Proliferative vitreoretinopathy: update in prevention and treatment

Atualizações na prevenção e tratamento da vitreorretinopatia proliferativa

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ABSTRACT

Proliferative vitreoretinopathy remains the leading cause of anatomical failure after rhegmatogenous retinal detachment repair, affecting 5 to 12% of primary detachment and up to 75% of redetachments. Although small-gauge vitrectomy, chromovitrectomy, high-definition intraoperative viewing systems and advanced preoperative imaging have revolutionized retinal surgery, the incidence of proliferative vitreoretinopathy has not decreased significantly over the past two decades. It represents a maladaptive wound-healing response in which inflammatory and fibrogenic pathways drive the formation of contractile preretinal, intraretinal, and subretinal membranes. This process typically occurs within 6 to 8 weeks after surgery, making timely prophylaxis critical. Surgical management of established proliferative vitreoretinopathy involves meticulous removal of the posterior hyaloid, residual vitreous and tractional epiretinal and subretinal membranes. The use of perfluorocarbon liquids (PFCL) and chandelier-assisted bimanual dissection improves visualization and membrane control. Brilliant blue dye enhances internal limiting membrane (ILM) identification, particularly when used under air to achieve negative staining. Small-gauge vitrectomy systems (23 to 27G) offer less invasive access, improved fluids and reduced postoperative inflammation. In complex cases, adjuvant techniques such as scleral buckling, retinectomy, and silicone oil tamponade are often required to achieve anatomical reattachment and prevent recurrence. Prophylactic therapies targeting the molecular drivers of proliferative vitreoretinopathy – such as corticosteroids, anti-inflammatory agents, anti-proliferative drugs, and biologics against cytokines, including tumor necrosis factor-alpha – are under investigation. Together, the integration of refined surgical technique, appropriate use of intraoperative adjuvants and emerging pharmacologic prophylaxis holds the potential to significantly improve anatomical and functional outcomes in patients with or at risk of proliferative vitreoretinopathy.

RESUMO

A vitreorretinopatia proliferativa (PVR) continua sendo a principal causa de insucesso anatômico após a cirurgia para descolamento de retina regmatogênico, afetando de 5 a 12% dos casos primários e até 75% das recidivas. Apesar dos avanços na cirurgia vitreorretiniana — como a vitrectomia de *gauge* reduzido, uso de corantes (cromovitrectomia), sistemas de visualização intraoperatória em alta definição e exames de imagem pré-operatórios sofisticados, a incidência de PVR não diminuiu significativamente nas últimas duas décadas. A condição representa uma resposta de cicatrização desadaptativa, em que vias inflamatórias e fibrogênicas promovem a formação de membranas contráteis preretinianas, intrarretinianas e subrretinianas. Esse processo geralmente ocorre entre 6 a 8 semanas após a cirurgia, tornando a profilaxia precoce essencial. O tratamento cirúrgico da PVR estabelecida exige remoção cuidadosa a hialoide posterior, do vítreo residual e das membranas tracionais epirretinianas e subrretinianas. O uso de perfluorcarbono e dissecção bimanual com auxílio de endoiluminação tipo "*chandelier*" melhora a visualização e o controle das proliferações. O corante azul brilhante facilita a identificação da membrana limitante interna (MLI), especialmente quando aplicado sob ar, permitindo visualização por coloração negativa. Sistemas de vitrectomia de pequeno calibre (23 a 27G) proporcionam acesso menos invasivo, melhor dinâmica de fluidos e menor inflamação pós-operatória. Em casos complexos, técnicas adjuvantes como introflexão escleral, retinotomia e tamponamento com óleo de silicone são frequentemente necessárias para o sucesso anatômico da cirurgia e prevenção de recidivas. Terapias profiláticas que visam os mediadores moleculares da PVR — como corticosteroides, agentes anti-inflamatórios, drogas antiproliferativas e biológicos contra citocinas, incluindo o fator de necrose tumoral alfa (TNF-α) — estão em investigação. A combinação de técnicas cirúrgicas aprimoradas, uso adequado de adjuvantes intraoperatórios e profilaxia farmacológica emergente tem o potencial de melhorar significativamente os desfechos anatômicos e funcionais em pacientes com PVR ou de alto risco.

INTRODUCTION

Proliferative vitreoretinopathy (PVR) is a term established by the Retina Society Terminology Committee in 1983 to describe the main complication associated with rhegmatogenous retinal detachment.[1] It denotes an active remodeling process triggered by retinal injury[2,3] and represents the leading cause of surgical failure, with an estimated prevalence of 5 to 12% of primary detachments.[4-6] It is characterized by the formation of proliferative fibrotic membranes in the posterior vitreous, located on the epi-, intra- or subretinal surfaces.

