Improving the Outcome of **Rhegmatogenous Retinal Detachment Repair**

Marc Veckeneer

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by Adding Pieces to the Puzzle

Historical review and recent contributions

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Improving the Outcome of Rhegmatogenous Retinal Detachment Repair by Adding Pieces to the Puzzle
Historical review and recent contributions

De resultaten van de chirurgische behandeling van rhegmatogene netvlieslosating verbeteren door puzzelstukken op hun plaats te zetten
Historische reflectie en recente bijdragen

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Introduction

The retina is the neuronal structure of the eye where the optical image of the outside world is transformed into a signal that can be transmitted to the brain.

Direct apposition of the retina to underlying retinal pigment epithelium (RPE) is essential for normal retinal function and detachment will cause profound loss of vision of the affected eye.

In rhegmatogenous retinal detachment (RRD), the most common form of retinal detachment (RD), a retinal "break" allows fluid from the vitreous cavity to gain access to the subretinal space, resulting in the separation of the retina from the RPE. The retinal break usually occurs at the time of a spontaneous vitreous detachment that causes traction on the retina in an area called the vitreous base where the vitreous is particularly well attached to the retina [*Le Goff*[1]*, Bishop 2008*].

The incidence of RRD has often been estimated at about 1/10000 [*Fraser*[2]*, Steel 2010*]. A recent study on the incidence of RRD in the Netherlands reported a significantly higher incidence of 18.2/100000 [*Van de Put*[3] *et al. 2013*]. These results are in accordance with the results from a nationwide study in Denmark that also showed an increasing incidence over an 11 year period [*Hajari*[4]*, la Cour et al. 2014*].

With increasing knowledge of the disease, the surgical success rates have improved dramatically from 1/1000 at the beginning of the 20th century to more than 75% in the late fifties [*Vail*[5] *1912*; *Custodis*[6] *1956*]. By that time only the RRD's complicated by vitreous opacification and/or retinal scarring remained beyond repair. Further progress in surgical technique and instrumentation in the past decades has made the re-attachment of the retina possible even in many of those complex cases [*Heimann*[7] *et al. 1984*].

Nevertheless, there is still a long way to go.

The functional fate of a re-attached retina has probably not improved significantly since the revolutionary contributions of Jules Gonin a century ago: “as then, nowadays, visual acuity returns to 20/50 or better in only 50% of patients after anatomically successful surgery” [*Burton*[8] *1982; Ross*[9] *et al. 2000*].

Despite extensive technological advances we still suffer primary anatomical failure in up to 10% of cases. 5% of cases will fail as a result of retinal scarring, better known as proliferative vitreoretinopathy (PVR) [*The Retina Society*[10] *1983*]. Surgical intervention can re-attach up to 90% of PVR detachments but functional results remain poor [*Aaberg*[11] *2010*].
To date, no effective pharmacological approach to prevent or treat PVR exists.

This thesis does not follow the typical structure of an introduction followed by the separate studies and a conclusion. The first chapter includes an extensive reflection on the historical breakthroughs in the field of RRD. The different surgical techniques that were introduced consecutively are reviewed and their value assessed in relation to our current understanding of the disease.
The second chapter contains a critical appraisal of current state-of-the-art treatment including an analysis of its potential drawbacks. The third chapter attempts to identify those causes of poor outcome that can be targeted by modifications of the current surgical techniques. Our own more recent studies on this subject are embedded in this chapter and presented in full in the appendix.

Chapter 1

Historical review

1.1. When nothing works, anything goes

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1.1. When nothing works, anything goes

Morgangi[12] described the anatomy of a retinal detachment in 1740 and his pathological findings were later confirmed by *Ware*[13] in 1805.

Retinal detachment was added to the list of causes for amaurosis, the general term used to describe visual loss in the otherwise normal appearing eye. A method for in vivo observation was lacking and the cause of the disease remained elusive.

Puncturing of the eyeball was probably the first surgical attempt at treating a patient suspected of suffering from a retinal detachment (also named black cataract or gutta serena). This technique, which originated in China, appears to have been introduced in Europe in the 17th century by an English battlefield surgeon named *Tuberville*. The procedure was originally intended for different eye diseases such as cataract and glaucoma. In the early 19th century, *James Ware,* based on his pathological observations, experimented with a puncture site situated further back from the corneal limbus. The first successful re-attachment using this technique was reported in 1812[14]. Despite careful and enduring post-operative immobilization, the effect of similar interventions would usually be temporary.

The introduction of the ophthalmoscope by *Helmholtz*[15] in 1850 allowed in vivo observation of the retina. A reliable diagnoses of RD became possible and the names black cataract or gutta serena could finally be abandoned.

Using the novel observation technique, *Coccius*[16] (1853) and *von Graefe*[17] (1854) were the first to describe retinal tears, but their significance would not be appreciated until much later.

In 1854, *von Graefe* and *Arlt*[18] posted their secretion theory (in analogy with pleural effusion), that implicated acute leakage of fluid from the choroid as the cause for retinal detachment.

Iwanoff[19] suggested that the tension that resulted from the fluid accumulation would cause distension of the eye wall (accommodating for the fact that RD occurred more often in myopic eyes) as well as retinal breaks.

Interestingly, the retinal breaks were judged to be a beneficial aspect of the disease as they would allow the fluid to escape to the vitreous.

In the late 19th century, several authors came very close to solving the mystery and deserve further mention.

Leber[20] studied enucleation specimens and concluded that microscopically visible vitreous retraction or shrinkage was present at the site of retinal breaks and that the breaks were usually situated in the area of retinal detachment.

Louis de Wecker[21]*,* a Paris based ophthalmologist, described in detail the course of a posterior vitreous detachment, with subsequent traction in the area we now call the vitreous base, generating breaks in the retina and eventually retinal detachment: *"..dès que le décollement du corps vitré atteint la région équatoriale, une lutte s'engage entre la rétine et le corps vitré qui adhère plus dans cette région..". de Wecker* distinguished traction (décollement par attraction) from distention (as in *Iwanoff's* hypotheses) as the cause for the formation of retinal breaks.

The understanding of the disease pathogenesis was shifting from secretion to vitreous traction but this did not bring about a new successful treatment. Maybe because there was strong opposition to the traction hypothesis by the "opinion leaders" of that era like *von Graefe*. Or because signs of traction would not have been easily identified using the dim illumination of the early ophthalmoscope.

Moreover, the significance of the breaks, namely the result of traction and cause of detachment, was still misjudged as *de Wecker* concluded: *“..si nous voulons réellement obtenir une guérison du décollement, notre but doit être tout d'abord de détacher la rétine du corps vitré..“*

By the end of the 19th century, hypotheses were based on previous pathological and more recent clinical observations. The presence of subretinal fluid, the distention of the eye wall and/or the retraction of the vitreous, a low intraocular pressure, a reduced adhesion of the retina to the subretinal layer, were all considered to be of importance. Nevertheless, the therapeutic attempts before *Gonin* would not aim to intentionally disrupt the communication between the vitreous and the subretinal space and as a result would usually remain unsuccessful.

Some of the practices at that time reveal the level of despair that involved dealing with RRD patients.

The following overview demonstrates how different hypotheses inspired a multitude of procedures.

- Traction

To reduce traction, *Stellwag*[22] (1861) and *Donders*[23] (1866) proposed complete immobilization in bed with sandbags to block all movement of the head. Division of vitreous strands with a knife to treat retinal detachment was reported by *Deutschmann*[24] (1895) and *von Hippel*[25] (1915). The first attempts to reduce the globe capacity by resection of full thickness flaps of sclera were performed by *Mueller*[26] in 1903.

- Subretinal fluid

Transscleral drainage was originally reported by *Ware*[27] in 1805. Several modifications like inserting a gold wire [*Ribard 1876*][28] or horse hair [*Ewers 1872*][29] into the drainage site were proposed to achieve a more lasting effect . Permanent drainage trough trephining or sclerectomy (inspired by the first successful glaucoma interventions by *Elliot*) was reported by de *Wecker*[30] (1872) and *Argyll Robertson*[31] (1876).

Evacuation of fluid towards the vitreous was advocated by *von Graefe*[32] who, in 1863, modified the drainage method by also puncturing the retina thereby intentionally creating retinal breaks to allow subretinal fluid to escape into the vitreous cavity. *Bowman*[33] would perform a similar procedure.

Müller[34] and others performed an iridectomy to create a route for fluid evacuation towards the anterior chamber.

In order to promote fluid absorption different substances were injected subconjunctivally. *Grossman*[35] (1883) and *Mellinger*[36] (1896) used hypertonic saline and *Sourdille*[37] advocated mercury cyanide for this purpose. *Bettremieux*[38] (in 1910) on the other hand would, in an attempt to increase fluid absorption towards the bloodstream, suture conjunctiva into a sclerotomy overlying the detachment.

- Pushing the retina back against the underlying tissues

Samelsohn[39] (1875) suggested applying pressure to the eye with a bandage.

Others tried to push the retina back by injecting various substances (rabbit vitreous, gelatin, protein solution, air) into the anterior chamber or vitreous cavity. Although many attempts ended in phthysis, the uncomplicated injection of air by *Ohm*[40] in 1907 can be considered as the first report of an intraocular tamponade.

Colmatage, introduced by *Lagrange*[41] in 1912 entailed extensive diathermy under a conjunctival flap in order to close schlemm's canal and increase the intraocular pressure.

- Promoting the adhesion to hold the retina in place

Retinopexy to increase the adhesion was inspired by observations of spontaneously healed detachments and their resemblance to a chorioretinitis scar. Several approaches were explored In order to achieve this "adhesive retinitis".
Faro injected iodine into the vitreous for this purpose and *Schöler*[42] would report on more than a few successes with this procedure.
Mechanical fixation was attempted by suturing of retina to sclera [*Meyer*[43] *1871*] or choroid [*Galezowski*[44] *1890*].
Penetrating thermocautary (very similar to the ignipuncture later described by Gonin) was first reported by *Abdie*[45] in 1881. When preceded by drainage of subretinal fluid, extensive sclera cautery to the entire area of detachment would have been successful on occasion as reportd by *Uhthoff*[46]. The breaks were most likely cauterized unintentionally in these cases.

Stargardt[47] considered all attempts to re-attach the retina doomed to fail and he advocated the use of extensive galvanocautery in an attempt to limit ("ab zu riegeln") the progression of the detachment in selected cases.

Motivated by ever increasing frustration with the poor results, the interventions became more and more invasive and serious complications often ending in phthisis were common. Any beneficial effect on the (extent of the) detachment occurred in spite of rather than thanks to these interventions. Temporary re-attachment that was recorded on occasion after a combination of some kind of fluid drainage and nursing practices involving strict bed rest and patching. As we now know, traction and fluid currents (resulting from eye movements) in the presence of a retinal break can overcome the strong physiological adhesion of the neuroretina to the subretinal layers. Although mainly by chance rather than intention, the nursing circumstances would have had an effect on these forces. In the immobile eye, traction and fluid currents are reduced allowing formed vitreous to occlude the break while remnants of subretinal fluid are slowly re-absorbed. Unfortunately in most cases, as soon as the patient was remobilized, the detachment would recur.

In conclusion: all pieces of the puzzle were there but remained scrambled. The different factors involved in retinal detachment namely adhesion, traction and fluid currents had all been suspected but the pivotal role of the retinal break had not been recognized. Consequently, although all basic components of modern day successful RRD therapy (drainage, creating a chorioretinal scar, reducing traction and injecting a tamponade) had been attempted, the success rate of RRD therapy at the beginning of the 20th century was extremely low as reported by *Vail*[5].
His poll among ophthalmologists in the United States on their results of treating retinal detachment showed a success rate of 1/1000.

1.2. From dismal to hopeful: the revolutionary impact of Jules Gonin

The significance of the retinal break

Jules Gonin changed the prospect for RRD patients from dismal to hopeful, and as such, the history of RRD repair can be divided into the eras before and after Gonin.
At the beginning of the 20th century, *Jules Gonin* began his quest to find a definite cure when he stated: "In order to effectively fight a pathological process, we must know its nature and anatomic conditions. Only the study of pathogenesis of spontaneous detachment, based on facts and not on hypotheses, will make it possible to find the treatment for this disease."

By meticulously linking his clinical observations to his knowledge of pathology, *Gonin* would “crack the code” and solve the mystery. Between 1898 and 1904 he studied pathological specimens and concluded that traction from altered vitreous in pre-equatorial chorioretinal foci is related to retinal tears and that retinal tears could be a possible cause of detachment. From 1906 until 1919, his clinical work focused on the retinal tears. Based on accurate localization and detailed drawing he targeted his surgical attempts towards the breaks and his convictions about their crucial significance grew steadily.

In 1919, more than 100 years after the first anatomical description and almost 80 years after the introduction of the ophthalmoscope, *Gonin*[48] reported on his first successful cases treated with ignipuncture.

The igni (“fire”)puncture was carried out under drop anesthesia with cocaine followed by a subconjunctival injection of novocaine. After accurately locating the retinal break on the sclera, a Paquelin thermocauter (basically a white-hot needle) was inserted into the vitreous at the site of the breaks. Withdrawing the needle was usually accompanied with drainage of subretinal fluid and cauterization (and sometimes incarceration) of the edges of the break at the drainage site, effectively closing the break in successful cases.

Great distrust with regards to *Gonin's* approach persisted for many years and surgeon's like *Sourdille* (a contemporary who strongly opposed the reports by *Gonin*) would continue to treat patients using the “old” methods.

The major breakthrough came in 1929, at the International Congress of Ophthalmology in Amsterdam, where *Gonin*, sided by his already influential disciples *Arruga, Weve,* and *Amsler,* convincingly proved to his audience that retinal breaks were the cause of retinal detachment and that closure of retinal breaks could lastingly re-attach the retina. The success rate of RRD surgery would improve dramatically: finding and closing all the breaks using the Gonin technique was successful in more than 50% of cases [*Gonin*[49] 1930].

Figure 1.
Image of the “low tech” environment in the operating room during RRD repair by Weve.
Reproduced from the thesis of J.G. van Manen:
Die diathermische Behandlung der Netzhautablösung in der Universitätsaugenklinik Utrecht und ihre Ergebnisse in Jahre 1935.

In conclusion: puzzle solved? With ignipuncture, a retinal break could be sealed in many cases by impeding fluid from passing into the SR space. Ignipuncture did not however reduce vitreoretinal traction. Consequently, success rates remained low in cases with multiple/large breaks or excessive traction with or without scarring.

1.3. Perfecting the external repair through better knowledge of the pathogenesis

During the decades following *Gonin's* invention, better understanding of the pathogenesis allowed the introduction of new techniques that further improved the efficacy of the external repair surgery.

- Tamponade

Injecting a tamponading agent with the aim to close a retinal break was first described by *Rosengren*[51]. He combined drainage, diathermy and air injection with post-op posturing in order to, as he stated, secure an efficient contact between retina and choroid during the process of healing. *Norton*[52] would later add the injection of SF6 gas to scleral buckling in order to improve the outcome in cases with large breaks. Other gasses like C2F6 and C3F8 were later introduced in order to prolong the tamponading effect in complicated cases like giant tear detachments.

In the eighties, the injection of a gas bubble to re-attach the retina would evolve into a technique called pneumatic retinopexy [*Hilton*[53], *Grizzard 1986*] in which the injection of gas is combined with cryo or laser retinopexy. Many authors have reported high success rates in the more straightforward detachments particularly when the breaks are located in the superior quadrants.

Cibis[54] introduced silicone oil (SO) as a tamponade for complicated cases with extensive scarring. A combination of physical properties including specific gravity, surface tension and viscosity on one hand and the optical transparency and biocompatibility on the other, has made SO the first choice when long-term tamponade is required. Although it has become a very popular tool in VR surgery, the use of SO has many disadvantages (cfr. infra).

