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Simple retinal detachments: identifying the at-risk case

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Abstract

The success rate of retinal reattachment surgery has now reached over 90%. The major cause of failure is attributable to the development of proliferative vitreoretinopathy (PVR). It is a complex process comprised of events that are similar to those of the wound healing response with inflammation, migration and proliferation of a variety of cells. These membranes can exert traction and reopen previously closed retinal breaks, create new breaks, and distort or obscure the macula.

In the early part of this century the success rate of retinal reattachment surgery was virtually nil and it was not until a better understanding of the pathophysiology of retinal detachment was gained that the success rate improved. It was Gonin who emphasised the relationship between vitreous detachment and traction resulting in retinal tears that led to treatment aimed at closing retinal breaks.

To increase even further the final success rate in the treatment of 'simple retinal detachments' a better understanding of the risk factors for PVR is needed in patients presenting with acute retinal detachments. Such risk factors can be broadly divided under the headings of preoperative risk factors, best surgical management and possibly adjuvant therapy.
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The success rate of retinal reattachment surgery has now reached over 90%.[1] The major cause of failure is attributable to the development of proliferative vitreoretinopathy (PVR).[1,2] It is a complex process comprised of events that are similar to those of the wound healing response with inflammation, migration and proliferation of a variety of cells.[3–5] These membranes can exert traction and reopen previously closed retinal breaks, create new breaks, and distort or obscure the macula.

In the early part of this century the success rate of retinal reattachment surgery was virtually nil and it was not until a better understanding of the pathophysiology of retinal detachment was gained that the success rate improved. It was Gonin who emphasised the relationship between vitreous detachment and traction resulting in retinal tears that led to treatment aimed at closing retinal breaks. It is interesting to note that Gonin's summary of the aim of retinal reattachment surgery stands true even today:

'Retinal reattachment to be durable requires that the traction exerted on the retina by the vitreous be eliminated or be counterbalanced by an appropriate chorioretinal adhesion. The possibility of such a reattachment is conceivable only after closure of the retinal break(s)'.[6] Subsequent improvement in techniques has since dramatically improved the success rate.

To increase even further the final success rate in the treatment of 'simple retinal detachments' a better understanding of the risks factors for PVR is needed in patients presenting with acute retinal detachments. Such risk factors can be broadly divided under the headings of preoperative risk factors, best surgical management and possibly adjuvant therapy.

Preoperative risk factors

To improve the prognosis of retinal detachment surgery, recent research has focused on the use of intravitreal pharmacological agents to prevent the occurrence of PVR.[7–13] As it is now possible to

treat patients at high risk of developing PVR),[14] it is important to identify and target those patients who would benefit most from this treatment. A similar principle is used to maximise efficacy and minimise side-effects of anti-scarring therapy in glaucoma filtration surgery.[15]

Many studies have been done to investigate the risk factors for developing PVR. The majorities of these studies have been retrospective and have looked at individual risk factors only. It is worth noting that many differences exist in methodology, definitions and statistical analysis in these studies and so they cannot be compared directly. Until recently the risk of developing PVR had not been investigated in a prospective study. Tolentino *et al* in 1967[16] suggested that vitreous haemorrhage and vitreous syneresis were risk factors. Chignell *et al*[17] found aphakia to be a significant risk factor. They postulated that aphakia made the localisation of small holes difficult and therefore led to treatment failure. They concluded that it was failure to close all retinal breaks that led to PVR.

Rachal and Burton[1] suggested that repeat surgery is associated with the development of PVR. This may have been due to a combination of preoperative risk factors such as aphakia and missed breaks, to intraoperative factors or inadequate treatment.

Bonnet *et al*[18] in a retrospective study found the following risk factors to be associated with postoperative PVR: preoperative grade C plus PVR, repeat retinal reattachment surgery and large retinal breaks exposing more than 3 disc diameters of pigment. In a later prospective study Bonnet[19] found preoperative Grade B and vitreous haemorrhage to be associated with the development of PVR.

