• Editorial •

PVR update: pathophysiology and clinical management

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Wound-healing diseases present complex challenges, and proliferative vitreoretinopathy (PVR) has been a problem in the surgical retina for 50y. PVR is a prolonged and abnormal healing response to retinal injury, such as primary retinal detachment (RD) or post-RD surgery, characterized by the formation of pre/subretinal membranes, retinal gliosis and shortening, retinal pigment epithelium cell (RPE) proliferation, and increased activity of glial cells (mainly Müller cells), fibroblasts, and inflammatory cells (macrophages and lymphocytes). This results in tractional retinal holes/breaks and can lead to multiple costly eye operations for patients[1]. Although it may subside independently, new surgical interventions can reignite it, resulting in a cycle of recurrence. Shearing forces of acute PVD or surgical maneuvers can cause mechanical injury to the inner retina and trigger a subsequent intraretinal glial healing response. That response is characterized by subclinical glial cell activation and proliferation that may then be amplified into full-blown PVR by coexisting pathologies such as retinal breaks and detachment[2]. Clearly, the disorganized release of monolayered RPE and retinal glial cells disturbs the delicate structure of the neural retina. We strive to understand the pathophysiology of PVR to overcome its intricate nature. To understand PVR comprehensively, it is essential to explore its developmental stages, cellular contributors, molecular mechanisms, and therapeutic implications. The interplay between cells, such as RPE, glia, vitreal and bloodborne cells, growth factors, and cytokines, is complex. Additionally, epithelial-mesenchymal transition (EMT) is pivotal as a pathophysiological event.

Generally, these therapeutical issues can be categorized into two main groups: a) an incomplete understanding of the fundamental pathobiology of PVR and the shortcomings of current *in vitro* and animal models; b) the lack of a modern uniform clinical classification and standardized surgical procedures. A study provides a comprehensive and convenient source of information on PVR animal models and animal models for pharmacotherapy[3]. New models have provided insights into pathophysiological events, and we have paid much attention to cellular events; however, their clinical relevance is not obvious, and clinical management has not changed. As no new approaches to establish PVR management have been identified, PVR remains a surgical disease.

Surgical interventions are the most effective way to tackle PVR and its related complications. The fundamental principles of rhegmatogenous retinal detachment (RRD) surgery with PVR are similar to those of RRD surgery without PVR. Both involve addressing tractional forces that lead to subretinal fluid accumulation and retinal breaks sealing. Improved postoperative visual acuity is directly linked to primary pars plana vitrectomy (PPV), limited extension of the PVR to the posterior pole, and the absence of significant postoperative inflammation in the aqueous humor[4]. Moreover, primary PVR increases the risk of secondary and tertiary surgical repair, as demonstrated by the healthcare claims data. Anterior PVR and multiple surgical interventions are associated with poor outcomes[5]. Repeat primary PVR, a complication of RD, often requires multiple surgeries and results in suboptimal visual outcomes.

Although PVR is a scourge for patients and surgeons alike, today's surgical approach is much better than previously due to modern technology and improved surgical techniques. This review summarizes our current knowledge. Following these decisive rules and tips is a prerequisite for successful reattachment in cases of PVR retinal detachment[6-7].

Concepts of SOAS or SSAS In retinal surgery, the terms "Single Operation Anatomical Success" (SOAS) and "Single Surgical Anatomical Success" (SSAS) describe anatomical restoration or repair after a single surgical procedure. As repeat surgery is a risk factor for PVR, the first surgery is paramount.

Scleral Buckle Although one report states that the SSAS rates of PPV, retinectomy, and silicone oil (SO) tamponade without scleral buckle (SB) for PVR-related recurrent RRD

are comparable to previous reports of similar surgeries incorporating SB[4], most authors favor the use of SB. The use of PPV/SB was associated with significantly higher SSAS scores and functional outcomes than PPV alone[5,8-9]. With SB in eyes with primary RRD and the risk factors for PVR, the overall SSAS rate was 71.5% after primary repair. In this cohort, the use of PPV/SB was associated with a significantly higher SSAS score than PPV alone[5]. In treating recurrent RD with grade C PVR, combining the SB procedure with PPV improves anatomical and functional outcomes[8]. After SO removal, the retinal redetachment rate was 4.0%. Implantation of the SB at the time of PPV is associated with a lower risk of retinal redetachment after vitrectomy in patients with PVR[9].

Complete Removal of the Vitreous Body The primary prerequisite for successful surgery is the complete removal of activated cells and membranes and the complete removal of the vitreous to remove the substrate for the proliferation of pathological cells. Vitreoschisis-induced vitreous cortex remnants (VCR) play a role in PVR development, where they can act as scaffolds for fibrocellular proliferation. VCR over a retinal surface should qualify as a risk factor for PVR formation. Detection and adequate removal of VCRs may improve the success rate of RD surgery[10]. Vitrectomy is likely to be completed with the routine use of triamcinolone (TA) for visualization and shaving of the vitreous base (VB) and VCR detection and removal posterior to the VB. Even without drug adjuvants, it should be possible to decrease redetachment rates to <10% when adequate TA-assisted VB shaving is performed and to <5% when combined with TA-assisted VCR detection and removal posterior to the VB[11]. The presence of peripheral vitreous cortex remnants (p-VCR) is associated with a higher incidence of PVR development. It might also result in more complex RD recurrence, suggesting the need for more aggressive VCR removal during the first surgery[12]. p-VCRs are missing links in the PVR treatment[13]. Early intravitreal TA injection for open globe injury effectively reduces traumatic proliferative vitreoretinopathy (TPVR), increases surgical success, and improves visual prognosis[14].