- Retinopexy

Creating a chorioretinal scar around the breaks establishes a permanent watertight seal that obstructs fluid currents and many different techniques to achieve a chorioretinal scar have been proposed since the Pacquelin cauter as used by *Gonin.*

Pioneering work by *Lincoff*[55] in the sixties led to the replacement of diathermy by cryotherapy that caused much less scleral destruction. Light coagulation was introduced in the fifties by *Moran-Sales*[56] and *Meyer-Schwickerath*[57]. The technology evolved from focused sunlight and xenon arc to LASER which came into general practice in the late seventies and early eighties. Both cryo and laser techniques are still widely practiced as part of RRD surgery.

- Evolving understanding of traction and the role of fluid currents

In the presence of a retinal break, the retina will detach when physiological adhesion is overwhelmed by a combination of traction forces and fluid currents. The importance of fluid currents in the presence of a retinal break was demonstrated nicely by *Lindner*[58] in 1933. Using a water-filled glass container with a gelatin lining the inside, he showed that rapid rotation will detach the gelatin layer when an edge is lifted, allowing water to pass underneath.

With ever improving methods of investigation such as slitlamp biomicroscopy and later B-scan ultrasonography came a re-emphasis on what *Leber* and *Gonin* had suspected (based on pathology), namely that traction is a major issue and that in case of (partial) vitreous detachment, sudden tractional forces are exerted at the site of vitreous insertion whenever the eye moves.

This concept of persistent vitreous traction on a break combined with fluid currents, also referred to as dynamic traction, was expertly described by *Machemer*[59] in his Edward Jackson memorial lecture. Targeting dynamic traction has had a major impact on the success rate of RRD surgery, particularly in cases with large and/or multiple breaks and significant vitreoretinal traction, as will be explained later in this chapter.

Recent imaging with swept source optical coherence tomography shows the importance of this phenomenon, also for several macular and optic disk diseases including macular hole development [*Johnson*[60] *2010*].

- Scleral indentation as an effective way of counteracting dynamic traction

Scleral indentation has been an extremely successful contribution because it addresses the different aspects of the disease. Effective scleral indentation can shorten the distance between the retinal pigment epithelium and sensory retina, displace subretinal fluid, reduce vitreous traction, interfere with fluid currents and promote a functional vitreous plug.

Shortening of the sclera to reduce the volume of the globe, introduced by *Mueller*[14] in 1903 can be considered as the first attempt. *Lindner*[61] and *Weve*[62] promoted a reefing stitch to achieve an indentation. *Jess*[63] performed the first buckling procedure in 1937 when he inserted a temporary tampon of gauze beneath the Tenon's capsule.

Still, it is *Ernst Custodis*[6] who is widely recognized as the father of scleral buckling (SB). He described the use of a retainable exoplant and using *Custodis's* buckling technique, the anatomical success rate improved from 50% in the Gonin era to more than 80% by 1956. Originally, the explant or “plomb” was manufactured from rigid plastic and its application often complicated by conjunctival erosion or even scleral rupture.

Figure 2.
Episcleral buckle made of silver, used by *Rosengren* in the 1940's. (Collection of Diana Mertens)

Early refinements of the buckling material include donor sclera and facia lata. The silicone encircling elements [*Schepens*[64] *1958*] and the silicone sponge [*Lincoff*[65] *1965*] were introduced soon thereafter and are still in widespread use today.

1.4. Transition to the internal approach: the introduction of vitrectomy

By the late sixties, in optimal conditions, up to 90% of all RRD cases could be treated with conventional external surgery with a success rate of up to 80%. The dismal cases that remained beyond repair were either complicated by non-clearing media opacities or the presence of tractional membranes caused by proliferative vitreoretinopathy (PVR). The level of despair that surrounded the management of complex RRD patients inspired some surgeon's to attempt unconventional approaches. The practice of placing the patient in a centrifuge, as treatment for giant retinal tear detachments, can be classified as one of the more extreme examples [*Hoppenbrouwers*[66] *et al*. *1971*].

The history of vitreous surgery dates back to 1895, when *Deutschmann*[24] was the first to attempt to cut vitreous membranes using the von Graefe knife in order to release the retina from the vitreous.

The external approach would, soon after its introduction by *Gonin*, become a widely adopted and successful treatment for the majority of detachment cases and vitreous surgery was abandoned.

It was more than 6 decades later when *Kasner*[68] introduced open sky vitrectomy as a new approach to vitreous surgery. After removal of the cornea, vitreous was removed using cellulose sponges and scissors. The procedure would mainly be used in trauma or complicated cataract surgery cases [*Kasner*[69] *1969*].

Kasners' work that proved conclusively that the eye could prosper without formed vitreous inspired *Machemer* to experiment with a mechanized vitrectomy instrument that could remove vitreous through a relatively small opening. The first pars plana vitrectomy in a closed eye was performed in 1970 with the Vitreous Infusion Suction Cutter (VISC) [*Machemer*[70] *et al. 1971*]. Further refinement of the pars plana approach by *O'Malley*, who introduced a multi port system and smaller gauge, formed the basis for current day instrumentation in VR surgery.

Pars plana vitrectomy (PPV) would have a revolutionary effect comparable to *Gonin's* ignipuncture as it allowed successful treatment of cases that had previously been abandoned.

1.5. Dealing with the scarred retina: the role of the Rotterdam Eye Hospital

(Some of the more anecdotal information for this section was obtained by separate interviews with *Relja Zivojnovic MD, Diane Mertens MD, and Ed Peperkamp* MD during the course of 2013)

- Step 1. Transition to subspecialty within ophthalmology in Rotterdam

In 1962, *Relja Zivojnovic* started his ophthalmic residency at the Rotterdam Eye Hospital under the supervision of *Flieringa.* His interest in ophthalmic surgery and particularly retinal detachment repair became obvious early on. At that time the treatment in Rotterdam would consist of an encircling Arruga wire, drainage, diathermy and sometimes a reefing stitch. The vitreous was considered an absolute “no go area” so nothing was ever injected into the eye. Postoperative care would often include several weeks of immobilization with strict posturing and bed rest.

Inspired by *Spira* and *Klöti* the first buckling procedures at the Eye Hospital were performed by *Zivojnovic* and *van Loenen* using donor sclera or fascia lata. The application of the nylon based

Arruga wire would on occasion be complicated with intraocular migration and was therefore replaced first by donor sclera and later a silicone band.

After 4 years of residency and 2 years of practice as junior consultant, *Zivojnovic* returned to Yugoslavia where he worked as a general ophthalmologist for four years.

He returned to Rotterdam in '72. During his absence, a number of developments had been adopted for the treatment of retinal disease. Xenon arc light coagulation had been introduced in 1970 by *Sava Riaskoff*, the ophthalmoscope replaced by the (much brighter light yielding) Bonnoscope and full thickness sclera diathermy by cryotherapy. *Riaskoff* had also experimented with pars plana vitrectomy in the early seventies using a single port Grieshaber system but, due to the high complication rate, abandoned this approach prematurely.

On his return to the Eye Hospital *Zivojnovic* noticed that some RD patients were doing much better than others. *Mertens* and *Riaskoff* had both been spending considerable attention to RRD management, operating as a team and getting promising results. At that time however, most surgeries were performed by ophthalmologists who practiced mainly outside the hospital but were allowed to operate their private patients regardless of the nature of the disease. Consequently, on average, the results of RD surgery were mediocre.

Convinced that devoted attention could improve the outcome, *Zivojnovic*, together with *Diane Mertens* and with the support of the medical director of the Eye Hospital Professor *Harold Henkes,* himself a pioneer in the field of electrophysiology, would strive to introduce subspecialization in Rotterdam. The basis for a successful transition from general practice was a combination of several factors. Firstly, *van Loenen Martinet* had set a precedent by focusing, with success, on corneal transplant surgery and secondly, *Zivojnovic* and *Mertens* were becoming ever more reluctant to treat the failed cases of their general ophthalmologist colleagues. The pledge made by the retina team to refrain from surgery in other fields like cataract and oculoplastics eventually allowed a breakthrough.

The resulting re-organization of the eye hospital and the genesis, in 1975, of the first subspecialty retina service in the Netherlands (and one of the first in Europe) would greatly accelerate introduction of innovative surgical methods in the subsequent years.

- Step 2. Gathering knowledge and inspiration

Zivojnovic was certain that, in order to further improve results, the techniques of other pioneers in the field had to be studied and observed. In the early seventies his attention was mainly focused on *Bonnett* in Lyon and *Lanott* in Paris. Poor knowledge of the English language delayed his contacts with the UK and US. The rumors of what was happening there, however, convinced him to study English and soon after he would visit Birmingham, Cambridge and Moorfields. He studied and was fascinated by the technique of *Scott*[71] who, inspired by *Cibis*[72], injected silicone oil into non-vitrectomized eyes to treat complicated retinal detachments. Scott visualized his surgery by indirect ophthalmoscopy and made use of the surface tension and hydraulic characteristics of silicone oil to separate the vitreous and tractional membranes from the retina (“the dynamic use of oil”). He would leave the oil in the eye permanently to tamponade the retina and stabilize the eye in the most difficult of cases.

At the same time, across the Atlantic, *Machemer* and *Parel* were designing a revolutionary technique to remove vitreous from the eye using a vitreous cutter that allowed effective clearing of the visual axis in a relatively non-traumatic way.

In '76 *Henkes* sent *Mertens* to observe *Zauberman* (who had trained with *Machemer*) in Jerusalem and study his improved technique of pars plana vitrectomy. The vitrectomy system, however, was out of order and remained so all through her 3 month stay. The use of the binocular ophthalmoscope and the sophisticated technique of buckling without retinopexy would nevertheless have an instrumental effect [*Zauberman*[73] et al. *1975*].

The re-introduction of pars plana vitrectomy at the Eye Hospital however was further delayed until 1978 when *Klöti* [74] (who introduced pars plana vitrectomy to Europe) had convincingly demonstrated its potential.

Figure 4.
Delegacy from the Rotterdam Eye Hospital responsible for selecting the new vitrectomy machine.
From left to right: Sava Riaskoff, Diana Mertens, Jan Renardel de Lavalette (medical director) en Relja Zivojnovic. (1977)

In the following years, *Zivojnovic* would further refine his skills of the *Scott* technique. The surgical procedures, all under indirect ophthalmoscope view, would often take several hours and were physically demanding. During that period, *Mertens* would rather direct her attention to the microscope guided vitrectomy.

By '79, complicated cases without media opacities where treated by *Zivojnovic* with *Mertens* assisting him, using the *Scott* technique. *Mertens* with *Zivojnovic* assisting would operate the cases complicated by media opacities using the Oertli® single port pars plana vitrectomy system, as introduced by *Klöti*.

Being frustrated by the complexity and the overall poor results of the *Scott* method and observing *Haut*[75] in Paris and *Leaver*[76] in London, *Zivojnovic* and *Mertens* started using silicone oil in combination with vitrectomy. The introduction of the oil was thereby greatly simplified and the oil could be used as a temporary (in contrast *Scott's* method) tamponade.

The approach to treating complicated RD cases had been changed for good [*Zivojnovic*[77] *et al. 1981*]. The news of their ability to re-attach the scarred retina, in many cases, soon spread throughout Europe and patients were referred to Rotterdam from many other centers.

Despite the pioneering work by *Cibis*, and mainly as a consequence of the legal difficulties concerning the use of silicone oil (not registered for use in patients), its popularity had faded fast in the US in the seventies. This appears to have considerably slowed the progress of complex VR surgery in the US in the early eighties. When *Zivojnovic* and *Mertens* attended the Gonvers course in Lausanne in '81 where *Machemer* lectured on the new developments in VR surgery, they realized that although they had been lagging behind in the field of vitrectomy in the late seventies, they had by then more than just caught up.

- Step 3. Pushing the boundaries: the road to "retinal" surgery

In the fall of 81, *Klaus Heimann* , who was a valued friend of *Zivojnovic* and one of the driving forces behind studies on the use of silicone oil in Europe, referred a bilaterally blind child (car crash) to Rotterdam. During the operation, *Zivojnovic* was unable to re-attach the retina despite his attempts that took many hours and involved radical removal of epiretinal membranes and several injections and removals of oil. Refusing to give up made him do what was then considered unthinkable: cut the retina. He cut the retina in an attempt to rescue the viable central area.

In '83 *Zivojnovic* (after *Landers* had observed his work in Rotterdam) was invited to the Vail vitrectomy meeting organized by *Machemer*. Despite his, at the time, modest abilities to present and still limited knowledge of the English language, he was placed at the centre of attention and was allowed to present and discuss some of the extreme cases he had treated. He was overwhelmed by the interest shown towards his work and the open discussion format of the Vail meeting, which he had not encountered before.

By the mid-eighties, retinal surgery, a new concept in ophthalmology, was established. It basically involved pars plana vitrectomy, extensive membrane peeling, followed by, if necessary, retinotomy to release the viable central retina and amputation (retinectomy) of the redundant peripheral flap, followed by the infusion of SO as tamponade [*Zivojnovic*[79] *1987*].

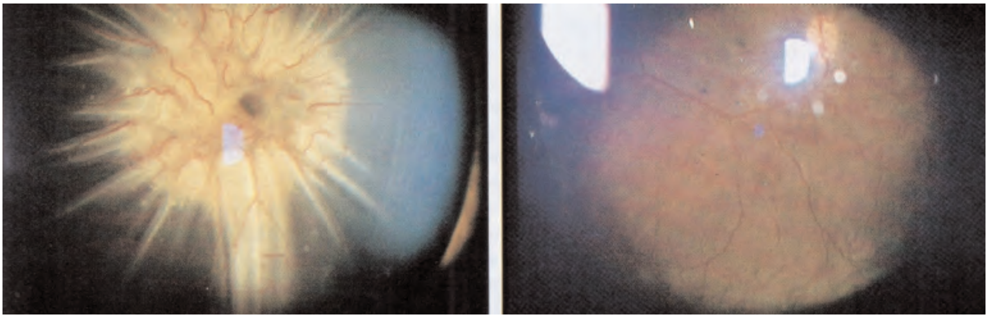

Figure 3.
Example of the remarkable anatomical results that could be achieved using the approach to PVR that was developed in Rotterdam in the eighties. Reproduced from Zivojnovic's "Silicone Oil in Vitreoretinal Surgery".

When these techniques became common practice, success rates of the surgical management of RRD complicated with severe PVR would rise sharply from anecdotal to more than 60% by the early nineties [*Silicone study report 1992*][80] .

The further refinement of this bold new approach has permitted invasive (sub-)retinal surgical techniques in the past 3 decades to flourish. Full macular translocation, retinal grafts (autologous or prosthetic) and tumor endoresection are but a few examples of currently performed procedures that were developed based on the pioneering work of *Machemer* and *Zivojnovic.*

- Step 4. Refining vitrectomy surgery by adopting technical innovation

During the early and mid-eighties several technical innovations made the surgical attempts to repair the “un-repairable” retina's ever more successful.

In Rotterdam, the VR team worked together closely with the photography department and *Ger Vijfvinkel*. *Vijfvinkel*, who started his career working in the basement of the eye hospital as surgical instrument developer, later founded his own company for VR equipment (DORC®). Being able to visit the operating theatre and witness the limitations of the instruments, he would, on an almost weekly basis, come up with new instruments that could be used in surgical practice straight away and further adjusted if needed. 23 gauge instruments for instance, originally designed for use in children, including a modified cutter for vitreous shaving, are still considered modern today but were developed by *Ger Vijfvinkel* back in the early nineties.

