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Review article

Major challenges in vitreoretinal surgery

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ABSTRACT

Since the first vitrectomy surgery was used for treatment of vitreoretinal diseases, surgical techniques and instrumentation have been rapidly improved in the past decades. However, there are complicated vitreoretinal diseases that cannot be successfully treated, even with state-of-the-art surgeries. The outcomes of some complicated cases are still poor due to different reasons and debates still remain in some areas regarding what are the best treatments. There is still a lack of full understanding on many complicated vitreoretinal diseases, such as the molecular basis of proliferative vitreoretinopathy (PVR), the role of scleral buckling (SB) in the management of rhegmatogenous retinal detachment (RRD), the optimal surgical consideration for pediatric RD, and the possibility of surgical management for various retinal degenerations and congenital retinal anomalies. This review discusses the current understandings of some complicated vitreoretinal diseases.

1. Introduction

Since the first vitrectomy surgery was used for treatment of vitreoretinal diseases, surgical techniques and instrumentations have been rapidly improved in the past decades. However, there are still some complicated vitreoretinal diseases that cannot be successfully treated, even with state-of-the-art surgeries. These challenges remain to be solved in the future. With advanced basic research and clinical technologies, we have a better understanding of some of the areas. This review tries to present the current understandings of some complicated vitreoretinal diseases.

2. Molecular mechanisms of proliferative vitreoretinopathy

Proliferative vitreoretinopathy (PVR) is a vision-threatening complication after rhegmatogenous retinal detachment (RRD) or RRD surgeries. It occurs in 5–10% of all RRD cases.[1,2] Although it can develop in untreated RD, PVR is more commonly seen after retinal reattachment surgeries and therefore is the most common reason of surgery failure.[3] The pathogenesis of PVR includes migration of cells such as retinal pigment epithelial (RPE) cells, macrophages, and glial cells into the vitreous cavity. Proliferation and transformation of these cells leads to the formation of preretinal and/or subretinal membranes that cause retinal wrinkling and traction.[4] It is commonly believed that PVR is an analog of the wound-healing process after retinal break formation or retinal trauma. Many factors, including vitreous, inflammation, and various growth factors and cytokines, may contribute to the pathogenesis of PVR.[5] Normal vitreous contains inhibitory factors that can prevent the proliferation of fibroblasts and the normal properties of vitreous also can inhibit membrane formation.[3,6,7] Alteration of the normal vitreous properties may be a crucial step in PVR development. Vitreous from patients with PVR has been shown to be able to stimulate RPE cells proliferation.[8]

Many growth factors and cytokines may also be involved in the pathogenesis of PVR. According to the growth factor and cytokine hypothesis of PVR development, RPE cells and intraretinal cells are exposed to vitreous containing growth factors and cytokines after retinal break formation. These growth factors and cytokines may stimulate and cause cell migration, proliferation, and extracellular matrix formation.[4] Platelet-derived growth factor (PDGF) and its receptor (PDGFR) have been shown to be involved in the pathogenesis of PVR. Biologically active PDGF exits as five different dimers (AA, AB, BB, CC, and DD) and its receptor exits as three dimers (PDGFR-$\alpha\alpha$, PDGFR-$\beta\beta$, and PDGFR-$\alpha\beta$).[9] The level of vitreal PDGF is higher in patients with PVR than that in patients without PVR.[10–12] Lei et al[11] found that PDGF-C was present in eight of nine patients

