453–457. Published online 2012 Mar 20. doi: 10.2147/OPTH.S26683

Vitreomacular Interface Diseases and their Management – *Susanne Binder, MD*

Anomalous PVD is a partial PVD with persistent attachment in the macular region, of anomalous strength, to one of more structures of the posterior pole, resulting in tractional deformation of retinal tissues. Liquefaction or gel contraction outpaces detachment of the vitreous cortex, and abnormal adhesion is present from the cortex to the ILM. Local anatomic variations (myopia, trauma, surgery) play a role as well. OCT has helped tremendously to better understand and classify vitreomacular adhesion, tractions, and macular holes.

The pathogenesis of vitreomacular traction is unclear. It could be inflammation, oxygen, or something else. OCT shows that tractive forces are one of the reasons for anatomic changes in the macula. Its diagnosis is important for further management.

Vitreomacular traction (VMT) is defined as macular attachment of the vitreous cortex within a 3mm radius of the fovea, and distortion of the foveal surface with structural changes and elevation, but no full thickness interruption of all layers. Focal traction (distorted surface, elevated foveal floor, and pseudocysts), and broad traction (generalized retinal thickening, vascular leakage on FA, macular schisis, cystoid macular edema), are subclassifications of VMT.

Clinical presentation of VMT is symptomatic metamorphopsia, deterioration of visual acuity, and visual loss.

Should the approach be watch and wait? 81% of patients have cystoid macular changes, and 67% still have cystoid macular changes up to 60 months, with a mean loss of 2 lines of vision.

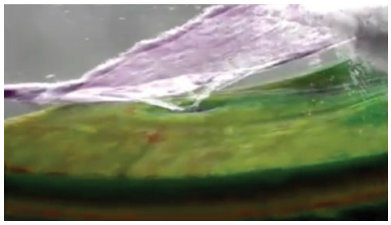
In an example of classic VMT, smaller than 1.5mm, no ERM with intraretinal cyst,

VA is 0.8, the presenter recommends enzymatic vitreolysis, a foveal sparing vitrectomy, or vitrectomy with intra-surgical OCT.

In an example of juxtafoveal traction, greater than 1.5mm, within 3 mm of the fovea, full visual acuity and no symptoms, the recommendation is to observe, and only do vitrectomy if it progresses.

And in a third example, multiple vitreoretinal tractions with an epiretinal membrane, and vision has deteriorated to 0.3, the choice is to perform a vitrectomy.

Macular holes have been divided into primary and secondary, and subclassified into small, medium, and large. For a full thickness macular hole with vitreous traction the treatment would be either pharmacologic vitreolysis or vitrectomy. The fellow eye is at increased risk to develop a full-thickness macular hole, and the recommendation of how to proceed with that eye is observation with OCT.



For lamellar macular holes, surgery is indicated only if there is a progression in size and traction, and vision worsens.

For macular pseudo-holes, clinical diagnosis is not always easy. They look similar to a small full thickness macular hole. However, they have no loss of foveal tissue, and centripedal traction or combined traction. If surgery is done it's to remove the ERM, if the patient has symptoms.

In summary:

1. OCT has brought better insight into vitreomacular interface diseases, and improved classifications
2. "Watchful waiting" of VMT can lead to irreversible retinal damage, cysts, and hole formation
3. Spontaneous separation of VMT occurs rarely
4. Vitreous surgery is indicated if there is vision loss or disease progression, but surgical trauma to the retina is possible as well as other complications
5. Pharmacologic treatment to vitreous separation may separate the vitreous in a timely way, in carefully selected cases, complications are also possible here

Tractional Detachments—Viscodissection, En Bloc Dissection with Small Gauge, Perfluoro-N-Octane (PFO) – *Maria H. Berrocal, MD*

Tractional retinal detachments (TRDs) can be associated to many vascular conditions (vein occlusions, sickle cell, Eales disease), but they are usually more common in diabetes. Indications for surgery include TRDs involving the fovea or posterior pole, progressive detachments that are threatening the macula, or metamorphopsia.