Yoshida *et al*[20] in a large retrospective series of patients with PVR treated with conventional scleral buckling procedures found the size of retinal breaks, severity of preoperative PVR, vitreous haemorrhage and postoperative choroidal haemorrhage to be risk factors.

Lambrou *et al*[21] reported that the use of silicone oil increases the risk of PVR. They looked at the effect of silicone oil, perfluoropropane gas or fluid in the vitreous cavity of rabbits. They reported that a higher proportion of silicone-filled eyes (83%) had severe proliferative vitreoretinopathy than either the perfluoropropane-filled (30%) or fluid-filled (10%) eyes. An *in vitro* proliferation assay using the vitreous samples showed that the silicone-filled vitreous had increased mitogenic activity for retinal pigment epithelial cells compared with the gas-filled or fluid-filled vitreous. They felt that silicone oil appears to increase proliferation by stimulating the release of more or different mitogenic factors as well as concentrating active factors into a smaller volume near the retina. Lewis *et al*[22] suggested that silicone oil causes perisilicone proliferation in eyes treated for advanced PVR. They found that 19 (61%) out of 31 eyes developed perisilicone proliferation and that this led to redetachment in 15 (49%) eyes. Zilis *et al*[23] also found a high incidence of perisilicone proliferation. In their series 21/55 (38%) developed perisilicone proliferation. The result of these studies must be viewed with caution as they were descriptive and not randomised or case controlled.

Cowley *et al*[24] in 1989 retrospectively analysed 607 eyes undergoing retinal reattachment surgery. Using stepwise discriminant analysis they found the use of vitrectomy to be a strong risk factor. Other risk factors in order of importance were the presence of preoperative PVR, preoperative choroidal detachment, and the amount of cryopexy applied.

Malbran *et al*[25] in a retrospective study of 1180 patients found vitreous traction on horseshoe or crescent-shaped tears to be the determining factor for the development of proliferative vitreoretinopathy (PVR) and that small or round holes were not complicated by PVR.

Fleury *et al*[26] prospectively analysed 60 eyes complicated by recurrent retinal detachment and PVR. They report a strong association with new breaks and postoperative PVR with a worse prognosis for new posterior tears. They concluded that new posterior breaks related to severe tangential traction and therefore represented a worse prognosis.

Nagasaki *et al*[27,28] looked at risk factors in aphakic eyes using regression analysis. They identified the following risk factors for developing PVR in order of significance: choroidal detachment, duration of retinal detachment longer than one month, occurrence of retinal detachment within one year following cataract surgery, and history of vitreous loss in cataract surgery.

Girard *et al* in 1994 conducted a large retrospective study of 1020 retinal detachments with no or mild preoperative PVR. Using multiple regression analysis they identified ten significant predictive variables for PVR. They were in increasing order of importance: minor intra- or postoperative haemorrhage, grade A preoperative PVR, preoperative choroidal detachment, giant tears, air tamponade, detachment involving more than two quadrants, cumulative break area larger than three optic disks, postoperative choroidal detachment, presence of uveitis at initial examination, and grade B preoperative PVR.

More recent work by Kon *et al*[29,30] has looked at biological risk factors. They have shown that vitreous protein and cytokines are predictive of PVR. Using

multiple logistic regression analysis they found vitreous protein, high levels of matrix metalloproteinases 2 and 9 and IL-6 to be independent risk factors. Limb *et al* also looked at biological risk factors and found elevated levels of IL-6, IL-1 and IFN to be associated with PVR.[31] They also found the cell adhesion molecule ICAM to be a risk factor for PVR.[32,33]

In a recent prospective study, Kon *et al*[34] looked at the risk factors for the development of PVR in patients undergoing a primary vitrectomy for a rhegmatogenous retinal detachment. They looked at 140 consecutive patients with rhegmatogenous retinal detachment in whom vitrectomy was considered necessary for a number of reasons, including giant retinal tear, posterior retinal break, the presence of preoperative PVR. Twelve clinical variables were recorded and vitreous samples obtained for measurement of protein concentration. Univariate and multivariate logistic regression analysis were used to determine the risk factors for PVR. This study has shown that PVR has an adverse effect not only on the surgical outcome but also on the final visual acuity achieved in successful cases. Using multifactorial analysis, the study has also shown that significant risk factors for the development of postoperative PVR are preoperative PVR, breached posterior capsule and high vitreous protein levels.