PATHOGENESIS

Initial retinal injury disrupts the blood-retinal barrier, activating cell populations that include retinal pigment epithelial (RPE) cells, glial cells (astrocytes and Müller cells) and macrophages.[7-9] Following retinal detachment, the exposure of the subretinal space to plasma proteins such as fibrinogen creates a pro-fibrotic microenvironment in which RPE cells play a central role.[8] These cells undergo epithelial-mesenchymal transition (EMT), shifting from an epithelial phenotype to a highly migratory, contractile, fibroblastic phenotype that produces extracellular matrix.[7-9] Through this process, they become myofibroblasts, which are responsible for the formation of fibrotic membranes and subsequent retinal contraction.[7]. Table 1 summarizes these pathophysiological elements. Among the molecular mediators, transforming growth factor beta (TGF-β) is considered a key driver of the EMT process. Other relevant factors include PDGF, vascular endothelial growth factor (VEGF), CTGF, interleukin (IL) 1, IL-6, tumor necrosis factor-alpha (TNF-α) and MCP-1.[7-9] Once activated, the involved cell populations start to produce their own growth factors, thereby amplifying the inflammatory response. The importance of autocrine and paracrine signaling is emphasized, with factors acting both on the originating cells and on neighboring cells.[7-9] During EMT, cells upregulate the expression of proteins such as alpha smooth muscle actin (α-SMA) and produce extracellular matrix components including fibronectin and type I collagen.[8] This leads to the formation of contractile membranes that induce retinal wrinkling and traction, ultimately resulting in redetachment.

Glial cells are co-protagonists in the initiation, progression and maintenance of PVR (Table 2). When activated following trauma or retinal detachment, they undergo a reactive gliosis process and shift their phenotype toward a more migratory and secretory state. In this state, they produce cytokines such as IL-6 and TNF-α, pro-fibrotic factors such as TGF-β, and extracellular matrix proteins including fibronectin and collagen. Their active role in fibrotic matrix production, sustained inflammation and retinal contraction expands the understanding of PVR beyond the exclusive involvement of RPE cells. Additionally, glial cells modulate intercellular signaling, promoting the migration and proliferation of RPE cells, macrophages, and fibroblasts, thus creating a self-perpetuating cycle that exacerbates fibrosis and retinal traction.[7-9]

Table 1. Summary of the main early cellular mechanisms involved in the pathogenesis of proliferative vitreoretinopathy, highlighting the central role of retinal pigment epithelial cell epithelial-mesenchymal transition, the inducing factors and the implications for anti-fibrotic therapeutic strategies

Aspects	Detail
Central event	Epithelial-mesenchymal transition of retinal pigment epithelial cells
Primary inducer	TGF-β
Celullar consequences	Migration, extracellular matrix production, contraction
Pro-fibrotic microenvironment	Inflammation plus exposure to plasma proteins
Proposed therapeutic target	Inhibition of TGF-β and blockade of epithelial-mesenchymal transition

TGF-β: transforming growth factor beta.

Table 2. Highlight of glial cells in the context of proliferative vitreoretinopathy, emphasizing their activation, mediation of inflammatory signaling and role in fibrosis, as well as identifying gliosis as a relevant therapeutic target

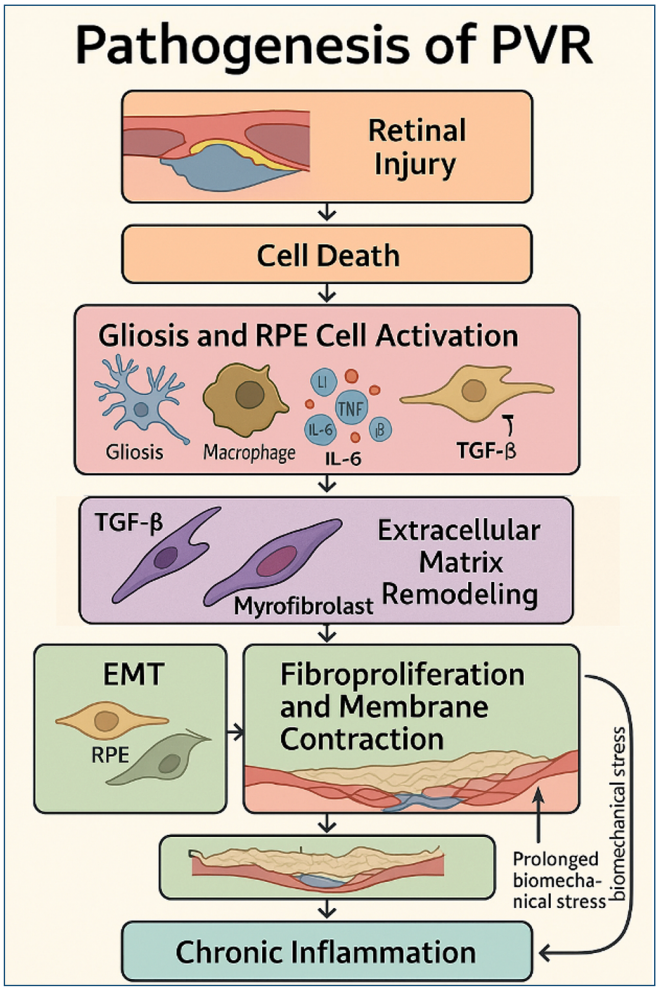
Aspects	Role of glial cells in PVR
Initial activation	Inflammatory response to retinal injury
Factor production	Secretion of inflammatory cytokines, pro-fibrotic factors and extracellular matrix proteins
Fibrosis contribution	Promotion of membrane formation and retinal contraction
Cellular interaction	Communication with retinal pigment epithelial cells, macrophages and fibroblasts
Therapeutic target	Modulation of gliosis to prevent PVR progression

PVR: proliferative vitreoretinopathy.