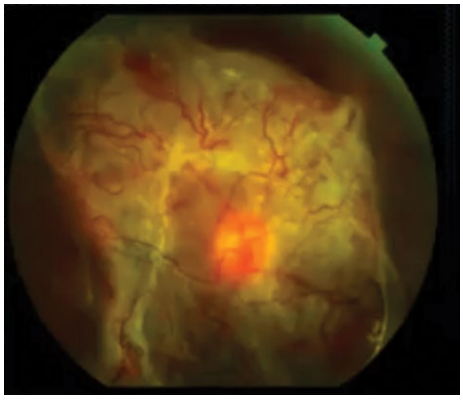
The purpose of vitrectomy is to remove opacities, because often they are accompanied by vitreous hemorrhage; to relieve traction; and to separate the fibrovascular tissues from the retina. Avoiding iatrogenic breaks is paramount. It is crucial because otherwise it converts into a rhegmatogenous component and the surgeon is forced to remove all of the fibrovascular tissue. In TRDs mostly just the traction in the posterior pole needs to be removed, but if there is a break everything must be removed, which makes the prognosis worse.

A number of things can be helpful for the surgical sequence:

1. Treat with a VEGF inhibitor if it is a very vascular case
2. Remove the peripheral vitreous
3. Find the plane
4. Remove all the traction in the posterior pole
5. If there is a lot of fibrovascular proliferation in the periphery, far away, that can be left alone
6. Usually a tamponade is not needed, but if the macula has been elevated, air or SF6 can be used
7. The benefits of smaller gauge vitrectomy are paramount in these cases, particularly because of the reduction of complications

There are several techniques to be familiar with:

1. Viscodissection
2. Perfluorocarbon liquid
3. En bloc dissection
4. Probe dissection
5. Lift and shave
6. Segmentation
7. Bimanual



Sometimes a combination of techniques is useful.

In conclusion:

1. It is important to feel comfortable with the armamentarium of different techniques for diabetic dissection
2. It's very important to avoid iatrogenic breaks
3. There needs to be good intraoperative hemostasis
4. 27g and 25g platforms are advantageous to reduce iatrogenic breaks and postoperative bleeding
5. Most cases require a combination of techniques

Session 13:

MEDICAL RETINA: DIABETIC MACULAR EDEMA (DME) AND DIABETIC RETINOPATHY (DR)

RG7716 – A Novel Bispecific Anti-VEGF/Anti-Angiopoietin-2 Monoclonal Antibody for Neovascular Age-related Macular Degeneration and Diabetic Macular Edema – *Pravin U. Dugel, MD*

This presentation shares information about an exciting new molecule, RG7716.

Ang2 and VEGF-A are key drivers of angiogenesis. The angiopoietin/Tie2 axis modulates endothelial cell stabilization. Ang1 will bind to the Tie2 receptor, which is a tyrosine kinase receptor, and is essential for cell survival and homeostasis.

In times when there is an angiogenic switch (hypoglycemia, and with certain cytokines and growth factors), Ang2 is upregulated. Ang2 is an antagonist of Ang1, and also binds to the Tie2 receptor. Ang2 will cause the endothelium to be destabilized leading to leakage and the attraction of inflammatory factors. Often coupled with this is an upregulation of VEGF-A, which can cause increased permeability as well as sprouting of abnormal and unstable vessels.

RG7716 neutralizes both Ang2 and VEGF-A, and maintains homeostasis and a healthy vasculature. Dual inhibition by RG7716 stabilizes the endothelium and maintains pericytes. It also reduces exudation and fluid leakage, and reduces the influx of inflammatory cytokines. VEGF-A increases the permeability of endothelial cells. RG7716 fully reverses VEGF-A induced dysfunction of the endothelial barrier.

Ang2 has been implicated in neoangiogenic pathology and is elevated in the vitreous levels in diseases such as neovascular macular degeneration, diabetic retinopathy and retinal vein occlusion. Ang1 is constitutively expressed to maintain vasculature homeostasis, whereas Ang2 levels are only expressed under pathological conditions. So, given a choice between developing an Ang1 agonist, and an Ang2 antagonist, the choice is an Ang2 antagonist.

RG7716 is a tailor-made ophthalmic bispecific monoclonal antibody that is specifically engineered for efficacy, improved pharmacokinetics, and systemic safety. It utilizes the Roche CrossMab technology and is a single molecule that potently neutralizes both VEGF-A and Ang2. And importantly, it maintains the desired Ang2/VEGF-A ratio with a single clearance rate.

A phase 1 study of RG7716 showed an excellent safety profile, and for efficacy the study showed that a single dose resulted in a median change of 7 letters improvement for the patients, and in the multiple dose arm improvement of 7.5 letters, with a concomitant decrease in central subfield thickness. Three phase 2 studies are now underway (AVENUE, BOULEVARD, and STAIRWAY).