Membrane Removal All tractional PVR membranes must be removed; subretinal PVR membranes without traction can remain in place. The reason is mechanical to allow reattachment and biological to prevent intraretinal damage and healing response[2].

Professional Care of the Macula Macular pucker associated with PVR is challenging and can impair vision and distort macular structure. Surgical removal of the macular pucker can restore macular function and anatomy, but visual improvement depends on the extent of macular involvement in the original RD[15]. As approximately 12% of all patients undergoing RD surgery develop epiretinal gliosis/macular pucker, peeling of the internal limiting membrane (ILM) is obligatory in cases of PVR. Recent reports have shown that postoperative macular membranes are a localized presentation of macular proliferative vitreoretinopathy (mPVR)[16]. Several studies have evaluated the benefits and risks of ILM peeling in RD and PVR and have reported mixed results. Some studies have found that ILM peeling reduces the need for reoperation[17-18], facilitates the removal of PVR membranes, decreases the risk of epiretinal membrane (ERM) formation[19], and improves functional outcomes. Other studies have reported no significant differences or adverse effects of ILM peeling, such as retinal thinning, microscotomas, or reduced contrast sensitivity. The long-term impact of ILM peeling on RD and PVR remains unclear and requires further investigation. Several ongoing studies can be found at *www.clincialtrials.gov*.

Modern Instruments Selecting suitable modern instruments facilitates optimal surgery. Widely available spectral-domain optical coherence tomography can be used preoperatively to image the mid-peripheral retina and guide surgical decision-making in the management of PVR[20-21]. Surgical instruments include wide-angle optics, such as a binocular indirect ophthalmomicroscope (BIOM), chandelier lights, perfluorocarbons (PFCL), and SO, particularly for PVR detachment. Compared with PPV alone, endoscopy-assisted vitrectomy seems advantageous for achieving better reattachment rates in complex RD with advanced PVR. Endoscopic visualization allows for thorough examination, extensive anterior PVR, and VB dissection[22]. Digitally assisted vitreoretinal surgery systems (DAVS) may also be useful[23].

Minimal-Maximal Surgery Finally, the philosophy of as much as necessary and as little as possible is essential. A retinal surgeon should know all techniques available when treating PVR cases, but the least invasive should be selected. PVR eyes have usually been previously operated on, and any further surgical intervention or wounding leads to subsequent inflammation, persistent stimulation of the PVR reaction, and additional damage.

Definition of RRD with a High Risk of PVR and Usage of Adjuvant Drugs (mainly anti-inflammation) The current classification has served to standardize PVR terminology to allow clinicians to compare treatment results; however, it appears to have more of a descriptive value rather than correlating with visual prognosis or reflecting the pathology and activity of PVR[1]. Intervention in the early stage (PVR A and B) might be the strategy for PVR control. Age, smoking, preoperative PVR, vitreous hemorrhage, aphakia or pseudophakia, macula off RD, the extent of RRD, and duration of RRD symptoms are risk factors for postoperative PVR in patients undergoing RD surgery[24]. The magnitude of

breakdown in the blood-retina barrier (BRB) and the amount of inflammatory growth factors present correlate with the extent and chronicity of the RD[25]. This knowledge helps identify high-risk patients and provide timely interventions to prevent established PVR (Grade C).

A retrospective analysis showed continuous improvement in anatomical and functional outcomes in patients treated for primary macula-on or off RRD when surgical methods shifted from SB to vitrectomy and surgeries were scheduled preferentially during the routine daytime program[26].

The three stages of PVR pathophysiology are inflammation, proliferation, and fibrosis[27]. Surgery mainly takes care of the last stage (fibrosis). Surgical interventions for PVR involve removing the vitreous gel and scar tissue as much as possible, but adjunctive pharmacological therapies are needed for better PVR control. Both cellular proliferation and the intraocular inflammatory response are realistic targets for adjunctive treatments in PVR[1]. Although the primary outcome measure failed to reach significance, the antiproliferative daunomycin trial found a statistically significant reduction in the number of vitreoretinal reoperations within one year for the first time, demonstrating an adjunctive treatment effect on the PVR process[28-29]. The number of postoperative macular puckers was also reduced (unpublished results). In those days, the vitreous removal was always incomplete. No further clinical trials on daunomycin were performed because of the promising but non-significant differences in primary outcomes, the difficulty of obtaining and utilizing an anti-neoplastic agent in an ophthalmologic setting, and the concerns about safety outcomes[30]. RRD surgery combined with steroid drug administration can significantly reduce the recurrence in the PVR grade A and B subgroups and the incidence of macular edema after surgery[31]. TA is a standard staining used for vitreous removal. Potential drugs include methotrexate[30], decorin, and inhibitors that target specific growth factors or cytokines[1]. However, until now, there has been no convincing publication about the clinical usefulness of these adjuncts. Currently, there is no approved or licensed medical adjuvant treatment or drug prophylaxis to prevent, reduce, or treat the formation of PVR in patients with RRD or to treat established PVR[1]. In the future, all PVR patients should be evaluated in trials based on standardized surgery and a standardized classification.

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