Vitreous cortex remnants represent another critical element that facilitates adhesion of inflammatory, glial and transformed RPE cells, as well as their migration along the retinal surface. Acting as a biological scaffold for the formation of epiretinal and subretinal membranes, the remnants support the persistence of proliferative stimulus.[7-10] The adherent cortex hinders normal regeneration of the vitreoretinal interface by concentrating cytokines and growth factors locally, thereby perpetuating an environment conducive to aberrant scarring. For this reason, complete removal of the posterior vitreous during surgery is considered a protective factor against the recurrence or worsening of PVR.[7]

Charteris et al. propose a paradigm shift in which PVR is conceptualized not merely as an exaggerated fibrotic response but rather as a failure of retinal regeneration. In this context, Müller cell transdifferentiation

is considered as pivotal as the EMT of RPE cells in the pathogenesis of fibrotic membrane formation. Upon activation, Müller cells acquire a myofibroblast-like phenotype, enabling them to generate contractile forces and secrete profibrotic mediators such as TGF-β, CTGF and key components of the extracellular matrix as well. The remodeled matrix – mechanically stressed and enriched in fibronectin and collagen – is not simply a downstream consequence but an active driver of disease progression. Within the self-sustaining cycle of PVR, this altered biomechanical environment imposes mechanical stress on retinal cells, upregulates TGF-β expression and perpetuates fibrogenesis.[10]



PVR: proliferative vitreoretinopathy; RPE: retinal pigment epithelial; TNF: tumor necrosis factor; IL: interleukin; TGF-β: transforming growth factor beta; EMT: epithelial-mesenchymal transition.

Figure 1. Schematic flowchart illustrating the pathophysiology of proliferative vitreoretinopathy. Illustration created with the assistance of an AI-based tool (ChatGPT, Open AI) and reviewed by the authors.

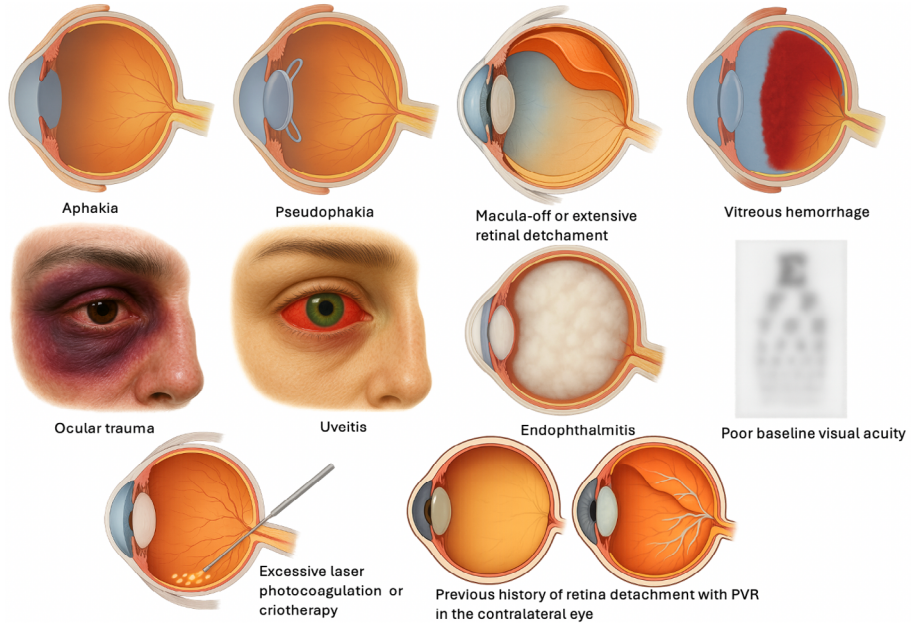
RISK FACTORS

Pro-inflammatory states occurring in the pre-, intra-, and postoperative periods have long been recognized as classical contributors to the development of PVR (Figure 2). In a comprehensive systematic review including 13,875 patients, Xiang et al. identified key ocular risk factors such as aphakia and pseudophakia, the presence of preoperative PVR, vitreous hemorrhage and retinal detachments involving the macula or with extensive spread. Systemic factors intrinsic to the patient have also been implicated, with older age and smoking being frequently associated with increased risk.[11] However, a recent review published in 2025 encompassing data from 57,264 eyes pointed to a distinct pattern, where younger patients and those with systemic hypertension exhibited higher susceptibility to PVR – a finding that underscores an age-related dichotomy in the current literature. Additional clinical predictors include poor baseline visual acuity, a history of ocular trauma, uveitis, choroidal detachment and endophthalmitis.[12] Notably, a prior episode of rhegmatogenous retinal detachment complicated by PVR in the contralateral eye increases the likelihood of PVR by 3.5 times in individuals aged 18 years and older.[13]