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with PVR whereas it was detected only in one of 16 patients without PVR. PDGF is also detected in PVR membranes.[13,14] Moreover, the PDGF level in vitreous is increased in experimental animals with PVR.[10,11] Of all the isoforms, PDGF-C is the predominant isoform detected in the vitreous of patients and animal models with PVR.[11] The PDGFR is also shown to be activated in PVR membranes.[15] An *in vivo* experiment has shown that expression of functional PDGFR is required for the development of PVR.[16] Blocking the PDGFR can attenuate experimental PVR.[17] Studies have further shown that activation of PDGFR-α is crucial for PVR development.[15] PDGF isoforms detected in the vitreous of patients with PVR are more likely to activate the PDGFR-α.[11] Lei et al[11] analyzed different PDGF isoforms in vitreous samples from control and PVR rabbits and from patients with PVR. They found that the level of PDGF isoforms that activates PDGFR-β was undetectable or very low in all of the samples tested. By contrast, PDGF isoforms that activate PDGFR-α were present at higher levels, especially the PDGF-C. Moreover, PDGFR-α is preferentially activated in PVR membranes and it is more efficient in inducing PVR.[15] Both *in vivo* and *in vitro* studies have shown that only activation of PDGFR-α but not PDGFR-β can induce experimental PVR.[18,19] Fibroblasts expressing PDGFR-β have a similarly low potential of inducing PVR with fibroblasts not expressing PDGFR at all, whereas fibroblasts expressing PDGFR-α can potently induce experimental PVR.[18] Normal or high-level expression of PDGFR-α can augment the PVR potential of RPE cells.[19] However, blocking PDGFs is not sufficient to prevent PVR induced by PDGFR-α activation, suggesting that PDGFR-α can also be activated by non-PDGF agents.[20] Neutralizing all PDGFs in vitreous from patients or experimental animals with PVR could only partially inhibit PDGFR-α activation.[21] Activation of PDGFR-α by growth factors outside of the PDGF family, namely non-PDGFs such as epidermal growth factor (EGF), basic fibroblast growth factor (bFGF), hepatocyte growth factor (HGF), and insulin was also involved in PVR development.[20,21] As a matter of fact, the indirect activation of PDGFR-α by non-PDGFs is a mechanism more important in inducing PVR than the direct pathway activated by PDGFs.[4] Direct activation by PDGFs leads to assembly of PDGFR-α monomers into dimers, which are rapidly internalized and degraded and thus the duration of the effect is short. However, the indirect pathway of PDGFR-α activation by non-PDGFs does not cause PDGFR-α dimers or rapid internalization and degradation of the receptor. Therefore, the activation is more persistent. Consistently, neutralizing non-PDGFs eliminates their abilities to activate PDGFR-α and therefore prevent experimental PVR.[10]

Vitrectomy surgeries are usually performed in patients with severe PVR. We also tend to perform vitrectomy for those RRD patients who have preoperative risk factors for PVR development such as trauma, intraocular inflammation, giant tear, and choroidal detachment. Complete vitrectomy should be performed in these patients, especially at the peripheral vitreous. Complete vitrectomy can eliminate molecules and cells in the vitreous that are associated with PVR development, such as PDGFs and RPE cells. It can also remove the plane where cell proliferation and membrane formation will occur. Excessive retinopexy should be avoided. An encircling element may be considered to reduce the risk of recurrent RD in cases where complete removal of the peripheral vitreous is difficult.[22]

3. Is scleral buckling still necessary?

Two major surgical methods used to treat RRD are scleral buckling (SB) and pars plana vitrectomy (PPV). Although both methods have been shown to have high success rates, there is still a large debate about which one is the optimal treatment for uncomplicated RRD. The decision of which method to be used is mainly dependent on the surgeon's clinical judgment, experience, and preference. There has been a trend of treating uncomplicated RRD using primary PPV in the past decades.[23,24] In 1999, 63% of RRD cases received primary PPV in the UK compared to only 1% in 1979–1980.[23] In a large Asian tertiary eye center, the percentage of patients who underwent primary PPV and PPV + SB was 39.2% in 2005 and it increased to 60.6% in 2011.[24] PPV surgeries allow the surgeon to identify and treat all retinal breaks, eliminate vitreous traction, and remove the vitreous containing various factors leading to PVR. Primary PPV seems to have better outcome in treating pseudophakic/aphakic RRD.[25–28] The Scleral Buckling versus Primary Vitrectomy in Rhegmatogenous Retinal Detachment (SPR) study is the largest prospective randomized controlled trial to date to compare the efficacy of SB and PPV in treating medium severity RRD. Forty-five surgeons from 25 centers in five European countries participated in the study. Patients with medium severity RRD were divided into phakic and pseudophakic/aphakic groups. Patients in each group were randomized to receive either SB (in some cases including encircling elements) or PPV with a sulfur hexafluoride-air mixture as endotamponade (in some cases with additional SB). The SPR study showed that the primary anatomical success rate was significantly better and the mean number of retina-affecting secondary surgeries was lower in pseudophakic/aphakic RRD patients treated with PPV compared to those treated with SB.[27] In a meta-analysis, pseudophakic/aphakic RRD treated with PPV was associated with a better final re-attachment rate.[28] In a large sample multicenter retrospective study, pseudophakic/aphakic uncomplicated RRD treated with PPV had a higher single-surgery reattachment rate.[25] The same group also recommended PPV as the preferred treatment for pseudophakic/aphakic patients with complex RRD when choroidal detachment, hypotony, a large tear, or a giant tear was present.[26]