Many of the operations were expertly documented by *Bert Smit* using, for that time, very high tech equipment including microscope mounted Ikegami® camera, panfundoscope and a transillumunation light source. The U-matic video recordings were shown at the international conferences, the instruments manufactured in the Eye Hospital were soon in great demand and observers from around the world would visit the OR in Rotterdam to learn about the new surgical techniques as they were being developed.

Interestingly, in spite of all the improvements made to the vitrectomy machine and instruments, *Zivojnovic* and *Mertens* would always consider vitrectomy for straightforward RRD cases bad practice.

In conclusion: the pioneering work of the VR team from the Rotterdam Eye Hospital has been a major contribution to the now widespread knowledge of, and expertise in, the field of complex retinal surgery. An overview of the revolutionary developments in surgical technique and equipment and the anatomical results that could be achieved in disastrous cases was well documented in “Silicone oil in Vitreoretinal surgery” by *Zivojnovic* [*Zivojnovic*[78] *1987*].

Chapter 2

Limitations of state-of-the-art RRD surgery one hundred years after Gonin

2.1. Introduction

2.2. Where are we heading in our persistent endeavor to improve the results

2.3. Is vitrectomy really the best option

2.1. Introduction

By the mid-eighties, more than 80% of new RRD cases were still managed with external buckling surgery. Giant tear, vitreous hemorrhage, PVR and failed buckles would be tackled using vitrectomy. Vitrectomy for RRD was often combined with an encircling band. The vitrectomy was a standard 20 gauge 3 port. Vitreous base shaving was performed using microscope light and a hand held flat contact lens aided membrane peeling. No wide angle viewing system was used. No dyes of any kind were available for intra-ocular use.

In the past decades, the standard approach has shifted from a basic external technique towards a more invasive internal type of surgery which is characterized by the widespread application of new technologies [*Klöti*[81] *1983*]. Vitrectomy for straight forward cases now often features chandelier illumination, perfluorocarbon liquid (PFCL), the use of long acting tamponade agents and adjuvants used to improve visualization of the vitreous or identify any epiretinal membranes.

The technology that was developed for, and greatly improved the outcome of, complicated cases is now routinely used to treat straightforward detachments despite, however, a lack of evidence suggesting a better outcome for this category of patients.

More disconcertingly, we have done still worse in terms of improving functional outcome. There are obvious limitations to any attempt at comparing present and historical outcome data but it appears that, despite vast technological progress, functional outcome in case of anatomically successful re-attachment, has not improved since the first reports by *Gonin* one hundred years ago.

The current results can be summarized as follows: 40% of patients with macula-off detachments will not achieve reading ability, between 10% to 40% will need more than one surgical procedure (including additional retinopexy or anterior segment surgery), and up to 5% of all RRD eyes will still suffer permanent anatomical failure [*Heimann*[82] *et al. 2007*].

To revolutionize RRD treatment once again, we will need a magic potion that improves functional recovery by regeneration of damaged neuroretina as well as an effective treatment for PVR.

For now, we can only attempt to improve results by carefully studying the commonly practiced technique in order to identify its shortcomings and to develop successful modifications.

2.2. Where are we heading in our persistent endeavor to improve the results

Comparing results of different surgical approaches remains challenging. Manuscripts from the past century up to the nineties report surgical technique and retrospective non-comparative results from case series at best. Inclusion criteria, definition of success, follow up etc. are usually not well defined. A meta-analysis of more recent reports would suggest (with some caution and taking the level of evidence into account) that, since the introduction of scleral buckling (SB), single procedure success rates continue to compare favorably to alternative procedures like pneumatic retinopexy or even pars plana vitrectomy [*Custodis*[6] *1956; Sun*[83] *et al. 2012; Soni* [84] *et al. 2013*].

The increasing popularity of PPV over SB has many reasons. Most surgeons will indicate that achieving a higher anatomical success rate is their main motivator and several studies have reported excellent results. In addition, there may be some hypothetical advantages of vitrectomy including reduced incidence of missed breaks, better release of vitreous traction and removal of the vitreous as a PVR-stimulating environment.
On the other hand, the large number of other indications for vitrectomy including vitreomacular interface disorders has greatly increased the familiarity with the technique.

Patient comfort has also become a major issue. In the first few post-operative days, transconjuctival sutureless vitrectomy surgery may provide better comfort, as compared to external bucking because this so called “MIVS” approach may be minimally invasive with respect to the ocular surface. With regard to the functionally relevant tissues, however, the numerous reports of early as well as late onset complications may suggest the opposite.

Increasing commercial aspects of medical care may also have an impact and high tech vitrectomy surgery seems to have more appealing “unique selling points” than the low tech buckling procedure.

And finally, the decision of which surgical approach is best suited for a particular case seems to depend less on the initial clinical presentation but rather on practical issues:

- Younger VR surgeon's for instance have often started their training with cataract surgery and may feel more comfortable with a microscope based approach. Therefore, they prefer vitrectomy over external surgery, even in young patients without a posterior vitreous detachment (PVD).
- Thorough pre-op assessment is essential for successful scleral buckling surgery but is not when choosing vitrectomy, as the visualization is optimal during surgery.
- Limited operating room availability on the other hand may guide the choice towards pneumatic retinopexy.
- The desire of the patient to get on an airplane straight after the operation or reimbursement issues may encourage the use of a SO tamponade.

2.3. Is vitrectomy really the best option

Many of the current day opinion leaders have made PPV their standard approach to RRD and seem unlikely to embrace buckling surgery with a renewed attempt to perfect the external technique. To support their transition to PPV, they rather prefer to reiterate the benefits of vitrectomy as compared to the potential complications of scleral buckling like diplopia and inadvertent scleral penetration resulting in subretinal bleeding or incarceration [*Binder*[85] *2012*].

Let us nevertheless evaluate the potential drawbacks of PPV. Although several authors have reported higher anatomical success rates with vitrectomy, particularly in pseudo and aphakic eyes, we should remain concerned about the numerous complications that may cause disappointing functional outcome.

The high incidence of cataract development after PPV as well as complications related to the surgical induction of a posterior vitreous detachment make this technique particularly unattractive for the younger age group [*Feng*[86] *et al. 2014; Higuchi*[87] *et al. 2012*].

Irreversible visual field defects may appear post-op and have been attributed to fluid-air exchange [*Hirata*[88] *et al. 2000; Yang*[89] *et al. 2006*]. Other factors that may promote their development are endoillumination related photo trauma, intra or post-op pressure spikes, and the use of intraocular tamponades [*van den Biesen*[90] *et al. 2000; Muether*[91] *et al. 2011*].

Incomplete removal of heavy liquids (PFCL) at the end of the procedure can cause bothersome remnants in the vitreous cavity or anterior chamber, sometimes necessitating a re-intervention [*Bartz-Schmidt*[92] *et al. 1996*].

Subretinal PFCL bubbles that can cause severe permanent damage to macular function have been reported with increasing incidence, possibly in relation to small gauge surgery. Interestingly, rather than emphasizing the profound impact on functional recovery, several authors report on yet other innovative techniques to remove the bubbles [*Garg*[93] *et al. 2012; Garcia-Arumi*[94] *et al. 2008; Lemley*[95] *et al. 2008; Lee*[96] *et al. 1998]*

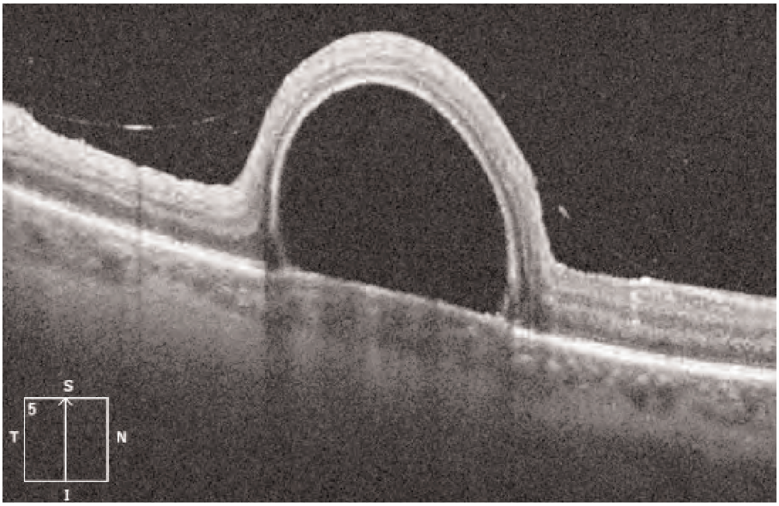

Figure 5
Subretinal PFCL bubble lodged under the macula as documented on post-op OCT.

Another consideration with regard to the use of PFCL that has not been investigated thoroughly is the oxidative stress that may result from PFCL injection. Suddenly increasing the oxygen tension at the photoreceptor level as a result of their re-approximation to the choroid, or by increasing the oxygen tension on the vitreous side of the retina triggering a constriction of arterial retinal vessels in an autoregulatory response, may cause a phenomenon that can be compared to reperfusion injury of the brain in case of stroke treatment [*Wilkinson*[97] *2009*]. Even without the use of PFCL, vitrectomy, as compared to buckling, causes some kind of stress to the cones in particular. It was demonstrated using 30-Hz flicker ERG that implicit times after re-attaching a macula-off detachment with PPV are delayed. This may represent an adaptive, regulatory response to increased oxygen diffusion to the retina after removal of the vitreous gel [*Schatz*[98] *et al. 2010*].

The introduction of SO tamponade in the eighties has improved our capacity to deal with PVR related (re-)detachments. In the past 2 decades, the use of SO has become very popular also in the management of more straight forward cases. Arguments to justify this trend include patient comfort (no posturing), airplane travel, or the surgeon's estimation of high risk of failure. Some authors have suggested the use of SO to facilitate vitreous base shaving and break localization [*Wong*[99] *et al. 2011*].

Not only does SO tamponade require a second intervention, its use has not been found to yield better results, particularly in uncomplicated cases [*Fraser*[2] *2010*]. In addition, the list of complications related to the use of SO is considerable. In the pioneering days of SO tamponade, the incidence of corneal endothelial damage and glaucoma was very high. Improved combined anterior- posterior surgery techniques allow effective management of lens opacification with IOL implantation and greatly reduce the risk of oil-endothelial touch.

An important and yet unsolved imperfection of SO that complicates long term tamponade is emulsification. Chemical as well as physical conditions inside the eye cause progressive degradation of the oil leading to release of small droplets that can infiltrate and occlude the trabecular meshwork [*Avitabile*[100] *et al. 2002*]. The incidence and severity of severe glaucoma is clearly related to the duration of the tamponde [*Halberstadt*[101] *et al. 2006; Honavar*[102] *et al 1999*].

Another complication that can occur when SO is used in combination with PFCL's, is the development of sticky oil. We have encountered this complication and reported a series of cases.

[Veckeneer[103] et al. An epidemic of sticky silicone oil at the Rotterdam Eye Hospital. Patient review and chemical analyses. 2008]

Chemical analysis of the SO samples collected from these eyes suggests that the occurrence is related to remnants of PFCL that remain at the time of SO infusion. We found impurities in sticky SO samples, PFCL and in SO straight from the vial that may have contributed to an increased interaction between the different phases, promoting the sticky behavior.
In vitro experiments have demonstrated that the purity of PFCL and SO is essential in this regard. As a direct contact between the different components required for sticky oil development seems crucial, the need for meticulous PFCL removal as well as performing a fluid to air exchange before injecting the SO, has been emphasized [*Dresp[104] et al. 2005*].

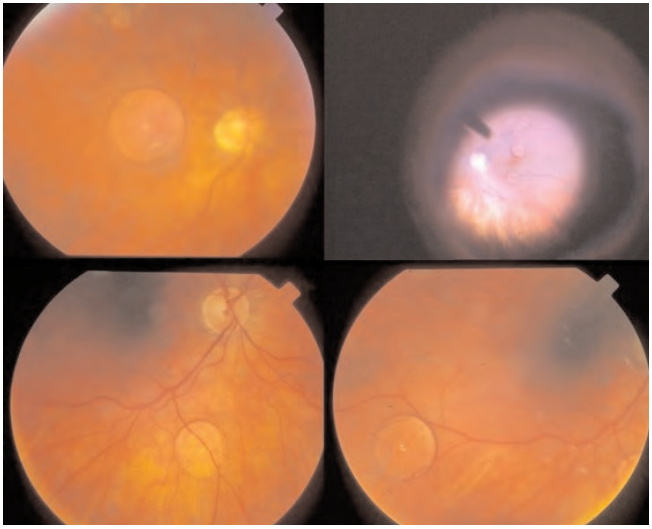

Figure 6.
Sticky oil phenomenon. Remnants of oil remain adherent to the retinal surface after the bulk of SO has been removed.

Unexplained visual loss while the oil is still in situ or immediately following oil removal can be yet another serious complication. The result can be devastating in patients that presented with a macula-on detachment and excellent vision pre-op but end up with count fingers without recovery. To date no satisfactory explanation for this phenomenon has been given [*Christensen[105] et al. 2012*; *Cazabon[106] et al. 2005; Shalchi [107] et al. 2015*].

Another dramatic complication of ocular surgery is endophthalmitis. Historically, the risk of endophthalmitis after posterior segment surgery was considered much lower than after cataract or glaucoma surgery. Reports of endophthalmitis after scleral buckling are extremely uncommon and based on a retrospective study reviewing data from 20 years of vitrectomy, a low incidence of 0.039% was reported [*Eifirg[108] et al. 2004*]. More recently, however, a 12 fold increased risk was reported after sutureless vitrectomy [*Kunimoto[109] et al. 2007*]. Several extra measures that have been proposed to avoid contamination/infection (including air tamponade, antiseptic irrigation, antibiotics at the end of the procedure) once again render the intervention more invasive, adding to the list of potential complications [*Chen[110] et al. 2009; Bahrani[111] et al 2010; Chiang[112] et al. 2011; Singh[113] et al. 2008*].

Regardless of the short term complications that can occur, the impact of vitrectomy on the general wellbeing of the eye has not been studied extensively. Although *Kasner's* open sky vitrectomy demonstrated back in the sixties that the eye can prosper after removal of the vitreous, a long-term harmful effect cannot be excluded.

More recently *Koreen*[114] reported on the increased incidence of primary open angle glaucoma after PPV for less severe indications such as vitreous floaters and macular pucker [*Koreen et al. 2012*]. Vitrectomized eyes, which were also rendered pseudophakic, were at particularly high risk of developing glaucoma with an incidence of 15%. *Chang*[115] hypothesized that increased oxidative stress after PPV may have a role in the pathogenesis [*Chang 2006*]. Indeed, a marked increase in oxygen tension is seen in the vitreous cavity after vitrectomy [*Siegfried*[116] *et al. 2010*] and combined or subsequent cataract extraction, by removing an oxygen sump, could increase the oxidative stress in the trabecular meshwork.

In conclusion: the shift in the standard approach to treating uncomplicated RRD towards vitrectomy is occurring without conclusive data supporting its superiority over external repair. Considering our inability to make real progress even with a more aggressive approach, we have to ask ourselves: are we aiming at the right targets? Especially keeping the pre-Gonin era in mind where several aspects of the disease were misinterpreted and surgeon's came up with ever more invasive therapies out of frustration with their inability to improve the results.