Intraoperative cryotherapy has been identified as an independent risk factor for the development of severe (PVR).[14] Similarly, pars plana vitrectomies performed using larger gauge instruments (20G or 23G) have been associated with a 3.6-fold increased risk of PVR development when compared to procedures conducted with 25G systems.[15] Additional intraoperative contributors include excessive panretinal photocoagulation, vitreous loss, incarceration of retinal tissue during subretinal fluid drainage and incomplete tamponade of retinal breaks. These conditions establish a permissive microenvironment for cellular migration and subsequent formation of contractile fibrotic membranes.[16] Notably, despite significant improvements in vitreoretinal surgical methods, the overall incidence of PVR has remained stable over recent years, as consistently demonstrated across the literature.[17]

Genetic background

The genetic susceptibility to PVR is not attributed to a single gene but rather to the combined influence of multiple genetic variants involved in inflammatory regulation, apoptosis and fibrogenesis.[17] Pastor et al. have proposed that polymorphisms in IL-6 and TNF-α may modulate the inflammatory response, suggesting that genetic background is a key factor when combined with environmental triggers such as surgery or intraocular inflammation.[18] Supporting this, a multicenter European study analyzed 224 single nucleotide polymorphisms (SNPs) across 30



PVR: proliferative vitreoretinopathy.

Figure 2. Major risk factors associated with the pathophysiology of proliferative vitreoretinopathy, including predisposing inflammatory, anatomical and surgical conditions. Illustration created with the assistance of an artificial intelligence tool (ChatGPT, Open AI) and reviewed by the authors.

inflammation-associated genes in patients with retinal detachment – with and without PVR – and reported significant associations between PVR and polymorphisms in the TNF, SMAD7 and PI3KCG genes.[19]

CLASSIFICATION OF PROLIFERATIVE VITREORETINOPATHY

The classification of PVR was first proposed in 1983 by the Retina Society Terminology Committee, focusing on morphological features and dividing the disease into four stages (A to D). This system was later refined by the Silicone Oil Study in 1989[20] and by Machemer et al. in 1991[21], who introduced a more detailed framework based on anatomical location and extent of disease, particularly within stage C. These updates, as presented in Table 3, aimed to improve standardization of surgical indications, technical approaches and prognostic evaluation.

In its simplified form, PVR classification includes:

- Stage A (minimal PVR): characterized by pigment clumps and inflammatory cells in the vitreous, associated with vitreous haze but without clinical evidence of retinal traction or membranes – reflecting early, mild inflammation.
- Stage B (moderate PVR): defined by partial-thickness folds on the inner retinal surface and/or wrinkling of retinal break margins. The retina often appears stiffer with localized vessel tortuosity, indicating the beginning of tangential traction.
- Stage C (severe PVR): marked by fixed, full-thickness retinal folds and the presence of epiretinal or subretinal contractile membranes. This stage is anatomically subdivided into anterior (C-A), posterior (C-P), or combined (C A/P) based on the location of the membranes relative to the equator. The extent of retinal involvement is graded as C1 (≤ 1 quadrant), C2 (≤ 2 quadrants), C3 (≤ 3 quadrants), or C4 (total retinal involvement). This stage is anatomically subdivided approximately at the level of the ocular equator into anterior PVR (C-A), posterior PVR (C-P), or combined (C A/P). On the basis of the extent of retinal involvement, grade C PVR is further classified as:
  - C1: up to one quadrant (3 clock hours).
  - C2: up to two quadrants (4 to 6 clock hours).
  - C3: up to three quadrants (7 to 9 clock hours).
  - C4: involvement of all four quadrants.

Table 3. Classification of proliferative vitreoretinopathy according to severity grade, anatomical location and extent of vitreoretinal alterations

Grade	Characteristics	Location	Extent
A	Vitreous cells	—	—
B	Retinal wrinkling, fixed folds	—	—
C-P	Tractional membranes	Posterior retina	1 to 4 quadrants
C-A	Tractional membranes	Anterior retina	1 to 4 quadrants

Stage D (massive PVR), previously described as full thickness fixed retinal folds involving all four quadrants,[1] was ultimately removed from the classification system. Despite significant efforts toward standardization, current classification schemes continue to show limited and inconsistent application in clinical practice. Studies have demonstrated a low rate of comprehensive use of these criteria, particularly concerning the detailed anatomical and severity-based description of grade C PVR.[22] Updating the existing clinical classification of PVR may provide clinicians with a more precise framework for subclassifying cases, enabling earlier recognition and treatment and ultimately improving patient outcomes.[23]