However, in phakic patients with uncomplicated RRD, SB seemed to have better functional outcomes and less complications compared to PPV while having comparable anatomical outcomes.[27–29] The SPR study showed that the SB group had significantly greater mean best-corrected visual acuity (BCVA) improvement and less cataract progression than the PPV group.[27] In a meta-analysis, SB was found to have better final BCVA and less postoperative cataracts compared to PPV in patients with uncomplicated phakic RRD.[28] Another meta-analysis also found no difference in the primary reattachment rate between SB and PPV in phakic eyes with uncomplicated RRD. The authors also found better BCVA at ≥6 months in phakic RRD eyes treated with SB and contributed this to the higher rate of cataract progression in phakic RRD eyes treated with PPV.[29] A large retrospective study even showed a significantly lower final failure rate in uncomplicated RRD patients treated with SB alone.[25] Moreover, SB is still the preferred treatment in some clinical settings of RRD, e.g., patients with localized RD and one single small retinal break, or multiple small neighboring breaks. Most of these patients are treated with SB.[30] Another setting is young patients with uncomplicated RRD who may otherwise need cataract surgery and lose the ability of accommodation if treated with PPV. Incomplete vitreous detachment in young patients also makes the removal of the peripheral vitreous technically difficult, which may lead to more intra- and postoperative complications.[22] In some cases, SB can also be used as an adjunct to PPV. An encircling element to support the peripheral retina and more importantly to release any remaining peripheral vitreous or a PVR is useful in cases where there is residual vitreous, severe preoperative PVR, an inferior tear, or a giant tear.[22,31–33]

4. Management of pediatric RRD

RRD in pediatric patients accounts for 1.7–8.0% of all RRD patients.[34–36] More boys than girls were reported, which may be

attributed to more trauma cases in boys.[34–39] Etiological factors of pediatric RRD include trauma, myopia, congenital-developmental anomalies, previous intraocular surgery, etc.[34–40] Many studies have shown myopia as one of the major risk factors of pediatric RRD, especially in the Asian population.[34,35,37] Although most RRD can be successfully treated with surgery in adults, pediatric RRD is a clinical challenge for many surgeons. Many patients present with long disease duration and poor function. Patients may have visual symptoms lasting for >1 month prior to presentation, which may be due to a lack of subjective complaints in children.[41,42] More importantly, 73–92% of patients have macular involvement on presentation, making visual recovery after surgery very difficult.[35,37–40] Wang et al[37] showed that the rate of macular involvement was 92.1% in patients <10 years of age and it was 76.2% in patients >16 years of age. Pediatric RRD also presents with a high rate of PVR, which may be due to both long disease duration and increased intraocular cellular activity.[43] Many studies have reported that >30% of the young patients had PVR (Grade C or worse) on presentation.[37–40] Younger patients seem to have a higher rate of PVR.[37,39] Soheilian et al[39] showed that the rate of PVR (Grade C or worse) was 57% in patients <10 years of age, 48% in patients between 10 years and 15 years of age and 36% in those >15 years of age. Similarly, Wang et al[37] demonstrated that PVR (Grade C or worse) was present in 55.3% of patients <10 years of age, in 47.7% of patients between 11 years and 15 years of age and in 41.7% of those >15 years of age.