Chapter 3

Modifying surgical technique to improve outcome

3.1. Reducing surgically induced injury

3.1.1. Tailored surgery

3.1.2. Improving vitrectomy technique in phakic eyes

3.1.3. Recognizing and modifying factors of the surgical intervention that may promote proliferative vitreoretinopathy

3.1.4. Retinotomy as a treatment for proliferative vitreoretinopathy related re-detachments: severe but often unavoidable surgical injury

3.2. Improving surgical precision: chromo-vitrectomy

3.2.1. Introduction

3.2.2. Triamcinolone-assisted vitrectomy: more effective and less traumatic vitreous removal

3.2.3. Membrane peeling in proliferative vitreoretinopathy and the key issue of visualization

3.3. Reducing the impact of retinal detachment on visual function and retinal adhesion

3.3.1. Introduction

3.3.2. The quality of attachment as therapeutic target

Modifying surgical technique to improve outcome

Our research presented here has tried to

- identify aspects of the disease that are not addressed effectively by current interventions
- modify available techniques to better address the critical causes of failure while eliminating certain elements that can adversely affect the outcome

3.1. Reducing surgically induced injury

3.1.1. Tailored surgery: selecting the approach that best suits the detachment

The initial clinical presentation of RRD can vary widely and is clearly correlated with outcome. Number of breaks, inferior break location, age, high myopia, aphakia, size of detachment, vitreous hemorrhage, hypotony, choroidal detachment and pre-operative PVR have all been associated with risk of failure [*Norton*[117] *et al. 1964; Heussen*[118] *et al. 2011; Wickham*[119] *et al. 2011*].

Studying all these factors in every patient can help tailor the surgical intervention to the pre-operative situation and consequently lead to better results.

Some choices are obvious and mostly not debated. Small superiorly located breaks in phakic eyes with a PVD may do very well with pneumatic retinopexy. In addition, this procedure is not only very cost effective but may also contribute to better functional outcome, particularly in longstanding macula off detachments [*Chan*[120] *et al. 2008*]. Pseudophakic eyes will usually do better after vitrectomy. An unclear hole situation (no break or not all breaks found on pre-op ophthalmoscopy) is more common in pseudophakic eyes because of the type of breaks (usually small) and their anterior location in combination with poor visibility caused by optical distortion and capsular opacification [*Salicone*[121] *et al. 2006*]. The clear visualization of the vitreoretinal traction during vitrectomy while using a wide angle viewing system and the demonstration of subretinal fluid reflux through a break during the injection of heavy liquids (if necessary after dye injection into the subretinal fluid [*Jackson*[122] *et al. 2007*]), can reduce the risk of missed breaks.

Much less agreement exists on the choice of approach in the phakic (non-cataract) eye, particularly in younger patients without a posterior vitreous detachment. To preserve the accommodating lens, external surgery should always be considered first. In addition, scleral buckling (SB) can yield excellent anatomical and possibly superior functional results in these cases. Several shortcomings of SB can be addressed to facilitate a re-appraisal of SB surgery:

- An alternative and safer method for securing encircling bands and local episcleral explants would be desirable. We have reported on the use of cyanoacrylate adhesive rather than sutures to secure the explant material. A technique that could be particularly useful in eyes with thin sclera.

  [Reyniers[123]*, Veckeneer, van Meurs et al. A case-control study of beneficial and adverse effects of 2-octyl cyanoacrylate tissue adhesive for episcleral explants in retinal detachment surgery. 2012, in appendix]*

- Others have modified the external technique to allow a microscope based approach making the surgery more attractive for a new generation of VR surgeons [*Zhang*[124] *et al. 2011*].
- New buckling materials as well as new routes of application are under investigation. The suprachoroidal injection of long-lasting hyaluronic acid solution using a specially designed catheter seems promising as buckle related complications such as extrusion and diplopia can be avoided [*El Rayes*[125] *et al. 2013*].

Another consideration in the choice between buckle and vitrectomy may be that phakic eyes seem to do worse with vitrectomy and several issues may contribute. For instance, poor visibility at the time of fluid air exchange due to sudden clouding of the posterior lens capsule may adversely affect fluid drainage as well as accuracy of retinopexy. More importantly, in order to avoid lens touch, less rigorous vitreous shaving is usually performed. This can lead to incomplete release of traction and incarcerated vitreous in the sclerotomy sites, predisposing to recurrent detachment. For that reason the addition of encircling buckles has been advocated. Interestingly in the SPR study[82], although adding a buckle to the PPV was allowed, the phakic eyes in the PPV group still fared worse.

When a vitrectomy is mandatory in phakic (non-cataract) eyes because of clinical presentation e.g. giant tear, significant vitreous hemorrhage or signs of PVR, combined lens extraction with IOL implantation will be the treatment of choice for many surgeons. There are however several good reasons to spare the lens in the first intervention:

- Reduce the risk of amblyopia in pediatric cases.
- Preserve the accommodating lens, at least temporarily, in young adults.
- Improve tamponade efficiency: combined with a tamponade such as gas or oil, the natural lens, because of its size and shape, has a “buckling” effect. By “indenting” the tamponade bubble, the bubble's effect can be enhanced because the part of the bubble volume that makes contact with the retina, is increased [*Williams*[126] *et al. 1999; Wetterqvist*[127] *et al. 2004*].
- Correct IOL calculation: a pre-operative detached macula or a dense vitreous hemorrhage can hinder reliable intraocular lens (IOL) calculation.
- Reduce inflammatory response: fibrin and anterior chamber (AC) flare are increased after combined surgery [*Hoshi*[128] *et al. 2012*].
- Anterior segment ischemia: sparing the lens in ischemic posterior segment pathologies may reduce the risk of iris neovascularization after vitrectomy [*Kadonosono*[129] *et al. 2001*].
- Ocular hypertension and glaucoma: pressure spikes in the early post-op period are very common after combined surgery [*Demetriades*[130] *et al. 2003*]. In addition, long term follow up suggests an increased incidence of open angle glaucoma after combined surgery [*Koreen*[114] *et al. 2012*].

3.1.2. Improving vitrectomy technique in phakic eyes

We have studied several modifications to our standard vitrectomy technique that can optimize anterior vitreous base shaving in phakic eyes and reduce the risk of lens touch.

One method uses transillumination with uncrossed light pipe indentation. In addition to the vitreous base shaving technique, indentation with the light pipe in the region adjacent to the vitrectomy port allows safe and complete (360°) access to the vitreous base without the need to cross the posterior pole of the lens with the ocutome. With this technique we reported equally high primary success rates in phakic and pseudophakic eyes.

[*Veckeneer*[131]*, Wong. Visualising vitreous through modified trans-scleral illumination by maximising the Tyndall effect. 2009, in appendix*].

Another technique to avoid lens touch during vitreous shaving is called intentional continuous shallowing of the anterior chamber (ICSAC), in order to establish an ICSAC, a temporary AC outflow route using a limbal stent (silicone wedge) is created. The corneal endothelium is protected by a dispersive viscoeleastic injected at the beginning of the procedure. The continuing drainage allows the lens to move forward into the AC, thus greatly improving access to the vitreous base opposite from the vitrectomy port, by allowing the vitreous cutter to cross even the most prominent posterior part of the lens, without touching it. In a recent prospective comparative trial, no increased endothelial cell loss related to the technique was documented.

[*Mulder*[132]*, Veckeneer, van Meurs et al.* Intentional continuous shallowing of the anterior chamber, a procedure to prevent lens touch during phakic vitrectomy. 2015, in appendix].

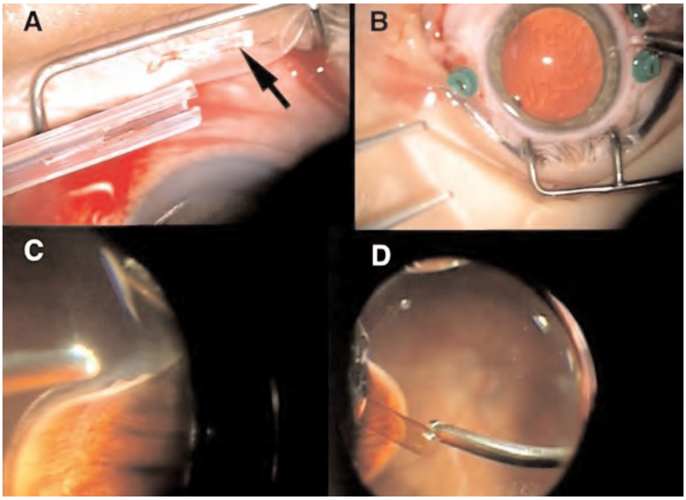

Figure 7.
Intentional continuous shallowing of the anterior chamber (ICSAC).
(A) Silicone stent is inserted through a side port incision and (B) a dispersive visco-elastic is injected to protect the endothelium.
(C, D) ICSAC allows anterior vitreous removal without lens touch in phakic eyes.

3.1.3. Recognizing and modifying factors of the surgical intervention that may promote PVR

In a Western population, proliferative vitreoretinopathy occurs in 5 to 10% of RRD cases [*Girard*[133] *et al. 1994; Gartry*[134] *et al. 1993*]. In an African setting, the incidence is reported to be considerably higher and the disease is usually obvious at presentation [*Asaminew*[135] *et al. 2013*].

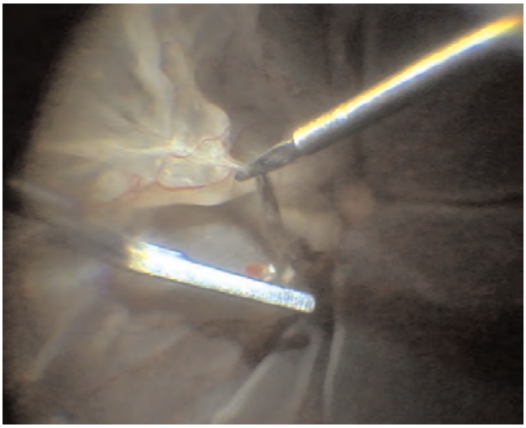

Figure 8.
PVR at presentation is extremely common in an East-African setting.
Personal experience at Kabgayi eye unit, Rwanda, fall of 2013.

In industrialized countries PVR often becomes apparent after surgery. PVR is the major cause of ultimate failure of retinal detachment surgery. Since the introduction of a successful surgical intervention in the eighties, we can permanently re-attach up to 60% of cases that have failed due to PVR. The consequences for functional outcome of PVR related failure nevertheless remain severe with less than 25% of eyes achieving useful macular function (VA of 20/100 or better). A far worse prognosis exists for pediatric RRD and severe penetrating trauma where the fibrotic response is particularly aggressive.

To develop an effective preventive as well as therapeutic strategy, complete understanding of the disease is essential.

A retinal break in combination with vitreous fluid gaining access to the subretinal space can set off a cascade of events that eventually may lead to PVR, an excessive cell mediated wound healing response that is driven by growth factors. An essential triggering event is the breakdown of the blood-ocular barrier (B-O B) that permits cytokines like monocyte chemotactic protein (MCP)-1 [*Abu El-Asrar*[136]*, Veckeneer.* Monocyte chemotactic protein-1 in proliferative vitreoretinal disorders. *1997*], interleukin (IL)-6, transforming growth factor (TGF)-β but also complement factors, immunoglobulins as well as extracellular matrix proteins, to gain access to the wound healing milieu [*Campochiaro*[137] *et al. 1984; DeJuan*[138] *et al. 1988*].

Several stages can be distinguished in the PVR response including the influx of inflammatory cells, migration and proliferation of cells, and deposition and remodelling of extracellular matrix, leading to the formation of contractile membranes on one or both sides of the retina, causing retinal re-detachment or preventing re-attachment [*Leiderman*[139] *et al. 2009*].

Whether or not this excessive wound healing will occur appears to depend on a complex interaction between:

- clinical aspects of the disease at presentation including aphakia, pre-op PVR, size of the detachment, number and size of retinal breaks, uveitis, low intraocular pressure and vitreous hemorrhage
- surgical procedures used to re-attach the retina
- genetic predisposition

Several models have been designed to help predict PVR development in high risk cases using these different variables [*Rojas*[140]*, Pastor et al. 2015*].

a. The impact of surgery on the blood-ocular barrier breakdown

B-O B breakdown has been shown to be elevated in eyes with retinal detachment [*Amann*[141] *et al. 1997*]. The degree of breakdown can be reliably and reproducibly quantified by measuring aqueous flare [*Guex-Croisier*[142] *et al. 1995; Herbort*[143] *et al. 1997*]. A correlation between increased pre-operative AC flare, increased levels of cytokines in the aqueous humor and the risk of PVR was recently demonstrated [*Schröder*[144] *et al. 2012; Hoerster*[145] *et al. 2013*].
B-O B breakdown isn't just important in relation to PVR. Vitreous haze, CME and macular puckering can be triggered by increased B-O B breakdown and RPE dispersion and may slow or limit visual recovery [*Kimball*[146] *et al. 1978; Bonnet*[147] *et al. 1996*]. Also, increased incidence of persistent SRF has been reported in relation to extensive cryo [*Kang*[148] *et al. 2008*].

b. Reducing B-O B breakdown pharmacologically

Studies in animals as well as clinical reports have suggested that corticosteroids may be useful in the prevention of PVR and this has been attributed to their attenuating effect on blood-retinal barrier breakdown and their inhibiting effect on proliferation of RPE cells and fibroblasts [*Chandler*[149] *et al. 1985; Sakamoto*[150] *et al. 2002*].

According to an animal model, pre-treating with steroids may be more effective in PVR prevention than when treatment was started at the time of injury or later [*Chandler*[151] *et al. 1987*].

In a prospective, placebo-controlled, double blind clinical trial we evaluated the effect of dexamethasone pre-treatment on the B-O B breakdown resulting from re-attachment surgery.

[Bali[152]*, Veckeneer, van Meurs et al. The effect of a preoperative subconjuntival injection of dexamethasone on blood-retinal barrier breakdown following scleral buckling retinal detachment surgery: a prospective randomized placebo-controlled double blind clinical trial. 2010, in appendix].*

In 34 patients with rhegmatogenous retinal detachment scheduled for conventional scleral buckling retinal detachment surgery, a subconjunctival injection of 0.5 ml dexamethasone diphosphate (10 mg) or 0.5 ml placebo was given 5-6 hours before surgery. Differences in laser flare photometry measurements taken 1, 3 and 6 weeks after randomization between dexamethasone and placebo were analyzed while correcting for the preoperative flare measurement. The use of dexamethasone resulted in a significant decrease in laser flare measurements at the 1- week post-operative visit.

Other clinical evidence supporting a role for steroids in prevention comes from a recent report by *Koerner*[153] [*Koerner et al. 2012*]. In a placebo-controlled clinical trial oral, prednisone reduced the incidence of epimacular membrane formation after primary surgery for uncomplicated RRD.

Although steroids may have a beneficial effect by stabilizing the B-O B, their effect on cell proliferation in vitro has been shown to be biphasic i.e. rather a stimulatory effect with lower concentrations [*He*[154] *et al. 1994*] and an inhibitory effect on proliferation of RPE in vitro at relatively high concentrations [*Liu*[155] *et al. 2001*]. Although these high concentrations can be reached by intravitreal injection, the outcome of surgery for established PVR was not improved significantly by adjunctive triamcinolone acetonide injection in silicone-filled eyes [*Ahmadieh*[156] *et al. 2002*].

Other pharmacological agents have been studied in the past. The impact of antimetabolite agents such as daunorubicin was investigated in several trials but the results remain inconclusive [*Wiedemann*[157] *et al. 1983; Khawly*[158] *et al. 1991*].

More recently the combined use of 5-fluorouracil and low molecular weight heparin did not show improved outcome in established PVR or in preventing PVR in unselected RRD cases [*Wickham*[159] *et al. 2007*]. Promising results with selected high risk patients [*Asaria*[160] *et al. 2001*], however, emphasizes the need for reliable identification of this subgroup in order to optimize the risk-to-benefit ratio of pharmacologic adjunct therapy. In particular, the observation of worse visual outcome in the treatment arm patients, has prompted safety concerns.