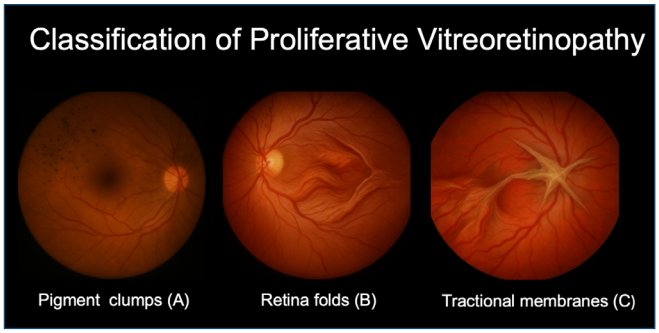


Figure 3. Simplified schematic representation of proliferative vitreoretinopathy classification. Illustration generated with de assistance of an artificial intelligence tool (Chat GPT, Open AI), subsequently adapted and validated by the authors.

Classification of contraction patterns in grade C proliferative vitreoretinopathy [21,22]

Posterior proliferative vitreoretinopathy (C-P)

Type 1: focal

Focal posterior contractions or localized traction with retinal folds confined to specific areas. Single starfold or multiple single isolated starfolds.

Type 2: diffuse

Presence of multiple retinal folds involving more extensive regions of the retina.

Type 3: subretinal

Formation of subretinal membranes, as illustrated in Figure 4, including:

- Starfolds posterior to the vitreous base.
- Confluent folds potentially obscuring the optic disc.
- Subretinal proliferation with annular or linear membranes.

Anterior proliferative vitreoretinopathy (C-A)

Type 4: circumferential contraction

Circumferential contraction exerting traction on the retina at the posterior margin of the vitreous base, pulling the peripheral retina centripetally, leading to distortion and potential shortening of the retina. These configurations may pose significant challenges to surgical reattachment due to the rigidity and fixed nature of the folds.

Type 5

Anterior displacement: anterior traction of the retina at the vitreous base, potentially leading to anterior displacement of the retina. This pattern pulls the peripheral retina forward, toward the vitreous base, ciliary body or even the posterior surface of the iris. The anterior traction causes the retina to fold or buckle anteriorly, often resulting in shortening of the peripheral retina. Such displacement may create a rigid trough-like configuration, making retinal reattachment more challenging and increasing the risk of retinal incarceration during surgery.

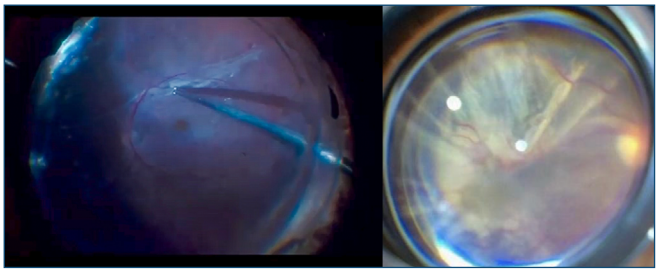


Figure 4. Examples of grade C-P proliferative vitreoretinopathy with subretinal membranes.

TREATMENT OF PROLIFERATIVE VITREORETINOPATHY

During the preoperative evaluation of patients with rhegmatogenous retinal detachment, it is important to consider:[18]

- The extent and duration of the detachment: the more extensive and prolonged the retinal detachment, the more pronounced the exposure of RPE cells and the release of pro-inflammatory cytokines is.
- The presence of grade B or C PVR at initial diagnosis: the presence of PVR at the time of diagnosis increases the risk of progression, even after complete surgical removal.
- Vitreous hemorrhage: the presence of blood cells in the vitreous cavity promotes cell migration and proliferation.

- Ocular trauma or history of previous intraocular surgery: disruption of the blood-retinal barrier facilitates the migration of inflammatory cells.
- Intraocular inflammation: eyes with uveitis represent an increased risk of developing PVR.
- Several of these risk factors are depicted in Figure 5.

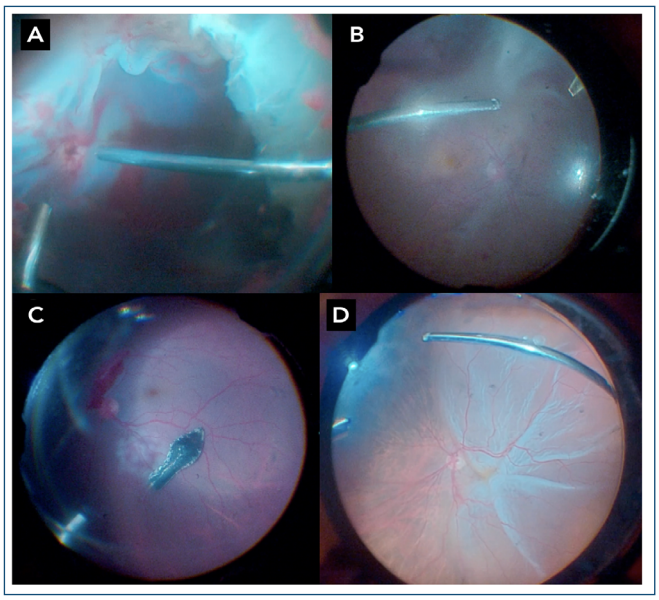


Figure 5. Preoperative risk factors for proliferative vitreoretinopathy development. (A) Retinal detachment following penetrating trauma with giant retinal tear and vitreous hemorrhage; (B) endophthalmitis; (C) trauma with metallic intraocular foreign body; (D) macula-off rhegmatogenous retinal detachment with grade B proliferative vitreoretinopathy.