The existence of preoperative PVR suggests that the cellular, extracellular and chemical elements required for wound healing are present. It is therefore not unreasonable to expect preoperative PVR to be a risk factor for the development of postoperative PVR. The pathological mechanism by which a breached posterior capsule could be related to the development of PVR is unclear. However, the breakdown of blood-ocular barrier may be significant.[35] Miyake[36,37] found that there was more disruption to the blood-retinal barrier after intracapsular compared to extracapsular cataract extraction. Miyake *et al*[38] also found that the outward active transport of fluorescein from the vitreous was reduced in aphakic compared to phakic eyes. They suggested that the posterior lens capsule may protect the anterior uvea (site of active transport) from mechanical and physical irritation by the vitreous gel. The disruption of blood-retinal barrier would, in theory, allow serum factors eg fibronectin to enter and remain in the vitreous and may enhance the development of PVR.

The total protein level represents the sum of all the detectable proteinaceous components in the vitreous and therefore does not provide specific information regarding individual enzymatic or cytokine activity. Nevertheless, the total protein level can provide information on the presence of inflammation, breakdown of blood-retinal barrier and the severity of subsequent wound healing. A significantly higher ($P < 0.05$) protein level in the vitreous of eyes with preoperative PVR was found compared to those without (mean of 5.72 mg/ml *vs* 2.89 mg/ml). This finding is in agreement with previous studies[3,39] although the difference in protein level between the PVR and non-PVR groups in this study is smaller. Connor *et al*[39] found a five-fold, Kauffmann *et al*[3] found a three-fold, while Kon *et al*'s study only found a two-fold increase.

Although protein levels are a significant risk factor, the measurement of protein concentration in the vitreous takes at least 45 minutes. Therefore, at present only clinical risk factors can be used clinically to assess risk. In a separate study, using a discriminant rule based on these risk factors, a formula was developed to prospectively identify those patients most likely to develop PVR.[40] This study has shown that using a clinical risk formula it is possible to identify individuals at greatest risk of PVR. The incidence of PVR in the group identified as at 'high' risk was significantly greater than that in the group identified as at 'low risk' ($P < 0.001$).

Intraoperative risk factors

The basic principles of treating retinal detachment are to reduce the factors that maintain retinal detachment, to optimise the factors promoting retinal adhesion and to create permanent retinal adhesion while creating minimal surgical trauma. The principles of treatment of detachments complicated by PVR are similar to those of detachments generally. These involve the identification and closure of retinal breaks and the complete release of retinal traction. To these can be added the prevention of reoccurrence of the proliferative process and its resulting traction.

The decision about the type of procedure for treating primary rhegmatogenous retinal detachments depends on several factors. The ocular factors include size and number of retinal breaks, the position of the break(s), the presence and grade of PVR and the presence of a posterior vitreous detachment. As advances are made in the science and technology of retinal detachments the means of treating detachments will change. In essence, at present, in every case of retinal detachment an understanding of the main forces that caused the retinal detachment is required. Careful examination with biomicroscopy and scleral indentation is needed preoperatively.

In the 1930s failure of retinal reattachment surgery was often attributed to high myopia, aphakia, extent of

retinal detachment and inflammation.[41] Inability to locate and treat the retinal breaks was not considered to be a major risk factor. It was not until 1964 that Okamura *et al*[42] stated that the major factor leading to failure of surgery was the inability to close all retinal breaks. In addition, as mentioned there has been an increasing realisation that the development of proliferative vitreoretinopathy is the main cause of eventual failure of retinal reattachment surgery.