When considering such adjuvant measures, a reliable marker for PVR prediction in each individual patient could be a step forward [*Ricker*[161] *et al. 2012*].

c. Reducing the surgically induced trauma of retinopexy

One particular aspect of RRD surgery that has been strongly implicated in increasing the B-O B breakdown is retinopexy [*Jaccoma*[162] *et al. 1985; Sato*[163] *et al. 1992*].

Dispersion of viable RPE cells is recognized as an important inciting event in the pathogenesis of PVR and is particularly promoted by cryotherapy as it weakens the adherence between the RPE and its basement membrane [*Campochiaro*[164] *et al. 1985*]. In a rabbit model, cryotherapy reduces the retinal adhesion for several days [*Kita*[165] *et al. 1991*]. This could be clinically significant in humans when extensive applications are needed to surround all the breaks. Intra-operative transscleral diode laser was compared to cryotherapy but B-O B breakdown was not evaluated [*Steel*[166] *et al. 2000*].

Avoiding intra-operative retinopexy altogether could have benefit and several authors have reported that buckling surgery can be equally successful without retinopexy [*Chignell*[167] *1977; Fetkenhour*[168] *et al. 1980; Figueroa*[169] *et al. 2002*]. Immediate sealing is not required when the break is closed by a buckle or tamponade (air, gas or silicone oil) and a permanent scar to seal the breaks is mandatory only when the buckle or tamponade is removed.

In a prospective randomized trial, we evaluated the benefit of avoiding intra-operative retinopexy during buckling surgery. We chose post-operative green laser coagulation delivered at the slit lamp with a contact lens, thus guaranteeing optimal visualization. The laser application proved to be straightforward in all patients. The retinal tears were easily accessible, thanks to the buckling effect that greatly facilitated the treatment to the peripheral edge of the tear. We consider this method of retinopexy to be superior, not only to cryopexy but also to intra-operative transscleral diode laser and indirect diode or green laser for the following reasons:

- Post-operative laser on an attached retina requires minimal energy and is consistently effective, whereas intraoperative laser can be ineffective because of residual subretinal fluid surrounding the break(s).
- Post-operative slit-lamp laser retinopexy greatly reduces surgical manipulation. The fact that laser is applied in a quiet eye (as confirmed by normalized flare measurements after 4 weeks) may further reduce the inflammatory response.
- Green laser (532 nm) is available in all ophthalmic units and obviates the use of expensive cryotherapy probes, transscleral laser probes, or an indirect laser system.

Post-operative flare values were significantly higher in the cryotherapy group than patients that underwent laser retinopexy, up to 4 weeks after surgery.

In order to assess, as clearly as possible, the impact of cryotherapy on the function, we studied eyes with macula on RRD and found visual recovery to be slower in the cryotherapy group. [*Veckeneer*[170] *et al. Randomized clinical trial of cryotherapy versus laser photocoagulation for retinopexy in conventional retinal detachment surgery. 2001*].

Lira[171] also recorded faster functional recovery after intra-operative laser than cryopexy [*Lira et al. 2010*].

The size of our study was too small (n=48) to show any relation between reduced flare and risk of PVR.

In a subsequent prospective non-comparative clinical trial we studied a larger group of 124 eyes (123 patients) undergoing retinopexy by means of post-op laser. Only 4 eyes failed due to PVR (3.2%) after a minimal follow up of 6 months. Since 7 eyes presented with PVR C1 and 12 eyes had vitreous blood pre-op, these results may be considered encouraging [*van Meurs*[172] *JC, Veckeneer M, et al. Postoperative laser coagulation as retinopexy in patients with rhegmatogenous retinal detachment treated with scleral buckling surgery: a prospective clinical study. 2002*].

Others have studied the impact of vitrectomy on laser flare measurements. *Hoshi*[128] recorded increased flare values up to 50 fotoncounts/ms one week post vitrectomy. As vitrectomy will usually include deep scleral indentation during shaving of the vitreous base as well as some form of retinopexy, these results are not surprising. Interestingly, the flare values reported in this study vastly exceed (almost by a factor 3) what we found after scleral buckling [*Hoshi et al. 2012*].

In conclusion: the more extensive the surgical manipulation, the more significant the impact on B-OB breakdown will be. Modifying surgical technique accordingly could result in better outcome.

3.1.4. Retinotomy: severe but often unavoidable surgical injury

As in uncomplicated RRD, the only way to preserve or regain function is to re-attach the retina. This is also an essential prerequisite to halt the PVR cascade [*Tsui et al. 2009*].

PVR can transform a detachment from rhegmatogenous into combined tractinal and rhegmatogenous in which stiffening and shortening of the retina will prevent re-attachment despite conventional efforts to close all retinal breaks. The primary goal of vitreous surgery in advanced PVR is to (first) relieve the traction on the retina as completely as possible. Only then will the retina re-attach in response to closing the breaks [*Abrams*[174] *et al. 1997*].

Several sources of traction need to be dealt with. The vitreous must be removed as completely as possible. The combination of PFCL, triamcinolone, wide angle viewing and indentation allows very rigorous vitrectomy [*Veckeneer*[131] *et al. 2009*], thereby releasing, as much as possible, the traction from the vitreous collagen on the retina at the vitreous base, as well as eliminating the scaffold for future membrane (re-)proliferation.

Fibrotic membranes on the retinal surface can contract and reduce the retina's plasticity. The epiretinal membranes (ERM's) are the main source of traction and the primary surgical target. In agreement with the 1991 classification of PVR, ERM's can be subdivided into those that cause full thickness folds and stiffness of the post equatorial retina, as opposed to membranes near the vitreous base that can cause contraction along the central margin of the vitreous base, with anterior displacement of the peripheral retina as well as traction on the ciliary body [*Machemer*[175] *et al. 1991*].

Membranes central to the equator (posterior PVR) can be removed by careful peeling, substantially relaxing the central retina. After meticulous posterior epiretinal membrane peeling the residual stiffness of the retina can be estimated by injecting heavy liquids or performing a fluid air exchange. Previously occult but taut subretinal membranes can become evident. Subretinal membranes are a common finding in longstanding detachments but they seldom prevent the retina from settling.

The (real) reason for failure is usually the presence of anterior PVR. The traction caused by anterior PVR can often not be relieved completely with membrane peeling, even when combined with an inferior buckle. Several issues in relation to membrane peeling in anterior PVR can make this procedure less effective and more traumatic:

- It is technically more demanding surgery as membranes are less accessible and often more difficult to visualize, even with wide angle viewing systems.
- Although the central part of the membrane can be stripped away from the underlying retina, it can often no longer be separated a-traumatically when the peeling progresses to the vitreous base. This surgical finding can be explained on the basis of recent histopathological data regarding the interaction of the vitreous collagen with the retina at the vitreous base, as well as the findings in retinectomy specimens:
    - In comparison to the posterior retina, at the vitreous base, collagen fibers of the vitreous cortex are very dense, orientated radial, or perpendicular (rather than parallel) to the retinal surface and insert directly into the internal limiting membrane and ''crypts'' within retinal cellular layers, forming an unbreakable adhesion [*Le Geoff*[1] *et al. 2008*]. This anatomical feature of the vitreous base is not only of critical importance for the development of retinal breaks at the time of PVD. Anterior PVR membranes also grow along the vitreous collagen scaffold and are thus intimately connected to the retina itself.
    - Evidence from animal work by *Lewis*[176] as well as immuno-histochemical images of human retinectomy specimens also suggests an important intra-retinal aspect of PVR [*Lewis*[176] *et al. 2002*]. The results seem to demonstrate that ERM's may not originate from RPE on the retinal surface but instead grow out of the retina and originate from Muller cell's [*Charteris*[177] *et al 2007; Pastor*[178] *et al. 2006*].

Although cutting the retina to re-attach it adds to the retinal injury and should always be considered a last resort, a retinotomy will be unavoidable in many severe cases.

The primary goal of the retinotomy is to rescue the central retina from anterior PVR.

An important decision is when to perform the retinotomy: i.e. when to re-operate on a re-detachment under silicone oil. As long as the macula stays on in these cases, timing can be governed by the surgeon's best estimate of disease activity. Preferably, re-intervention and retinotomy should be performed when PVR is quiescent, not in the early inflammatory phase but after the membranes have matured and contracted [*Williamson*[179] *et al. 2010*]. As the surgical intervention proceeds, a retinotomy should only be considered after meticulous (dye-assisted) epiretinal membrane peeling.

Location is another important issue. Of course one will try to preserve as much of the viable central retina as possible. The ideal location could be at the border between the epiretinal membrane-free central retina and the peripheral scarred retina that is beyond repair. Precise identification of this border remains difficult but recent experience suggests that intra-operative OCT may become a useful tool.

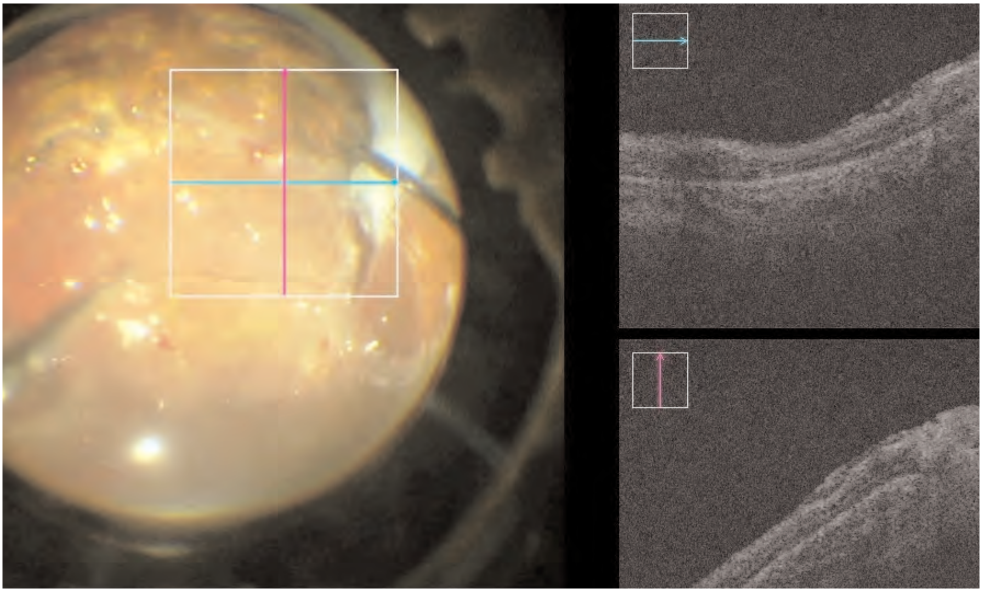

Figure 9.
This intra-operative OCT image confirms that the central retinotomy edge is not membrane free.
Acquired during a visit to Grazia Pertile, Negrar, June 2015.

Finally, the retinectomy is important as it removes this redundant retina thus limiting the risk of hypotony and iris neovascularization [*van Meurs*[180] *et al. 1996*].

We have investigated the impact of the timing of retinopexy. The position where the posterior retina settles immediately after the retinotomy, should not be considered unchallenged and thus, intra-operative anchoring of the retina in this position may not be optimal. Several issues may have bearing on this:

- The time course of PVR remains unpredictable and identification of the phase of the disease based on clinical signs is almost impossible. The timing of surgery is usually based on (impending) macular detachment. A retinotomy may thus be performed when the fibrotic response is not yet in a quiescent phase.

- In re-detachments that necessitate relaxing retinotomies, the retina is usually diffusely thickened and tense even after meticulous membrane peeling. This is demonstrated by the often quite marked central displacement of the retina that can be observed immediately after performing the retinotomy. Inspection of the edge of the retinotomy usually shows a tense and shortened inner retinal surface, while the outer surface appears corrugated and redundant, possibly resulting in a poor apposition between the outer retina and the retinal pigment epithelium (RPE), even under heavy liquid.
- To induce laser burns at the retinotomy edge, high energy is usually required. The resulting scars can, rather than just seal the retinotomy, increase the blood-ocular barrier breakdown and cellular proliferation, promoting further fibrosis with shortening and traction.
- The trauma of cutting the retina, although immediately releasing traction, may (re-)activate the scarring process.
- Re-attaching the retina, while essential for functional recovery and ultimately inhibiting the PVR response may, according to the feline model, initially activate Muller cell outgrowth.

We hypothesized that in the case of an ongoing event like retinal shortening in PVR, avoiding retinopexy at the time of retinotomy could allow central slippage of the viable remaining retina, as well as inward curling of its edges. Eliminating traction over the laser scars could thus reduce the risk of re-detachment. Once the fibrotic response has run its course and the retina has relocated to an unchallenged position, post-operative laser can create retinochoroidal adhesion in that position and possibly reduce the number of re-detachments after oil removal.

As argued before, when a long-lasting “tamponade” like a buckle or silicone oil closes off the subretinal space, instant sealing of the retinal defect is not required for re-attachment.

This modified surgical approach to PVR could, at least in theory, improve functional outcome by reducing the incidence of macula-off re-detachments under oil.

[*Veckeneer*[181] *et al. Deferred laser photocoagulation of relaxing retinotomies under silicone oil tamponade to reduce recurrent macular detachment in severe proliferative vitreoretinopathy. 2014, in appendix*]

In a series of 13 eyes of 13 patients judged to be at high risk of recurrent retinal shortening and re-detachment, we delayed laser surgery until several weeks after the procedure. We performed slit-lamp laser photocoagulation of the retinotomy edges, central to the curled areas, and assumed that the retina would by then be in a position no longer under traction. In addition, some recovery of the physiological adhesion between the retina and RPE would have occurred and the retinal swelling subsided, reducing the need for extensive and heavy laser.

We observed signs of curling or central slippage in 10 patients, confirming our assessment of residual fibrosis. Postponed laser allowed oil removal in all 13 patients. Recurrent detachment, however, developed in five (three with their macula off) after some weeks. Hence, the overall anatomical outcome is not superior to previous reports.

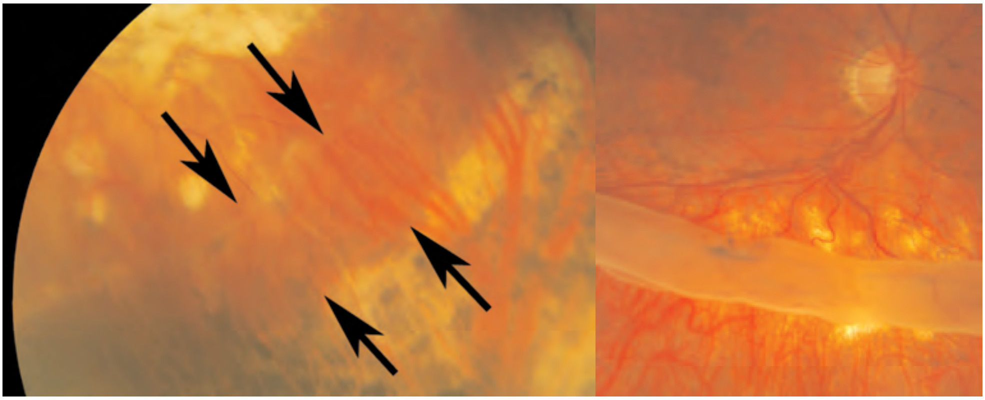

Figure 10.
The slippage and curling that occurs in most cases demonstrates that the position of the central retinotomy edge during surgery should not be considered unchallenged.