The main intraoperative risk factors include:[24] iatrogenic retinal breaks; intraoperative hemorrhages; prolonged surgical time with excessive tissue manipulation; choroidal detachment; and excessive laser application and cryotherapy.

Surgical management of PVR involves complete removal of the residual vitreous, posterior hyaloid, and both epiretinal and subretinal membranes responsible for retinal traction. The PVR formation cycle is known to extend over approximately 90 days. However, in cases of recurrent retinal detachment due to early membrane formation, it may be advisable to delay reoperation until membrane maturation to facilitate dissection and reduce the risk of exacerbating the inflammatory response associated with early surgical intervention. Moreover, mature membranes are typically easier to identify and remove. In contrast, if the redetachment involves the macula, immediate reintervention is imperative to preserve the patient's visual prognosis.[26]

Small-gauge vitrectomy systems (23, 25 or 27 G) have significantly advanced the surgical management of PVR by enabling a less invasive approach, characterized by smaller incisions, reduced ocular trauma, and faster postoperative recovery. These platforms provide superior fluidic control and enhanced intraocular stability, which are critical for the effective removal of both epiretinal and subretinal membranes. Furthermore, the use of chandelier illumination and bimanual techniques – facilitated by small-gauge systems – improves visualization and enhances safety during complete vitreous and tractional membrane dissection. These factors contribute to higher rates of anatomical success, reduced postoperative inflammation and subsequently lower recurrence rates of PVR.[(27)]

In the context of membrane identification, chromovitrectomy has emerged as an essential tool in the surgical management of PVR. Brilliant blue dye plays a particularly important role in the visualization and effective removal of the ILM, which may serve as a scaffold for the recurrence of epiretinal membranes. Brilliant blue provides excellent staining of the ILM, facilitating membrane peeling even in peripheral regions or in areas with structural alterations secondary to PVR. The dye can be applied following fluid-air exchange to achieve a higher concentration over the retinal surface, enhancing visualization of preretinal membranes through a negative staining effect (Figure 6). Moreover, brilliant blue stands out for its superior safety profile when compared to other dyes, such as indocyanine green, demonstrating lower retinal toxicity at clinically used concentrations.[28] Consequently, its use may reduce the risk of PVR recurrence and contribute to improved anatomical and functional postoperative outcomes.

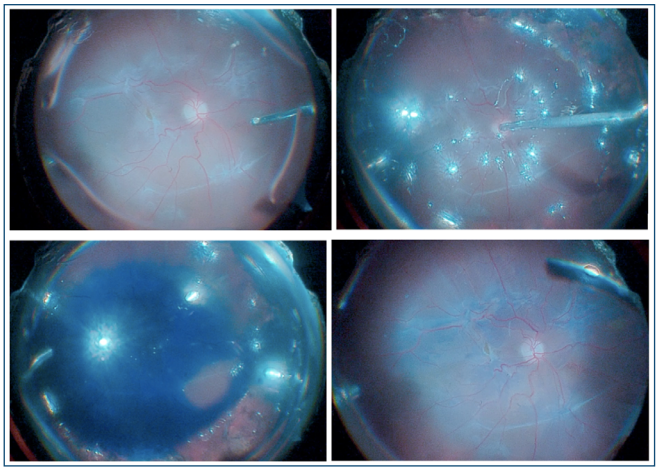


Figure 6. The phenomenon of negative staining is observed, in which a fluid-air exchange is performed followed by injection of brilliant blue dye under air. Upon BSS infusion, areas of proliferative vitreoretinopathy become highlighted adjacent to the internal limiting membrane stained by the brilliant blue dye.

The surgical technique for the removal of PVR requires meticulous maneuvers, in which the use of retinal forceps plays a central role. High-precision forceps are employed to peel both epiretinal and subretinal membranes. A critical initial step is the identification of the most accessible adhesion point of the membrane, often revealed following staining with brilliant blue dye. Using delicate forceps, such as the Eckardt type, the surgeon initiates a pinch-and-peel maneuver, gently lifting the membrane to separate it from the retinal surface. Frequently, the posterior pole – particularly the macular region – is the preferred site for initiating membrane dissection. In advanced PVR cases, membranes are often densely adherent or interdigitated with the retina, requiring adjunctive techniques such as delamination or bimanual dissection. In this approach, one hand manipulates the forceps while the other uses a pick or spatula to dissect the interface between the membrane and the retina. Accessory chandelier illumination is essential in this context, allowing bimanual manipulation and enhancing stereoscopic visualization. Perfluorocarbon liquid is widely used to stabilize the retina during these maneuvers by flattening detached areas and providing counter-traction, thus facilitating membrane removal with reduced iatrogenic risk (Figure 7). Additionally, PFCL may serve as a temporary tamponade during retinectomies or aid in the exclusion of active subretinal traction (Figure 8).[29,31] The precise combination of appropriate surgical instruments and intraocular adjuvants such as PFCL is essential for optimizing visualization, minimizing trauma and improving surgical success rates in complex cases of PVR.