Closure of all retinal breaks is a prerequisite to achieving retinal reattachment. If the break is closed the forces tending to reattach the retina can overcome the traction tending to reopen the breaks. These forces can even overcome what appears to be clinically quite severe PVR. As mentioned, inability to close the retinal break has been quoted as the major cause of failure by many authors.[17,43] Gerhard and Flament[1] reported that inability to close a known break was the main cause of failure in their series.

An inadequate buckle either poorly placed, too narrow, or too shallow is another major risk factor related to failure of retinal reattachment surgery.[17,43]

Closure of the retinal break is achieved by creating a chorioretinal scar along the edges of the retinal break. This adhesion is usually achieved using either cryotherapy or laser. Laser photocoagulation is preferred as cryotherapy has been shown to increase the dispersion of RPE cells[44] and theoretically the development of PVR. However, in one series following cryotherapy for giant retinal tears there was no PVR.[44] It is important to apply adequate treatment to achieve chorioretinal adhesion. Chignell *et al*[17] in their series found that 30% of primary failures were reattached by repeat photocoagulation alone suggesting that there was insufficient chorioretinal adhesion from the initial treatment.

The development of new retinal breaks is another major risk factor for failure.[1,17] New retinal breaks have been reported in up to 23% eyes following pneumatic retinopexy.[45] It is thought that eyes with visible traction bands between the retinal break and another area of the retina are particularly at risk.[46] Primary vitrectomy has also been associated with the development of new retinal breaks in up to 26% of cases.[47] A careful examination of the retina is indicated after vitrectomy to detect new retinal breaks so that they can be treated at the same seating.

Some authors have suggested that all primary retinal detachments should be done in specialist vitreoretinal units. Comer *et al*[48] audited the success rate of the vitreoretinal specialists (90%) which was greater than that of the general ophthalmologists in non specialist units (ranging from 47% to 77%), despite case selection by the general ophthalmologists. They concluded that the outcome of primary retinal reattachment surgery can be improved if surgery is performed by an experienced vitreoretinal surgeon. They also suggested that the current standard for retinal reattachment with a single procedure should be set in the region of 85–90%.

Therefore, a knowledge of the preoperative risk factors that lead to PVR should alert the retinal surgeon that meticulous surgical techniques should be followed to achieve retinal reattachment. There will be some cases of failure that are unavoidable with present surgical management, in particular the development of PVR and new retinal breaks. All other causes of failure can be minimised with improved utilisation of current surgical techniques.

Adjuvant therapy for the treatment of PVR

PVR is a complex process involving cellular proliferation of a variety of cells and secretion and remodelling of the extracellular matrix.[49] Laboratory and clinical studies suggest that pharmacological adjuvant therapy can modify the proliferative disease process and improve the success of surgery. There are a number of studies showing a potential benefit of a variety of pharmacological interventions including: retinoic acid,[7–17,50,51] dexamethasone,[11–13,52,53] colchicine,[14,15,54] taxol[16,17,55] and daunorubicin.[18,19,56] However, none of these regimens are in routine clinical use.

5-fluorouracil (5-FU) has been shown to be effective in reducing the rate of PVR in animal models.[20,21,57] Toxicity studies using either single or multiple intravitreal injections of 5-FU produced no morphological or electrophysiological changes in the rabbit retina at low dosages.[22,23,58] A prospective study in human eyes showed that a single injection of 10 mg of 5-FU was well tolerated.[59] However, both this study and another also using a single injection of 1 mg of 5-FU[12] did not improve the success of surgery. Recent laboratory work from our center has shown that short exposures to 5-FU result in prolonged cellular growth arrest of Tenon's capsule fibroblasts.[25,26,27,60] Subsequent experiments have shown that 30-min exposure *in vivo* can cause cellular growth arrest of RPE cells.[61]