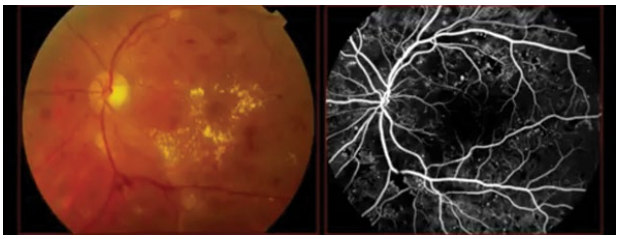
In conclusion:

1. Ang2 levels are elevated in the vitreous of patients with retinal diseases
    a. the “Delta” between normal homeostasis and pathology is Ang2, not Ang1
2. RG7716 met its goal in demonstrating safety and a biological signal in its Phase 1 study
3. RG7716 was well tolerated with an overall favorable safety profile in patients with neovascular AMD
4. Three phase2 studies are now under way to further assess the efficacy, safety and durability of RG7716 in patients with neovascular AMD and DME

Characteristics of Patients with Diabetic Macular Edema Treated with Anti-VEGF Agents According to the Vitreomacular Interface – *Marcio B. Nehemy, MD*

The purpose of this presentation is to evaluate baseline characteristics of patients with diabetic macular edema (DME) and their short-term response to anti-VEGF treatment, according to the vitreomacular interface.

DME is a major cause of central vision loss. Anti-VEGF is an effective treatment. DME has a complex and multifactorial pathophysiology, which could explain differences in response to anti-VEGF agents. These variations may occur for several reasons:



Severity of the disease

1. Age, genetics, comorbidities
2. Baseline visual acuity
3. Absence of surface wrinkling retinopathy
4. Foveal atrophy
5. Perifoveal laser scar

The role of vitreous in the anti-VEGF response has been investigated for retinal vasculopathies, mostly AMD. Most of them showed a better response to anti-VEGF in eyes with vitreomacular adhesion (VMA). For DME studies, it was also suggested that VMA was associated with a better visual outcome at 6 months.

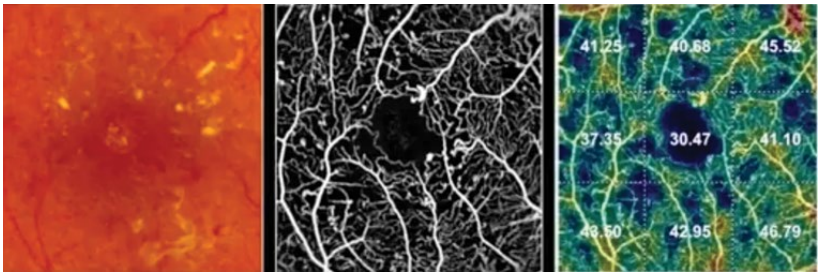
For a better evaluation, this group began a study in 2012, including patients with DME examined between 2009 and 2016. Their conclusions were:

1. Eyes with or without VMA presented anatomic and visual improvement 1 month after intravitreous anti-VEGF

2. At baseline, VMA was associated with thicker central retina
3. In a short-term period (1 month), eyes without VMA had a better visual and anatomic outcome
4. For better VMA evaluation, macular OCT is not enough. Other exams such as biomicroscopy, optic disc OCT and HD-OCT are also needed
5. Additional studies with rigid inclusion and exclusion criteria are still required

New Insights into Imaging DME and DR: Where Are We, and Where Are We Going – Richard B. Rosen, MD, DSc(Hon)

OCT angiography (OCT-A) reveals all of the fine vascular structures in diabetic retinopathy. It can show microaneurysms, vascular loops, nonperfusion, FAZ erosion, venous bleeding, neovascularization, and multiple capillary beds. Currently, however, it is too fast to detect leakage. But it shows exquisite structure of the avascular membranes. In the future we may be able to use a combination of variable scans to be able to differentiate slow flow in neovascular membranes.



One of the striking features about OCT-A is its ability to give us quantitative perfusion mapping, both local and globally.

The current standard for grading diabetic retinopathy is the ETDRS severity scale, which has been around for about 35 years. It measures by summing up the number of lesions and ascribing a number, which gives a risk of progression. Many doctors don't have time or inclination to use this scale in their offices. Something similar can be done with quantitative OCT-A mapping. Using perfusion density mapping is an easy way to translate the images of the details of the fovea, by color coding, which allows differentiating the areas of non-perfusion. Over time as the disease progresses the color coding of the affected areas will become more prominent.