In the HSO (heavy silicone oil) study, heavier-than-water silicone oil was compared to lighter-than-water silicone oil, but no difference in the rate of recurrent retinal detachment was found. However, recurrent retinal detachment did develop in the quadrants where an aqueous compartment was left. A large inferior retinotomy without retinopexy may therefore be an interesting indication for HSO tamponade, as it may reduce the re-detachment rate under oil by preventing the excessive curling we have seen in some of our patients.

Since we only included challenging cases with poor prognosis in this series, the hypothesized mechanism of recurrent RD after relaxing retinotomy in relation to intra-operative laser photocoagulation may be realistic, and postponing laser may merit consideration in selected patients considered to be at high risk of future inferior recurrent RD under silicone oil. Further studies in search of the optimal tamponade in these cases are mandatory.

In conclusion: although performing a retinotomy at the wrong time in the wrong place after incomplete membrane peeling can be disastrous [*Gupta*[182] *et al. 2008*], when executed well, a retinotomy can help to achieve lasting anatomical success with some degree of functional recovery in most cases including those complicated by severe anterior PVR.

3.2. Improving surgical precision: chromo-vitrectomy

3.2.1. Introduction

The target tissue for ocular surgery is often (semi-) transparent. From the introduction of the ophthalmoscope by *Helmholtz* in 1851 to the binocular operating microscope with wide angle viewing systems and fiber optic light, improving visualization has been an essential prerequisite for progress in ocular surgery.

More recently, several adjuvants have been introduced for this purpose. For instance, better identifications of the anterior lens capsule using trypan blue dye, has been a great contribution to cataract surgery [*Melles*[183] *et al. 1999*].

3.2.2. Triamcinolone-assisted vitrectomy: more effective and less traumatic vitreous removal

Improving the visualization of vitreous, an essentially transparent tissue, has been an important goal.

Correctly identifying the vitreous cortex using staining agents has had a fundamental impact on our ability to cope with particularly difficult cases like tractinal retinal detachments and detachments in high myopia. In these eyes, although the vitreous may appear detached on slit-lamp examination, vitreous cortex remnants are often still attached to the retinal surface [*Spaide*[184] *et al. 2005*]. Staining the vitreous cortex intra-operatively has greatly improved our understanding of this phenomenon also called vitreous schisis [*Li* [185] *et al. 2010*].

Meticulous removal of vitreous is also an essential part of the surgical strategy to reduce the incidence and severity of PVR. Vitrectomy releases vitreoretinal traction, removes growth factors, seeded RPE cells and hyalocytes, as well as of the collagen matrix for cell attachment.

Nevertheless, vitrectomy itself can be harmful. Iatrogenic entry site breaks are an important concern in this regard [*Ramkissoon*[186] *et al. 2010*]. Vitrectomy through cannulated ports seems to significantly reduce the incidence of entry site breaks by protecting the vitreous base [*Cha*[187] *et al. 2013*].

Another concern with regard to surgical trauma is the additional breakdown of the blood-ocular barrier that is induced by an extensive vitrectomy [*Hoshi*[128] *et al 2012*].

Better identifying the target tissue can help to reduce the trauma of posterior segment surgery while making it more effective. Several staining agents including sodium fluorescein and trypan blue have been tested for the purpose of better vitreous visualization [*Das*[188] *et al. 2004; Farah*[189] *et al. 2008*].

Triamcinolone acetonide (TA) crystals very effectively identify vitreous. The use of TA in VR surgery is longstanding. *Machemer* and coworkers investigated its potential to inhibit PVR back in the eighties and it was introduced as an intra-operative aid by *Peyman*[190] in *2000* [*Peyman et al.* 2000]. Rather than truly staining, the TA crystals seem to form a coating by adhering to the surface of the vitreous cortex.

We have developed a method that facilitates the detection of vitreous remnants. For our technique, PFCL is used to confine the aqueous environment to the anterior vitreous while also stabilizing the mobile detached retina. TA is added to increase light scatter. In our modified approach, visualization of the vitreous is possible using low light levels, by enhancing the scattering effect [*Veckeneer*[130] *et al. 2009*]. The technique clearly differentiates vitreous from PFCL and infusion fluid, and facilitates trimming of the vitreous base without the need for deep scleral indentation. The impact of the surgical trauma may also be reduced by the pharmacological anti-inflammatory effect of TA [*Sakamoto*[149] *et al. 2002*].

Using this technique, our primary anatomical failure rate in a consecutive series with a follow up of at least 6 months, decreased from 9.8% to 5.8%. Other authors have also reported on the enhanced safety of TA assisted vitrectomy [*Yamakiri* [191] *et al. 2007*].

The potential retinal toxicity of TA, particularly when injected after ILM peel nevertheless requires cautious application of this substance during vitreous surgery [*Szurman*[192] *et al. 2007*]. In addition, although most of the TA will be removed by a complete vitrectomy, the impact steroids can have on cataract progression and ocular hypertension, should encourage vigilant follow up.

3.2.3. Membrane peeling in PVR and the key issue of visualization

In addition to complete vitrectomy, membrane peeling has been shown to be an absolute requirement for success in PVR surgery [*Aaberg*[193] *et al. 1988; Abrams*[173] *et al. 1997*].

The problems that complicate membrane dissection are the limited ability to properly asses the full extent of the membranes and the a-traumatic removal in a reasonable time span.

To achieve a higher re-attachment rate and perhaps reduce the need for relaxing retinotomies or additional episcleral buckles, a technique is needed that reduces traction more effectively and reproducibly. The surgical goal should be a more complete and less traumatic removal of epiretinal membranes.

For this purpose, we evaluated several vital dyes for their ability to enhance the visibility of membranes on the retinal surface. In an ex vivo study we demonstrated that trypan blue (TB) stains PVR membranes effectively. We further established the limited toxicity of low concentrations of TB in a rabbit model [*Veckeneer*[194] *et al. Ocular toxicity study of trypan blue injected into the vitreous cavity of rabbit eyes. 2001*]. In clinical practice, the application of trypan blue dye can confirm the presence and extent of ERM's more precisely. Using this technique we reported a low rate of re-detachment following silicone oil removal [*Feron*[195]*, Veckeneer et al. Trypan blue staining of epiretinal membranes in proliferative vitreoretinopathy. 2002*].

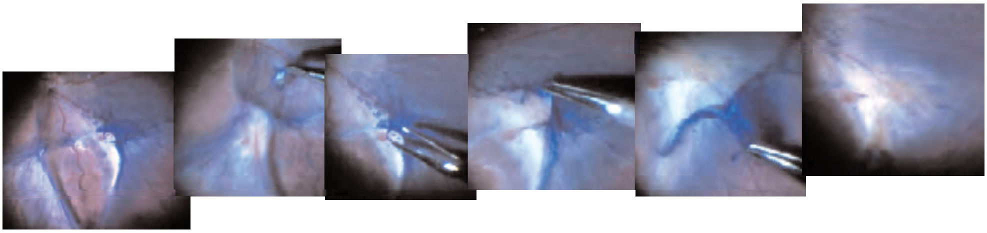

Figure 11.
TB helps to visualize the presence and extent of epiretinal membranes in PVR.

Several authors have confirmed that the use of TB to stain membranes in PVR surgery, reduces mechanical surgical trauma as well as operating time [*Vote*[96] *et al. 2004; Nawrocki*[197] *et al. 2005*].

Another important concern with regard to the long term outcome of PVR surgery is that of post-operative re-proliferation. As discussed previously, surgery performed in an active stage of the disease may increase the risk of incomplete membrane removal. Additionally, membranectomy and retinotomy cause further trauma and re-attaching the retina may initiate a cellular response, promoting re-proliferation.

To reduce the risk of re-proliferation, many have advocated removing the collagenous scaffold for new membranes. As discussed, vitreous base shaving is part of this strategy.

More recently, the internal limiting membrane (ILM) of the retina has also been identified as an interesting target in PVR surgery, particularly in the area where the ILM is thickest namely the posterior pole. We have observed, and many others have reported, that dye assisted membrane peeling can effectively protect the macular area against membrane recurrence. Not only in PVR but also in other diseases with a high rate of reproliferation like uveitis [*Almony*[198] *et al. 2012*]. *Odrobina*[199] recently reported a significant reduction of the reproliferation rate in a prospective series of PVR cases where the incidence of epimacular membrane reformation was 0/33 in the peel group as compared to 9/52 in the no-peel group [*Odrobina et al. 2012*].

Despite the fact that the use of vital dyes has caused a major breakthrough in the visualization of different ocular tissues, several limitations need to be addressed in order to optimize so-called chromo-vitrectomy.
Ever since the introduction of indocyanin green (ICG) in 2000 by *Kadonosono*[200], much research has focused on the aspect of dye-related toxicity [*Kadonosono et al. 2000*]. ICG was implicated early on as the cause of poor post-operative outcome in patients treated for macular holes [*Tsuiki*[201] *et al.*

2007; Engelbrecht[202] *et al. 2002; Haritoglou*[203] *et al. 2002*] and toxicity was later confirmed in cell culture studies. In contrast, infracyanine green (IfCG), although it contains the exact same chromophore as ICG, contains different additives (iodine in ICG) and a different solvent (water in ICG, glucose in IfCG). We reported on the importance of hypo-osmolarity on dye related toxicity in an RPE culture model [*Stalmans*[204]*, Veckeneer et al. Toxic effect of indocyanine green on retinal pigment epithelium related to osmotic effects of the solvent. 2002*]. A more recent study has shown that the use of a solvent such as polyethylene glycol (PEG), that has limited impact on osmolarity can reduce the toxic potential of a dye [*Awad*[205] *et al. 2011*].
Another concern in relation to dye assisted membrane peeling is the cleavage plane. In particular, ICG appears to alter the surgical plane, thereby potentially causing significant sub-ILM damage [*Schumann*[206] *et al. 2009*]. The tissue-modifying abilities of ICG in relation to the photosensitization-dependent cross-linking of collagen could have bearing on this. Conversely, *Kenawy*[207] found that, rather than the dye, the type of disease and thus the membrane that is peeled, determines the cleavage plane and the associated collateral damage [*Kenawy et al. 2010*].

Further research is also needed to improve the effectiveness of the dyes. Ideally, one dye would stain all of the different tissues that we want to target. Unfortunately, the affinity of a certain dye is governed by the composition of the tissue. Not only does the composition of for instance vitreous cortex differ greatly from that of an epiretinal membrane or the ILM, the degree of staining of a certain tissue also differs between disease entity, severity and stage. Epiretinal membranes in PVR are dynamic structures and their cell and matrix composition will change with the progression of the disease, as will the affinity of a specific dye. *Lesnik Oberstein*[209] has shown that cellularity and active proliferation is particularly prominent in "fresh" PVR whereas "older" membranes are much less active in that regard [*Oberstein et al. 2011*]. Intra operative application of trypan blue selectively stains degenerating cells which are usually present in PVR membranes but particularly common in "older" membranes. This is in accordance with our findings on membrane staining at the time of oil removal [*Feron*[210]*, Veckeneer et al. 2002*].
To deal with the issue of variable tissue composition we found the use of more than one dye to be effective [*Stalmans*[211]*, Veckeneer et al. Double vital-staining using trypan blue and infracyanine green in macular pucker surgery. 2003*]. The practice of double staining uses trypan blue to first identify and remove the ERM followed by the application of IfCG for ILM peeling.
Novel dyes have been developed to optimize the contact between dye and tissue as well as to make use of different affinities. We recently conducted a multicenter trial evaluating the staining efficacy of two novel PEG-enriched dye preparations and found a strong correlation between the recorded density of staining and the reported "ease of membrane peeling".

[Veckeneer[212]*, Melles et al. Novel 'heavy' dyes for retinal membrane staining during macular surgery: multicenter clinical assessment. 2014, in appendix].*

Although our initial clinical results suggest the combination of TB with brilliant blue green (BBG) to be superior for staining PVR membranes, this needs to be confirmed by others.
Several authors have attempted to improve user friendliness. Until recently, all available dyes were dissolved in balanced salt solution, resulting in a density and viscosity similar to that of the infusion fluid used during surgery. To optimize the intensity of staining and to avoid 'swirling' of the dye throughout the vitreous cavity, a fluid-air exchange needs to be performed before injecting the dye. This procedure also improves the contact between the staining agent and the tissue. Because a fluid-air exchange may interfere with optical clarity, several authors have experimented with dye formulas with increased density (glucose, deuterium) [*Lesnik Oberstein*[213] *et al. 2007; Gerding*[214] *et al. 2011*]. Cooling the dye has also been recommended [*Schmid*[215] *et al. 2011*].
We have reported on our experience with solutions of TB and/or BBG that, in order to safely enhance their density and viscosity, were dissolved in polyethylene glycol (PEG). Staining efficacy of these PEG-enriched dyes at room temperature was reported to be adequate in 125 out of 127 patients without fluid-air exchange [*Veckeneer*[210]*, Melles et al. 2014*].

In conclusion: chromo-vitrectomy has had a fundamental impact on the field of VR surgery by making membrane peeling a straightforward procedure. Further research is certainly needed to demonstrate conclusively the benefit of membrane peeling for each specific disease entity. Better understanding of the precise interaction of a dye with a certain tissue may guide the surgeon's decision "to peel or not to peel", turning the dye into an intra operative diagnostic tool.

3.3. Reducing the impact of retinal detachment on visual function and retinal adhesion

3.3.1. Introduction

The disappointing functional outcome and the slow recovery of adhesion are two crucial unsolved riddles concerning the surgically re-attached retina. Based on our review of the current knowledge on this subject, we hypothesize that both are interrelated. Therapeutic measures that target adhesion may consequently also improve function.

An attached macula is the vital precondition for visual function. Functional recovery after re-attachment of the macula, measured as best corrected visual acuity, is almost invariably incomplete. Several other aspects of the post-operative quality of vision may also be suboptimal. Poor contrast and color vision, displacement and/or metamorphopsia can chronically disturb the binocular function.

The comparison of current functional outcome results with historical data, has limitations. Reporting functional results reliably (if at all) is a rather recent practice. Still, the results reported in the 1930's by *Weve and Binckhorst* seem comparable to those reported in 1982, when Burton studied 953 consecutive cases of primary rhegmatogenous retinal detachment treated with external surgery. Over 80% of cases with macula on achieved 20/50 acuity or better, compared with 20% of cases with macular involvement [*Burton*[8] *et al. 1982*]. Only two percent of patients with macular detachment regained 20/20 acuity. Overall only 42 percent of all re-attached cases were documented with at least 20/50 acuity in that study.

Other surgical techniques like pneumatic retinopexy and pars plana vitrectomy, have gained popularity in the past 30 years but the reported functional outcomes have largely remained the same [*Fraser*[2] *et al. 2010*].

Factors involved in functional recovery remain a major research subject. Of all the variables that have been studied so far, the optimal function of the pre-op attached macula is by far the most relevant and repairing the detachment before the macula detaches gives the best chance of good functional outcome. When organizing the ideal logistical conditions to achieve this goal, we may consider the following:

- To increase the proportion of patients that reach the VR unit with the macula still attached, we should improve patient awareness [*la Cour*[216] *2006*].
- Once the patient is admitted, with adequate posturing, early progression to foveal detachment is unlikely [*Ho*[217] *et al. 2006, Hajari*[218] *et al. 2014*].
- Treating a retinal detachment in an emergency setting may not yield the best results [*Koch*[219] *et al. 2012*].
- Pre-op macular attachment, as defined by ophthalmoscopy, does not guarantee the absence of fluid on optical coherence tomography (OCT) images [*Ricker*[220] *et al. 2011*].

Until about fifteen years ago, a fundoscopically re-attached macula was considered a success and the reasons for poor function remained unclear. New imaging technologies such as OCT, have revolutionized our capacity to study the macula in vivo and we can now visualize in great detail the anatomy of the retina. Images of ever increasing resolution have revealed damage that is mainly located in the outer retina, with a disruption of the photoreceptors and the external limiting membrane [*dell'Omo*[221] *et al. 2015*].