High PVR rate on presentation leads to low reattachment rate, multiple surgeries, and poor visual outcomes in patients with pediatric RRD. Complete final retinal reattachment has been reported to be achieved in only 67–85% of the cases.[35,37–40] The rate of retinal reattachment after one surgery is even lower, ranging from 52% to 72%.[37,39,40] Younger patients seem to have a lower final retinal reattachment rate. In a study, the final retinal reattachment rate was 61% in patients <10 years of age, 72.4% in patients between 10 years and 15 years of age and 69.7% in patients >15 years of age.[39] Another study showed anatomical success rates of 60.5% in patients <10 years of age, 85.0% in patients between 10 years and 15 years of age and 90.1% in patients >15 years of age.[37] The etiology also seemed to affect the final retinal reattachment. Pediatric RRD caused by myopia or previous congenital cataract surgery has the highest percentage of patients having the retina attached at the last follow-up.[39] In another study, non-myopic RRD was one of the predictors of poor surgical outcome.[35] Many patients need multiple procedures for recurrent RRD, cataract surgery, or silicone oil removal. The mean number of total surgical procedures per eye ranges from 1.34 to 1.6.[37–39] Gonzales et al[40] reported more than one subsequent surgeries in 50% of the patients. The presence of PVR of Grade C or worse has been shown to be associated with poor anatomical outcome.[35,40] Patients with PVR (Grade C or worse) require more surgeries. It has been shown that the average number of surgeries in eyes with PVR Grade C or worse is significantly higher than that for eyes with PVR lower than Grade C.[39] Visual outcomes of surgeries for pediatric RRD are poor, due to the reasons mentioned above. Although BCVA is improved in some patients after surgery, in many patients BCVA remains unchanged or even worse. BCVA was improved in only 42.8% of eyes, remained unchanged in 32.3%, and worsened in 19.1% of eyes in a study.[35] Forty-six point five percent of eyes were considered functionally visually lost at the last follow-up in one study[39] and 31% of eyes with the final vision of non-light perception (NLP) in another study.[38] Factors associated with poor visual outcomes include vision of light perception only, or undetermined vision prior to surgery, macular involvement, presence of severe PVR (Grade C or worse), non-myopic RRD, the need for vitrectomy, and the use of silicone oil.[35,38]

One of the reasons of poor surgical outcomes in pediatric RRD patients is postoperative PVR due to incomplete removal of the vitreous. Complete posterior vitreous detachment and vitrectomy are difficult to perform in children. There have been studies using autologous plasmin enzymes to facilitate vitreous removal.[44,45] Encircling buckling or silicone oil may be helpful to patients with incomplete vitreous removal. Aside from the poor surgical and visual outcomes of pediatric RRD, many patients also have ocular pathologies in the fellow eye. About 37% of the fellow eye was found to have sight-threatening ocular pathologies in a study.[40] In another study, retinal pathologies were detected in 82.2% of the fellow eye.[39] Therefore, extensive examination on presentation and close follow-up of the fellow eye is necessary for patients with pediatric RRD.

5. The possibilities of vitreoretinal surgeries for retinal degeneration and retinal defect

RPE and photoreceptor damage at the macula are the major pathologies in retinal degenerative diseases such as age-related macular degeneration (AMD), retinitis pigmentosa (RP), and Stargardt's macular dystrophy. A surgical approach has been explored to reconstitute RPE and photoreceptors at the macula to restore vision or to slow disease progression. Macular dislocation has been used for the treatment of various macular disorders including those caused by AMD and high myopia. In 1993, Machemer and Steinhorst[46] first reported three cases treated by full macular translocation (FMT). A 360° retinotomy at the peripheral retina was created after vitrectomy. Rotation of the retina for 30–80° was then carried out and the fovea was laid on healthy adjacent RPE. Laser photocoagulation was applied to the peripheral retina and intraocular tamponade was then used. Ninomiya et al[47] modified the method in 1996. Instead of creating a 360° retinotomy, they used a 180° retinal flap. The extent of rotation was also reduced to 10–20°. In 1998, de Juan et al[48] further modified the technique which was called "limited macular translocation (LMT)". The LMT reduced the risk of postoperative RD and PVR formation by significantly decreasing the size of retinotomy.[48] They retrospectively reviewed 1-year outcomes of the LMT in a case series of 102 eyes with neovascular AMD. In 86 eyes that completed the 1-year follow-up, 39.5% of eyes gained two or more Snellen lines in BCVA and 40.7% of eyes achieved BCVA of 20/100 or better. The incidence of recurrence at 12 months was 34.6% in eyes which had received successful macular translocation and completed laser photocoagulation of the choroidal neovascularization (CNV) complex. The recurrence was mainly subfoveal and led to BCVA decease.[49] Toth and Freedman[50] improved the FMT with better surgical techniques and instrumentation, which led to a decrease in surgery time and complications, and to better visual outcomes. In a prospective study by the same group, all of the 61 eyes with choroidal neovascularization (CNV) due to neovascular AMD underwent successful macular translocation and completed 12 months follow-up. Distance vision was improved by one or more lines in 52% of patients and the median distance visual acuity letter score was improved from 62 letters at baseline to 69 letters at 12 months after surgery.[51] Near vision and reading speed were also improved at 12 months after surgery.[51,52] The efficacy of macular translocation in improving patients' vision was confirmed by a meta-analysis consisting of 32 studies using FMT or LMT. Mean BCVA was improved from 20/133 prior to surgery to 20/111 at final follow-up and 31% of patients gained two or more lines in vision. However, 27% of patients had deteriorated by two or more lines and 16% had recurrence. The complication rate was also high (71%) after the surgery.[53] FMT has also been used for treatment of dry AMD. Eckardt and Eckardt[54] treated