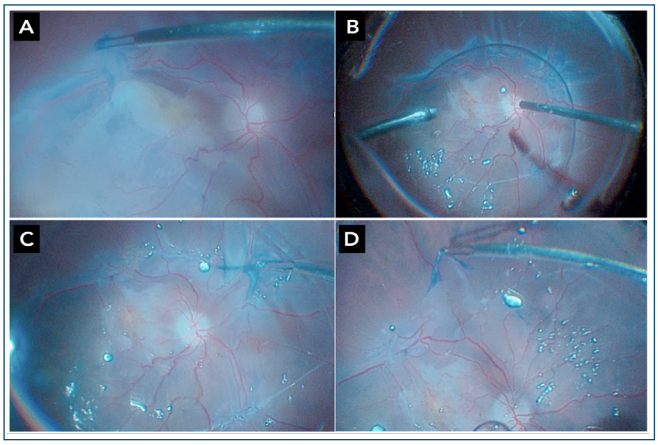


Figure 7. (A) Membrane dissection is initiated at the macular region; (B) perfluorocarbon liquid is applied to stabilize the posterior pole; (C and D) removal of preretinal membranes under perfluorocarbon using forceps.

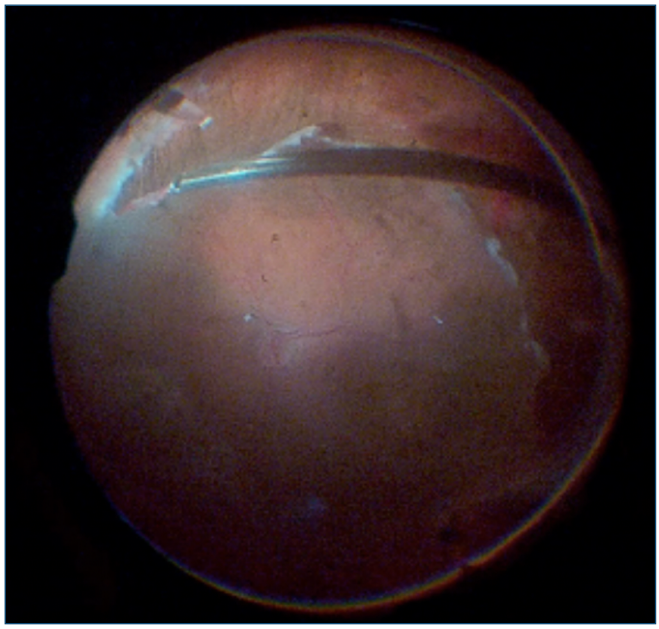


Figure 8. Advanced case of recurrent retinal detachment due to proliferative vitreoretinopathy, in which an inferior retinectomy was performed with the aid of perfluorocarbon liquid to stabilize the posterior pole.

SURGICAL STRATEGIES TO MAXIMIZE RETINAL ATTACHMENT SUCCESS

Combination pars plana vitrectomy and scleral buckle

Some studies have shown that single surgery attachment success (SSAS) is higher in eyes predisposed to PVR, most likely because the buckle mitigates residual circumferential and antero-posterior traction at the vitreous base. In a series of 389 eyes, SSAS was 80.8% with PPV-SB *versus* 67% with PPV alone.[6]

The combination of these techniques provides additional mechanical support to the retina. Retrospective analysis has demonstrated a significantly higher rate of anatomical success compared to PPV alone, particularly in cases involving inferior retinal breaks and advanced PVR.[32] Moreover, scleral buckling may be especially beneficial in pseudophakic eyes, where vitrectomy alone may be insufficient to manage peripheral traction.[33] Therefore, the combined approach should be considered in cases of recurrent retinal detachment due to PVR, with the aim of optimizing both anatomical and functional outcomes.

Extended internal limiting membrane peeling

Removing the ILM beyond the vascular arcades could help eliminate a potential scaffold for cell proliferation.

Two retrospective series showed the benefit of "arcade to arcade" ILM peeling in improving anatomic success and reducing PVR-related redetachments.[34,35] Prospective, randomized trials are still lacking; nevertheless, converging observational evidence supports incorporating extended ILM peeling to maximize anatomic and visual outcomes.