Many different factors that may influence recovery after re-attachment have been identified. Pre-op visual acuity, age, the duration and height of macular detachment, the use of cryotherapy and post-operative features such as persistent subfoveal fluid, cystoid macular edema and macular pucker have all been reported to be of importance in relation to functional recovery [*Ross*[222] *et al. 2005; Heussen*[223] *et al. 2011*].

Studying the relative impact of the different variables remains challenging. For instance, visual acuity and height of the detachment may be very difficult to measure correctly due to media opacities, an overhanging bullous detachment, or the urgency surrounding the pre-op assessment.

Establishing the duration of macular detachment is even more problematic. Patients often experience the posterior vitreous detachment as a sudden drop in vision and the accuracy to differentiate this from the actual macular detachment based on just history, is poor [*van Eyck, unpublished data ROI 2014*].

Nevertheless, from clinical practice we know that poor functional outcome is to be expected when signs of longstanding macular detachment are present. A recent meta-analysis of the literature confirms a strong relationship between duration of detachment and recovery of vision [*van Bussel*[224] *et al. 2014*]. Evidence from a feline animal model confirms the critical impact of time. A detachment of only a few hours may not induce long-lasting changes in the retina but, a detachment lasting more than a day, may already cause structural damage and cellular responses including photoreceptor and bipolar cell death and Muller cell proliferation [*Lewis*[175] *et al. 2002*].

Another important feature we can now study in detail, is the post-operative persistence of subretinal fluid (PSF) in cases where the macula is considered attached on ophthalmoscopy. Submacular fluid remnants, preventing the immediate post-op re-apposition of PR to the RPE, have been shown to occur in up to 94% of "successful" RRD repair cases [*Ricker*[218] *et al. 2011*].

The impact of PSF on the final functional outcome remains debated but there is accumulating evidence suggesting that suggests that visual recovery is slower in patients with PSF [*Kim*[225] *et al. 2014, Ricker*[218] *et al. 2011, Rashid*[226] *et al. 2013, Rossetti*[227] *et al 2010, Seo*[228] *et al. 2008*]. Although the submacular fluid remnant may only be shallow or bleb-like, long term follow up may show progressive atrophy of the neuroretina.

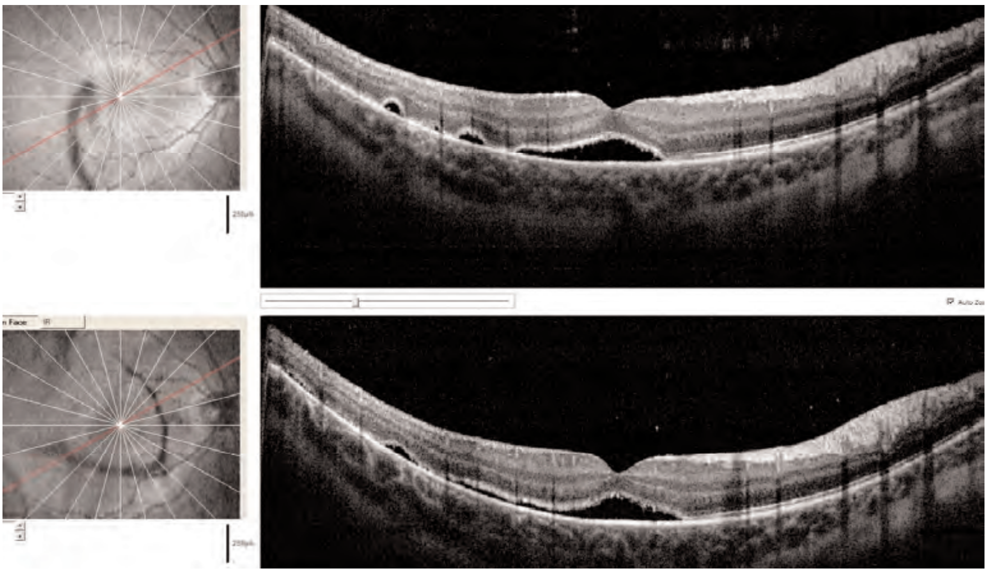

Figure 12.
Typical case of PSF: 8y old boy treated for macula involving RRD caused by oral dialyses.
BCVA remains unchanged 3 months post-op at 0.2 Snellen.
Above: image 3 months post-op, below: 4 weeks post-op. Minimal changes in pattern and height of SRF.

To devise a strategy to deal with PSF, we have studied the potential causes of its occurrence.

[*Veckeneer[229], Van Aken et al. Persistent subretinal fluid after surgery for rhegmatogenous retinal detachment: hypothesis and review. 2012*]

PSF after RD surgery has been reported more often after buckling than vitrectomy. This seems related to selection bias. Case characteristics such as phakic lens status, absence of PVD, and small breaks, predispose a patient to be treated with a buckle rather than vitrectomy. The non-syneretic vitreous in these eyes, by tamponading the retinal breaks, may slow the progression causing longstanding detachments that can persist even after effective closure of all the breaks. This hypotheses is supported by data from a recent study [*Tee[230], Veckeneer, Laidlaw. Persistent subfoveolar fluid following surgery for macula involving rhegmatogenous retinal detachment: An SD-OCT guided study on the incidence, etiological associations and natural history. Submitted to EYE, 2015*] on 61 cases, showing a much higher incidence of PSF in the patients with round hole detachments, as compared to horseshoe tear detachments.

The peculiar composition of the SRF, that results from slowly progressive longstanding detachment in RRD, may promote the persistence of fluid after surgical repair:

- Oncotic pressure gradient: as the fluid accumulates over time, its composition and physical properties will change, making its re-absorption more difficult. Large molecules such as proteins and glycosamonoglycans (GAG), as well as cells and cellular debris, are concentrated in the subretinal space and reduce, or even reverse, the oncotic pressure gradient favoring fluid to enter, rather than leave the SR space.

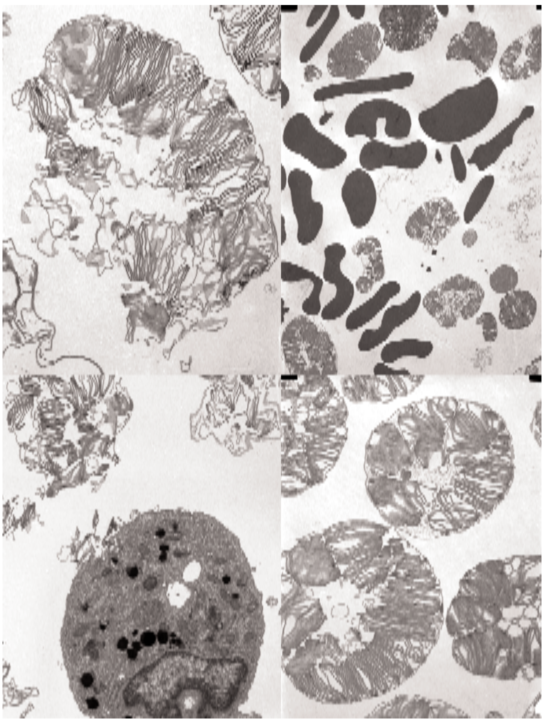

Figure 13.
Photoreceptor outer segments and other cellular debris, found in subretinal fluid of a patient with clinical signs of longstanding detachment.

- Viscosity: higher viscosity may increase adherence to retinal pigment epithelium, causing fluid remnants after drainage.
- Phagocytosis: large molecules and cellular debris can only be removed through phagocytosis. Interestingly, histological specimens show loss of microvilli on the apical side of the RPE. In addition, GAG's like hyaluronic acid, present in vitreous and SRF, can inhibit the RPE phagocytotic activity and may be of importance in this regard [*Gregory*[231] *et al. 1990*]. This may also be one of the reasons why hyaluronic acid can maintain an experimental RD over long periods of time [*Zacks*[232] *et al. 2004*]. The accumulation of larger molecules and debris is also suggested by the increased optical density of SRF with time [*Kashani*[233] *et al. 2015*].
- Barrier: RPE with impaired pumping capacity, but intact intercellular junctions, has a barrier effect that opposes fluid absorption, as was demonstrated by *Negi*[234] [*Negi et al. 1983*]. In those circumstances, destruction of the RPE layer facilitates fluid transport towards the choroid.

These same characteristics may also slow the recovery of the natural adhesiveness. The adhesive force in a healthy eye is considerable, as is demonstrated by the fact that most retinal breaks do not progress to a detachment. Based on long-term studies of asymptomatic breaks, the ratio comparing the prevalence of retinal breaks to that of RRD is 83:1 [*Byer*[235] *et al. 1982; Byer*[236] *et al. 1998*].

The importance of an active RPE pump is demonstrated by the rapid decrease of retinal adhesion, that can be observed within one hour after enucleation, as well as the strong dependency of retinal adhesion on oxygen [*Marmor*[237] *et al. 1994; Kim*[238] *et al. 1993*]. Additionally, the hydrostatic and oncotic pressure gradients across the RPE barrier also favor fluid moving towards the choroid [*Frambach*[239] *et al. 1982; Marmor*[240] *2006*].

Mechanical adhesion is another important component of retinal adhesiveness. Several aspects of the RPE-photoreceptor interface contribute. The way RPE microvilli extend and surround the photoreceptor outer segments may provide a frictional resistance or an electrostatic force, that opposes separation. More importantly, the interphotoreceptor matrix contains a viscous material composed of glycoproteins, proteoglycans, and GAG's. Enzymes that degrade proteoglycans have resulted in marked loss of adhesion in primate eyes. The strength of the mechanical adhesion is further demonstrated by pigment adherence to the neuroretina, seen when peeling the retina in post-mortem experiments [*Endo*[241] *et al. 1988*].

As a result of this strong adhesion, only a combination of persistent traction on the retinal break in combination with fluid currents (also known as dynamic traction), can overwhelm the forces of retinal attachment, allowing liquefied vitreous fluid to pass through a retinal break into the subretinal space.

It is important to realize that even in the absence of persistent fluid on OCT, the physiological interaction between the neuroretina and the RPE has been fundamentally affected by detachment.

Liquefied vitreous in the subretinal space can have a severe and long-lasting impact on natural adhesion. Our surgical intervention, when successful, will overcome the dynamic traction forces, but it does not restore the mechanical, oncotic and RPE pump adhesion forces that may be reduced for days or even weeks.

This could well be an aspect of the strong relationship between size of the detachment and the risk of anatomical failure. Before *Gonin*, although no experimental data on reduced retinal adhesion existed, many interventional measures intended to increase the adhesion but because the central cause was not targeted, positive results would not have been observed. *Gonin* showed that closing the retinal breaks is condition sine qua non for successful re-attachment but, one can wonder why

Weve achieved such high success rates back in the 1930's, with the simple technique of drainage and diathermy. Was it because of the extensive surface diathermy he performed in the entire area where the retina had been detached? By doing this he may have promoted the early recovery of post-op adhesion.

3.3.2 The quality of attachment as therapeutic target

What options do we have to restore adhesion and prevent or treat PSF?

Most of the research into retinal adhesion was done more than 20 years ago and the results were never translated to common clinical practice.

Acetazolamide, somatostatin and mannitol promote fluid transport across the RPE barrier but not to an extent that they could be useful for the treatment of RRD [*Wolfensberger*[242] *et al. 2000; Marmor*[243] *et al. 1982; Missotten*[244] *et al. 2007; Kita*[245] *et al. 1991*].

Lowering calcium concentration and increasing the temperature of the fluid facilitates the artificial induction of a RD but no effective application has been demonstrated using the opposite characteristics [*Szurman*[246] *et al. 2006*].

Laser photocoagulation in animal experiments creates adhesion between the retina and the RPE. After photocoagulation of intact retina, the adhesive force was reduced by 50% at 8 hours but increased beyond normal (to approximately 140%) by 24 hours [*Yoon*[247] *et al. 1988*]. Photocoagulation of retina that had just settled after experimental detachment produced similar results [*Folk*[248] *et al. 1989*]. Early adhesion induced by the laser may thus be enhanced in areas where the retina has been recently re-attached. Several authors have reported a low incidence of retinal re-detachment after 360 degrees laser retinopexy, which may reflect the positive effect laser can have on general adhesion [*de Silva*[249] *et al. 2008; Falkner-Radler*[250] *et al. 2015*].

Intense thermal laser results in a full thickness chorio-retinal scar that would generate an unwanted scotoma when applied to the entire area of detachment. Less aggressive forms of laser such as micro pulsed selective retina therapy have been shown to effectively disrupt the RPE barrier, promoting fluid re-absorption without irreversible neuro-retinal damage. This effect has been applied successfully in chronic CSR, diabetic macular edema and several cases of PSF [*Yadav*[251] *et al. 2015; Mansouri*[252] *et al. 2014; Koinzer*[253] *et al. 2008*].

We hypothesized that a surgical technique, that restores the neuroretinal-RPE interface as closely as possible to the pre-detachment condition, may prevent the occurrence of PSF and promote early recovery of adhesion.

We have suggested that a modified drainage technique accompanied by a rinse-out of the SR space could be a surgical approach to better restore the RPE-PR interface. Removing large molecules and cellular debris may effectively restore the oncotic pressure gradient and reduce the RPE blockade on fluid flow.

We designed a prospective study to evaluate this hypothesis.

[*Veckeneer*[254] *et al. Subretinal lavage to prevent persistent subretinal fluid after rhegmatogenous retinal detachment surgery: a study of feasibility and safety. 2011*].

We included twelve non-consecutive patients with primary macula-off RRD. Selection criteria included cases of RRD that arose from retinal breaks situated away from the area with the most elevated detachment and estimated retinal detachment duration of at least 1 week. In these cases, draining all the fluid through the existing breaks can be very difficult. Rather than creating an additional break to drain the residual fluid, we modified our technique. The surgical procedure comprised a 23-gauge 3-port pars plana vitrectomy. Bimanual manipulation was facilitated by chandelier illumination. Rather than flattening the retina with perfluorocarbon liquids, we performed modified transscleral drainage. Briefly, a 27 gauge needle, fitted with an insertion tool (normally used for fluid drainage during conventional buckling surgery), was connected by tubing to a 3-way stopcock with two 5cc syringes, one filled with balanced salt solution (BSS). The needle was introduced into the subretinal space in the area of highest retinal elevation. The subretinal space was then inflated with BSS in order to dilute the viscous SRF. The intra-ocular pressure was normalized by venting vitreous fluid through a flute needle positioned in the mid-vitreous cavity. Then, after turning the stopcock, SRF was aspirated into the second syringe; this resulted in partial flattening of the RRD. At least 2 cycles of inflation and aspiration were performed. Finally, the needle was removed from the subretinal space as the retina was approaching the RPE. The evacuation of any residual peripheral SRF was accelerated by raising the infusion pressure to increase the hydrostatic pressure in the vitreous cavity.

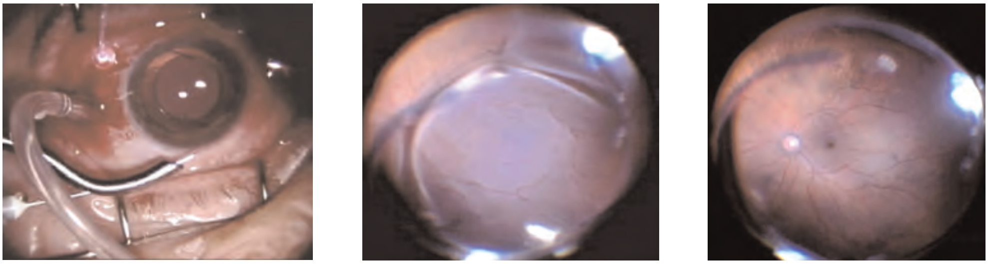

Figure 14.
Modified technique for fluid drainage. (Left) Drainage tool. (Middle) Trans-scleral 27gauge needle allows lavage and drainage. (Right) Bullous inferior detachment flattens completely without the need to create an additional retinal break for endodrainage.