seven patients with geographic atrophy (GA) with FMT and reported improved vision of two or more lines in three patients, stable vision in four patients and reading vision gained in five patients. However, one patient had rapid RPE atrophy development and GA progression at the new fovea after surgery. This complication was further confirmed by other studies where rapid foveal RPE atrophy occurred in GA patients after FMT.[55,56] Several studies have also reported the use of FMT or LMT to treat non-AMD, such as macular degeneration caused by high myopia.[57,58] In one of the studies, 38% of eyes gained more than three lines, 31% had a final VA of 20/50 or more, and 56% had a final VA of 20/100 or more. However, there was no significant difference between mean final BCVA and mean BCVA prior to surgery.[57] In a study using LMT to treat pathological myopia, the mean BCVA was improved from 20/125 to 20/80 after 2 years, with 32.9% of eyes having vision of 20/50 or more and 72% of eyes having vision of 20/100 or more. However, the reading ability of specific materials descended from 65.8% of eyes at 6 months to 59% at 1 year and to 43% at 2 years.[59]

Some researchers have tried to use stem cells to preserve or restore vision in patients with retinal degeneration. Stem cells can be induced to differentiate into RPE cells or photoreceptors that are used to replace the damaged cells. Stem cells can also alter the local cellular microenvironment by means of releasing cytokines and cell interactions to repair the injured tissue.[60] Schwartz et al[61] transplanted RPE cells derived from human embryonic stem cells into the subretinal space of two patients, one with dry AMD and the other with Stargardt's macular dystrophy. The vision of the patient with Stargardt's macular dystrophy was improved from zero to five letters on the early treatment diabetic retinopathy study (ETDRS) chart 4 months after the surgery, with subjective improvement of color vision, contrast sensitivity, and dark adaptation. Optical coherence tomography also showed increased pigmentation at RPE at the region of subretinal injection. The vision of the patient with dry AMD was increased from 21 to 28 early treatment diabetic retinopathy study (ETDRS) letters. Siqueira et al[62] used intravitreal injection of autologous bone marrow-derived mononuclear cells in patients with RP or cone-rod dystrophy. Although no adverse event was observed over a period of 10 months, no significant improvement in visual function was achieved either. Four of five patients had one-line improvement in BCVA 1 week after the injection and maintained the same until the end of the follow-up. There are several other studies of stem cells having been used in animal models of retinal degeneration showing promising results which need to be confirmed clinically. In fact, several clinical trials using stem cells to treat retinal degeneration are already underway.[63]

Our group has published a case where a patient was treated with retinal translocation to repair a retinal defect at the macula. The patient was diagnosed with bilateral fungal endophthalmitis and a large retinal defect was found at the macula of the left eye during vitrectomy. A retinal flap with vasculature was divided from the inferior-temporal retina and translocated to the region of retinal defect. The vision of the left eye was improved from finger counting at 20 cm prior to surgery to 10/500 after silicone oil removal 2 years later. Optical coherence tomography (OCT) showed intact junction between inner segments and outer segments of the retinal photoreceptors on the translocated retina. Normal autofluorescence was shown under the translocated retina, indicating the survival of the RPE. The patient had no complaints of image tilting during follow-up.[64] Although the technique of retinal translocation using the adjacent retinal flap is immature and there are problems such as damage to the retinal nerve fiber layer and survival of the graft, the availability and autologous nature of the graft is a great advantage of the technique.