Low molecular weight heparin (LMWH) is a multipotential drug useful in the treatment of PVR. LMWH has been shown to reduce postoperative fibrin following vitrectomy[62] and to have less haematological complications compared with non-fractionated heparin.[63]

Heparin binds to fibronectin and to a wide range of growth factors including acidic and basic fibroblast growth factors and platelet derived growth factors.[64]

Animal work has shown that LMWH is effective in reducing the rate of tractional retinal detachment and produced no toxic effects in the rabbit eye when infused using a dose of 5 IU/ml.[62]

Only two large prospective trials have so far been reported on the use of adjuvant therapy to treat PVR. The first used daunomycin. Daunomycin is a very effective antiproliferative agent and its action is independent of the cell cycle.[56] Daunomycin arrests cell proliferation and migration but not contraction *in vitro*.[65] There are only a few reports on the use of daunomycin in human eyes. In a series of 15 eyes[56] with PVR following trauma infusion of 7.5 μg/ml for 10 min of daunomycin after pars plana vitrectomy, anatomic success was the result in 93% of patients. Visual acuity improved in all patients and there were no clinical signs of toxicity to the cornea, lens, retina or optic nerve.

Wiedemann *et al*[10] went on to treat a further 69 patients with advanced PVR with vitrectomy and silicone oil tamponade and adjuvant daunomycin therapy. After long-term follow-up 73% were attached and 89% had a vision of 20/800 or better. They found no specific toxicity due to daunomycin. The authors also found the reoperation rate to be less with treatment.

Both these studies gave the impetus to test the use of daunomycin in a randomised control trial in patients with PVR. Two hundred and eighty-six patients with stage C2 (Retina Society Classification, 1983) or more advanced PVR in whom surgery with silicone oil was carried out, were randomised. Standardized surgery plus adjunctive daunomycin perfusion (7.5 μg/ml for 10 min) was compared with surgery alone. Six months after standardized surgery, there was no significant difference in complete retinal reattachment without additional vitreoretinal surgery between the daunomycin group (62.7%) *vs* the control group (54.1%) ($P = 0.07$, one-sided). However, in the daunomycin group, significantly fewer vitreoretinal reoperations were performed within the subsequent year ($P = 0.005$, one-sided) to achieve the same overall 1-year retinal reattachment rate. The rate of primary success rate was 65.5% in the daunorubicin group *vs* 53.9% in the control group. There was no difference in the best-corrected visual acuity between the two groups. No severe adverse effects related to daunorubicin were found. The authors did not recommend routine use of this treatment but did conclude that pharmacological intervention is possible.

A recently published study used a combination of 5-FU and low molecular weight heparin in high risk patients. One hundred and seventy-four high risk patients were randomised to receive either 5-FU/heparin therapy or placebo. Patients were selected from all patients undergoing primary vitrectomy for rhegmatogenous retinal detachment. As 5-FU and LMWH are effective in different aspects in the PVR process it was felt that a synergistic approach to the prevention of PVR would be advantageous. The primary outcome measure of postoperative PVR was evaluated in 167 patients (82 in the placebo and 85 in the combined group). These data were missing in seven patients (five in the placebo and two in the combined group). The rate of postoperative PVR in the placebo group was 26.4% (23/87) and 12.6% (11/87) in the combined treatment group. The Mantel–Haenszel chi-square test yielded a P value of 0.02 for a treatment effect.

The final visual acuity outcome was also significantly worse in the placebo-treated group ($\chi^2_{(2)} = 3.9$, $P = 0.048$). In conclusion it was shown that by using adjuvant treatment with 5-FU and LMWH it is possible to significantly reduce the rate of postoperative PVR.

Both these studies have shown that it is possible to use adjuvant therapy to treat PVR and therefore reduce the incidence of this visually devastating disease. As these and other more specific treatments become available the need to define the risk factors and thereby those most likely to benefit will become more important.

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