A commercial software application about to be released (AngioAnalytics) gives both superficial and deep plexus, and soon will include the full thickness retina, which will allow patients with cystic macular edema to be followed.

The other very significant thing is that OCT-A reveals vascular defects that are unseen with conventional fundus imaging. So the question looked at was, "How can we assess the significance of these areas of non-perfusion?" Software was developed to quantify the areas of nonperfusion in diabetic retinopathy, using a normative-based OCT-A mapping technique.

In conclusion:

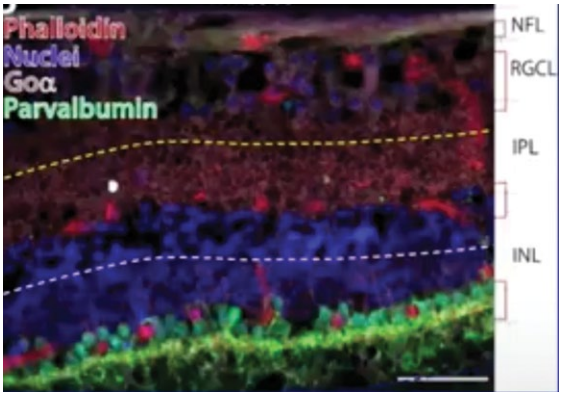
1. OCT-A opens the door to quantitative mapping of progressive diabetic vasculopathy
2. Perfused capillary density can define the stage of deterioration
3. Normative perfusion deviation mapping grades the impact of nonperfusion according to anatomical location which may predict function
4. The sensitivity of OCT-A anticipates the next generation of minimally invasive therapeutics which will treat diabetic retinopathy in its earliest stages

OCT Angiography for DME—Does It Give Us a New Understanding of Pathophysiology and Facilitate Outcomes? – *Nadia K. Waheed, MD, MPH*

This talk discussed some of the clinical applications of OCT angiography (OCT-A) and what looking at OCT-A has taught us about pathogenesis of disease.

Retinal vasculature develops from the optic nerve outward, and at the same time, from a superficial to a deep level, so for the fully mature circulation at the macula there are at least three and probably four different plexus that happen at the macular area. Typically the OCT-A machines in the clinic divide these into two different plexus, superficial and deep. These are "summed" images; anything above the inner plexiform layer appears as the superficial plexus and anything below that appears as the deep capillary plexus.

Fluorescein angiography primarily images just the superficial retinal plexus because of the absorption of light as it enters into the deep plexus. One advantage with OCT-A is that because it's depth resolved, you can separate the superficial vasculature and the deeper vasculature. We know from histopathologic studies that the deeper vasculature is more likely to be affected earlier in patients with diabetes.



What lessons have been learned in diabetic retinopathy with OCT-A?

1. Independent viewing of vascular layers enables improved visualization of capillary abnormalities in DR
    a. Total retinal projection obfuscates plexus-specific features
2. Diabetic vasculopathy starts much sooner than diabetic retinopathy becomes clinically apparent

So in the clinic, diabetics need to be monitored for worsening of DR, and checked for macular edema, macular ischemia, and neovascularization. Sometimes widefield imaging is a good idea to see if there is any nonperfusion in the periphery.

For progression of retinopathy, OCT-A enables early visualization of diabetic changes in the eye and allows for quantification of these images, and therefore better follow up and evaluation of the degree of progression.

OCT-A also allows for correlation of the structure with the vasculature and can help in understanding the results that are being seen. It also allows for better monitoring of PDR. Because no leakage is seen on OCT-A, the size of the neovascularization can be mapped out and followed as it regresses, and watched over time for regrowth.

The main shortcoming of OCT-A is that it's not able to get widefield imaging.

In summary:

1. OCT-A is a promising new approach to the visualization of retinal vascular pathology
2. It is noninvasive, fast and reliable, and allows monitoring of disease over time
3. It allows for correlation of structure to vasculature to better understand the pathologic basis of diabetic eye disease
4. Software enhancements in the future will allow for better evaluation of blood flow and true widefield imaging

There is a tremendous amount of information in these pages. There are discussions of new techniques and state of the art instrumentation being used in the most innovative ways, and of methods and approaches still to come. The inaugural Retina World Congress brought together experts from around the world and presented a well planned and executed agenda in order to learn from each other and to stimulate new ideas. Certainly anyone in attendance at the meeting, or who studies these pages, has the opportunity to learn more, and take these ideas and grow them into something better.

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