6. Vitreoretinal surgeries for congenital retinal anomalies

X-linked retinoschisis is a congenital retinal degeneration that mainly affects young boys. It is estimated to occur in 1/5000–1/25000 of the population.[65,66] About 20% of the patients with X-linked retinoschisis develop RD and one third of the patients may develop vitreous hemorrhage (VH). Both complications can cause severe vision loss.[67–69] Observation is usually recommended for patients with X-linked retinoschisis when there are no complications such as RD and VH.[70,71] However, we have found that patients with progressive X-linked retinoschisis treated with nonsurgical methods are more prone to develop complications compared to those treated with early surgery. Moreover, patients who have surgery after occurrence of complications tend to have worse visual outcomes compared to those who have early surgery prior to when complications occur.[72] We defined progress X-linked retinoschisis as X-linked retinoschisis without complications such as RD and VH, but demonstrating progressive decrease in vision and expansion of macular schisis or peripheral schisis threatening the macula during more than 6 months of follow-up.[72] We divided the patients into two groups. One group was treated with close observation and laser photocoagulation when indicated. The other group was treated with combined vitrectomy, internal limiting membrane peeling (ILMP), endolaser photocoagulation (in some cases), and gas tamponade. RD occurred in 72% of the untreated eyes and VH occurred in 18% of the eyes in the nonsurgical group. By contrast, only 6% of eyes developed RD and no eye had VH in the eyes treated with early surgery. The schisis cavity expanded in 82% of the eyes in the nonsurgical group, whereas the schisis cavity resolved greatly in all of the eyes treated with early surgery. The mean BCVA decreased from 20/100 at baseline to 20/400 at the final follow-up in the nonsurgical group; final BCVA worsened in 91% of eyes. In the early surgery group, the mean BCVA was improved from 20/125 at baseline to 20/55 at the final follow-up, with final BCVA improved in 82% of eyes.[72] Although vitrectomy is usually suggested in patients with expanding schisis cavity and RD or VH,[73,74] complete PVD is usually difficult to perform in children and inner schisis wall retinectomy was used in some early studies.[73,74] However, this technique results in loss of retinal ganglion cells and interneurons. Autologous plasmin enzyme has been used to facilitate PVD.[44,45] ILMP was also useful in removal of residual vitreous at the macula, while preserving the other layers of the retina.[72,75]

Optic disc pit is another common congenital anomaly which equally affects men and women. About 25–75% of patients with optic pit may develop schisis and serous RD at the macula.[76] Because vision outcome of patients with untreated optic pit maculopathy is poor, treatment is usually recommended.[77] Several treatments including laser photocoagulation, intravitreal gas injection, and the combination of both have been proposed.[78–80] Vitrectomy is currently used in patients with optic pit maculopathy. The surgery is sometimes performed along with laser photocoagulation, ILMP, and gas tamponade.[81–83] Hirakata et al[81] reported 11 cases of optic pit maculopathy treated with vitrectomy and gas tamponade without laser photocoagulation. Complete retinal reattachment was achieved in 10 eyes at the last follow-up. Later, they treated optic pit maculopathy with vitrectomy alone in eight eyes. Mean follow-up was 26 months and seven of eight eyes had complete retinal reattachment.[84]

Vitrectomy has also been used in familial exudative vitreoretinopathy (FEVR) and persistent hyperplastic primary vitreous (PHPV). In a study using vitrectomy to treat FEVR complicated with RD, the final reattachment rate was 85.7% and BCVA was improved in 71.4% of eyes.[85] Another study also showed that vitrectomy was effective for FEVR patients with RRD, especially those without

foveal dragging.[86] About 50% of patients who underwent surgery for PHPV would achieve useful vision.[87] In a further study, lensectomy and vitrectomy were effective for bilateral combined anterior and posterior PHPV, with BCVA of 20/300 or better achieved in 71% of eyes and 20/100 or better achieved in 57% of eyes.[88]

7. Conclusion

With the improvements in surgical techniques and advancement in instrumentation, vitreoretinal surgeries have evolved rapidly in the past decades. Surgeons now are able to treat many vitreoretinal diseases with higher success rates than before. They can even tackle diseases which were considered untreatable in the past. However, there are still many challenges for vitreoretinal surgeons. The outcomes of some complicated cases are still poor due to many reasons. Debates still remain in some areas regarding what are the best treatments. With further investigations into the mechanisms of vitreoretinal diseases and with more well-conducted clinical trials, we will be able to offer better solutions to these challenges in the future.

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