Vitreous-base management

Vitreous-cortex remnants appear to be an important intraoperative contributor to PVR, and complete removal of these scaffolds at the vitreous base is recommended during vitrectomy in high-risk eyes.[7] Triamcinolone acetonide staining markedly improves visualization of the posterior hyaloid and vitreous remnants, permitting more thorough excision and lowering the likelihood of residual scaffold. In a prospective series of eyes undergoing rhegmatogenous retinal detachment repair complicated by early PVR, triamcinolone-assisted vitrectomy achieved higher hyaloid removal and lower membrane recurrence rate.[36]

Amniotic membrane patching

Human amniotic membrane patches placed over large retinal breaks or retinectomy edges could also work as both a physical barrier and a biologically active TGF-β-suppressive matrix.[37] Although this therapy is not widely available and is rarely used, it may nevertheless serve as a valuable adjuvant in eyes with complex PVR.

Tamponade selection

Tamponade selection influences both the mechanical stability of the retina and the biological environment in which PVR evolves. Silicone oil is the vitreous substitute of choice in cases of retinal detachment associated with PVR, particularly in complex scenarios involving multiple retinal breaks, subretinal traction and peripheral retinectomies.[38] However, the Silicone Oil Study,[39,40] multicenter prospective randomized trial, and the European Vitreoretinal Society Retinal Detachment Study found no significant difference in anatomical success between perfluoropropane gas and silicone oil.[41] Collectively, these data support the use of either C_3F_8 or standard-viscosity (1,000 or 5,000 cSt) silicone oil in eyes with established or high-risk PVR, while discouraging the use of short-acting gases. When extensive and complex inferior pathology is present, heavy silicone oils or short-term perfluoro-octane tamponade may still confer additional mechanical benefit.[38] It is always important to consider potential complications associated with prolonged use of silicone oil, such as ocular hypertension, cataract formation in phakic patients and silicone oil emulsification.

PHARMACOLOGIC APPROACH

Methotrexate

Folate antagonism offers dual anti-proliferative and anti-inflammatory effects – both of which target key pathways in the development of PVR. Methotrexate has emerged as the most promising pharmacologic agent in this context. In phase 3 GUARD trial, 13 intravitreal injections of methotrexate 0.8% (ADX-2191) administered over four months reduced the rate of redetachment within six months from 39% in historical controls to 24% in treated eyes, achieving statistical significance and meeting the trial's primary endpoint.[42] Other series have reported similar findings with alternative low-dose methotrexate regimens; however, some studies, including multicenter trial, have shown no significant difference in overall rates of PVR formation.[43] These mixed outcomes suggest that while methotrexate appears to be a feasible pharmacologic adjuvant in selected cases, further well-designed prospective studies are still necessary to confirm its efficacy, define optimal dosing strategies and fully establish its safety profile.[43-45]

Corticosteroids

One of the first classes of agents studied to prevent PVR were systemic corticosteroids. However, systemic corticosteroid therapy has yielded conflicting results in this context.[(46,47] Intravitreal triamcinolone acetonide, although commonly employed for its anti-inflammatory properties, has not shown consistent efficacy in preventing recurrent retinal detachment or improving anatomical outcomes in eyes with PVR. Sustained-release corticosteroid delivery systems have also been investigated, but results have been similarly inconsistent.[48] Nevertheless, it remains a valuable adjunct in managing postoperative cystoid macular edema.[49]

Antimetabolites and alkylating agents

5-fluorouracil (5-FU) combined with heparin has shown inconsistent outcomes; large, randomized trials found no anatomical benefit.[50,51]

Melphalan, widely used in the treatment of intraocular retinoblastoma, is currently undergoing a first-in-human safety assessment clinical trial led by a Brazilian group at the *Escola Paulista de Medicina*. Its rationale is based on its potent nucleic acid alkylating mechanism

and a potentially favorable low-dose ocular safety profile,[52,53] and it may offer a promising new therapeutic alternative for managing PVR in the coming years.

Infliximab

Infliximab is a chimeric monoclonal antibody that targets tumor necrosis factor-alpha (TNF-α), a pro-inflammatory cytokine involved in the pathophysiology of several ocular and systemic inflammatory diseases. Its prior success in treating autoimmune and ocular inflammatory conditions supports its potential utility in modulating the inflammatory cascade that drives PVR progression.[54,55] The FIXER trial evaluated a single 1 mg intravitreal injection of infliximab into the air-filled globe prior to silicone oil placement during vitrectomy for grade C PVR. The study reported modest improvements in final visual acuity but no significant difference in anatomical outcomes.[56]

PERSPECTIVE

Several ongoing clinical trials are exploring novel pharmacological strategies for the prevention and treatment of PVR. Among the most promising are Rho-kinase (ROCK) inhibitors, such as topical netarsudil, and intravitreal melphalan, an alkylating agent currently undergoing first-in-human evaluation. While many of these agents remain investigational, methotrexate continues to be the only therapy supported by phase 3 evidence demonstrating reduction in redetachment rates in high-risk eyes.

Looking ahead, combination therapies that sequentially target both the inflammatory and proliferative phases of PVR are a rational next step. In parallel, the integration of artificial intelligence tools – integrating clinical data, ultra-widefield imaging and genetic risk markers – may enable individualized risk stratification and optimize prophylactic strategies. These advances have the potential of shifting PVR management from reactive treatment to proactive prevention.

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