Four weeks after surgery, ophthalmoscopy showed re-attached retina's in all twelve patients. No remnants of fluid were found in any of the patients on the post-op OCT. A self limiting choroidal hemorrhage developed at the drainage site in one eye. No other complication was seen. Theoretically, increased turbulent fluid flow in the subretinal space resulting from the lavage, could have a deleterious effect on the outer retina.

The effect of the lavage procedure on re-attachment may be twofold. On one hand it may promote a more complete drainage, on the other, the diluted composition of any fluid remnants at the end of the surgery, makes it more likely that they will be easily absorbed.

Possibly, support for our hypothesis can be deduced from the excellent results reported by *Martinez-Castillo*[255], who performs RRD surgery without the use of tamponade [*Martinez-Castillo et al. 2007*]. The surgical technique entails extensive vitrectomy, followed by meticulous SRF fluid drainage by way of repeated fluid air exchange. This seems to sufficiently restore adhesion intra-operatively, allowing just laser around the breaks to keep the retina attached, even without tamponade.

In conclusion: the condition of the retina-RPE interface after re-attachment may negatively influence function and adhesion. Options to improve this situation are limited and although function and retinal adhesion may, at least in theory, benefit from better SRF drainage, its clinical value remains to be proven.

Chapter 4

The future

The future

As discussed previously, the best results are achieved when we treat the patient with a retinal detachment before the macula has detached. We could be even more effective if we would focus more on the patient at risk before his retina detaches. The following considerations have bearing on this aim of prevention:

- Pharmacological modification of vitreous aging and detachment: our understanding of vitreous remodeling during aging has increased steadily. One important observation is that the area of tight interaction between vitreous collagen fibers and the inner retina, that we call the vitreous base, progresses during life from the ora towards the equator, possibly as a result of production of collagen by Muller cells [*Ponsioen*[256] *et al. 2008*], [*Ponsioen*[257] *et al. 2010*]. On the other hand, syneresis in combination with weakening of the reversible bond between vitreous and area of the retina posterior to the vitreous base, eventually leads to a posterior vitreous detachment. During a posterior vitreous detachment, because the anterior attachment is irreversible, breaks can develop as the detachment progresses anteriorly.
- Weakening the attachment of the posterior vitreous to the retina using plasmin enzyme and its synthetic analog microplasmin, has recently been reported [*de Smet*[258]*, Veckeneer et al. 2009*]. This novel treatment clearly holds promise for vitreomacular tractional pathologies including macular hole. Unfortunately, microplasmin does not weaken the anterior vitreoretinal attachments. Promoting a posterior vitreous detachment pharmacologically can consequently induce, rather than prevent, traction in the area of the vitreous base as is shown by the occurrence of retinal breaks following injection [*Stalmans*[259] *et al. 2012*].
- Enzymatic collagen cross-linking is an essential step in the development of the irreversible attachment of the vitreous cortex to the retina at the vitreous base [*Ponsioen*[260] *et al. 2009*]. We have demonstrated that inhibiting enzymatic collagen cross-linking can effectively prevent the assembly of the collagen matrix in the developing vitreous of the chick embryo [*Veckeneer*[261] *et al. 2008*].

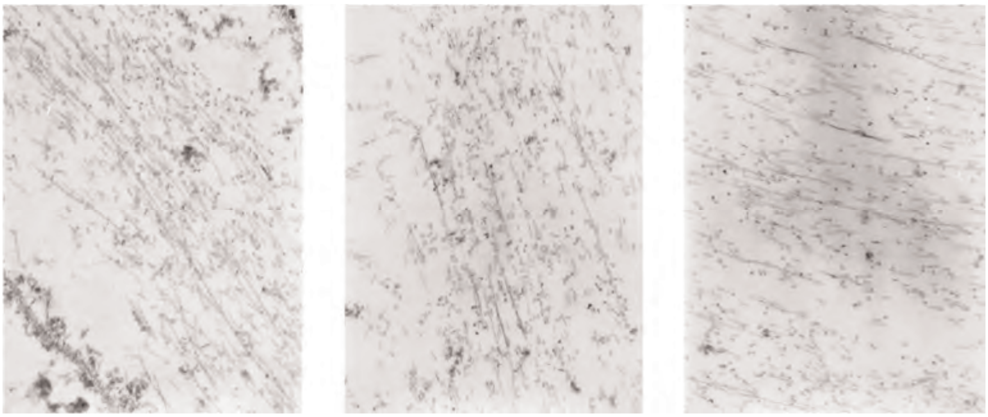

Figure 15.
Chick embryo experiments. Intravitreal administration of BAPN inhibits enzymatic cross linking and prevents the assembly of vitreous collagen fibrils. From left to right: control, low dose, high dose BAPN.

- In order to pharmacologically overcome the vitreoretinal adhesion near the vitreous base in adult human vitreous, we need to induce a similar collagen breakdown. Proteolytic enzymes such as matrix metalloproteinases are possible candidates for this purpose but major obstacles including tissue selectivity and the presence of neutralizing substances in native vitreous need to be overcome.

- Optimizing prevention using retinopexy and/or encircling buckles: precise identification of the vitreous base in vivo may allow more effective prevention by accurately treating the area where breaks are likely to occur. New imaging technologies should enable us to visualize in great detail, the retina anterior to the equator, where pathological traction can occur.
- Identifying and counseling high risk patients: a recent study by *Bjerrum*[262] and *la Cour* irrefutably confirms that cataract extraction, even when uncomplicated and using minimally invasive surgical techniques, greatly increases the risk of a retinal detachment and this risk remains elevated for up to ten years after surgery [*Bjerrum et al. 2013*]. Other important considerations include fellow eye status and family history, particularly when including genetic testing [*Hajari*[263] *et al. 2014*], [*Kirin*[264] *et al. 2013*], [*Nikopoulos*[265], *Veckeneer et al. 2011*].

Concerning the patient with a retinal detachment, we should aim at preserving surgery as the mainstay of treatment. The greatest asset of surgery over most drug treatments, is the ability to permanently alter the course of the disease with a single intervention. Pharmacotherapy on the other hand can transform an acute disease into a chronic drug dependent state, with a huge impact on quality of life and cost effectiveness. Consider the treatment of primary open angle glaucoma: the difference between a single successful filtering procedure, as compared to life-long drop medication with all its limitations including cost, need for follow up, drug side effects and patient compliance.

In our continued quest to truly redefine minimally invasive surgery, let us abandon the current doctrine that defines minimally invasive as removing of the clear lens and vitreous through a small incision.

Several topics may be considered when designing a therapeutic fusion incorporating all the best options:

- Development of new surgical techniques. As the surgical procedure evolves, the surgeon can tailor his approach as other disease characteristics, that become apparent intra-operatively, inspire him to alter his approach. This flexibility has always been of service for the development and introduction of new techniques. However, it may also prove a major drawback, as the considerable number of disease aspects that influence outcome in combination with uncontrollable intra- and inter surgeon variability, make reliable and reproducible comparative trials difficult and their value limited. More detailed pre-operative imaging, genetic and biomarker typing on the other hand, may help to better tailor the approach in each individual case, including for instance adjuvant therapy to reduce the risk of PVR.
- Minimally invasive surgery. The development of the retinal break in itself relieves the vitreoretinal traction to a certain extent and as long as the retina has not been detached, treatment of a retinal break can be very simple and extremely effective [*Wilkinson*[266] *et al. 2013*]. As soon as the break is associated with detachment, however, additional procedures i.e. buckle, tamponade or vitrectomy are required because we cannot accomplish immediate retinopexy and because of the profound reduction of the retinal adhesion. The following options can be considered in order to achieve attachment less invasively:
    - Temporary relieve of dynamic traction by immobilization: a very effective and non-invasive method to tackle the dynamic traction (cfr. supra) is by immobilization. Several authors have reported the benefit of posturing and binocular occlusion [*Lean*[267] *et al. 1980*], [*Adams et al. 1973*]. *Algvere* reported a complete re-attachment in up to 45% of patients using a traction suture [*Algvere*[269] *et al. 1977*]. Retrobulbar anesthesia could be an even more effective approach to reduce ocular movements. In order to optimize the motor blocking effect of the local anesthetic, adding clonidine can be considered [*Górniak*[270], *Veckeneer et al. 2014*]. Immobilization results in a temporary reduction of traction and fluid currents allowing spontaneous absorption of the SRF.

Once the retina has re-attached, simple retinopexy to seal the breaks would suffice to achieve success in uncomplicated cases. Alternatively, this approach could serve as a bridging strategy while awaiting surgery.

- Temporary buckle: reducing the traction using a temporary buckle similar the Lincoff balloon [*Lincoff*[271], *Kreissig 1981*], such as the supra choroidal injection of visco-elastics [*El Rayes*[124] *2013*], could be an interesting modification to our technique. Once the breaks have been permanently sealed with retinopexy, in most cases, the buckling effect is no longer required to maintain attachment.
- Instant retinopexy: on the spot sealing of the retinal breaks may be achieved when the photoreceptors are in direct contact with the RPE. *Wilson Heriot* demonstrated in a rabbit animal model, that a "dry" interface permits immediate fusion between photoreceptors and RPE, even at low temperature [*Heriot. Thermofusion of the retina with the RPE to seal tears during retinal detachment repair. Submitted to Graefes 2015*]. A surgical technique that reproduces these conditions would reduce the inflammatory response that follows high power laser or cryo, which is necessary when fluid remnants are present. In addition, since the breaks are immediately sealed, the need for buckle or tamponade would diminish. The report by *Martinez-Castillo*[255] acts as proof of principle but his technique involves pars plana vitrectomy with repeated fluid air exchange, accompanied by meticulous drainage [*Martinez-Castillo et al. 2007*]. We have suggested that reducing the viscosity of the SRF fluid by dilution (lavage), could optimize the intra-operative fluid drainage and as a result drying near the break [*Veckeneer*[251] *et al. 2011*].
- Improved intra-operative visualization: intra-operative high resolution OCT in combination with safer and more effective dyes will allow more precise and thus less invasive surgery.

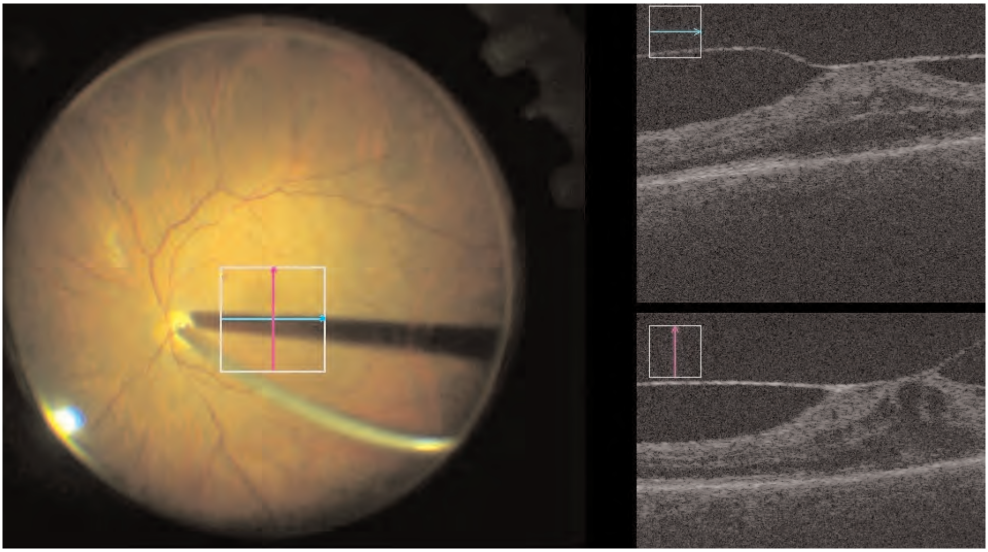

Figure 16.
OCT guided induction of PVD. Intra-op OCT clearly visualizes the vitreo-macular traction as seen on the right.
(Image acquired during a visit to Grazia Pertile, Negrar, June 2015)

- As described previously, the use of the currently availably endotamponades has many disadvantages. The list of optimal characteristics of the ideal vitreous substitute is long. Closely resembling most of the features of native vitreous, in addition to tamponading retinal breaks in all quadrants and easy intra-operative manipulation, requires a complex combination of physical and chemical properties. Several polymers and "smart" hydrogels do show potential [*Donati S*[272] *et al. 2014*].

- Macular injury: with regard to functional recovery, although we are convinced that repositioning the macula ASAP is beneficial, future modifications of surgical technique may focus on the safest rather than the fastest way to re-attach the macula. Since the oxygen for the fovea is mainly supplied from the choroid, pushing the macula back into place using heavy liquid may cause hyperoxic trauma. Reducing this "reperfusion injury" may indeed be an important consideration. Instead of focusing primarily on limiting the duration of detachment, we may also aim to improve the condition of the detached retina, as well as the environment in which the retina returns after re-attachment. Surgical techniques that focus on reliable and safe access to the subretinal space, similar to the modified lavage-drainage method, may than prove useful for the application of neuro-protective and/or regenerative agents that could reduce, or even repair the neuroretinal injury.

In conclusion: when incorporating new technologies in the design of the future treatment, looking back may help us to better target our efforts and solve the puzzle of rhegmatogenous retinal detachment repair.

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Appendix to chapter 3

APPENDIX TO CHAPTER 3

- Intentional continuous shallowing of the anterior chamber, a procedure to prevent lens touch during phakic vitrectomy

- Deferred laser photocoagulation of relaxing retinotomies under silicone oil tamponade to reduce recurrent macular detachment in severe proliferative vitreoretinopathy

- Novel 'heavy' dyes for retinal membrane staining during macular surgery: multicenter clinical assessment

- Vital stains for vitreoretinal surgery

- Subretinal lavage to prevent persistent subretinal fluid after rhegmatogenous retinal detachment surgery: a study of feasibility and safety

- Persistent subretinal fluid after surgery for rhegmatogenous retinal detachment: hypothesis and review

- A case-control study of beneficial and adverse effects of 2-octyl cyanoacrylate tissue adhesive for episcleral explants in retinal detachment surgery

- The effect of a preoperative subconjuntival injection of dexamethasone on blood-retinal barrier breakdown following scleral buckling retinal detachment surgery: a prospective randomized placebo-controlled double blind clinical trial

- Visualising vitreous through modified trans-scleral illumination by maximising the Tyndall effect

Intentional continuous shallowing of the anterior chamber, a procedure to prevent lens touch during Phakic vitrectomy.

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Summary

Thorough cleaning of the vitreous base is an important step to prevent vitrectomy related complications. In phakic patients this is difficult to achieve without touching the lens and consequent rapid cataract formation. Therefore, vitrectomy is often combined with Phaco-emulsification. In pediatric and young adult patients, however, it may desirable to preserve their accommodating lens; also, with a preserved lens, the contour of a silicone oil tamponade has a larger arc of contact and is thereby more effective.

We describe a method to shallow the anterior chamber during vitrectomy, by inserting a wedge in a paracentesis opening to allow continuing drainage of the anterior chamber, while protecting the endothelium with a layer of viscoelastic. This way, sclerotomies and vitreous base are perfectly accessible without lens touch. Available data from an aborted RCT suggest that endothelial loss is limited.

Introduction

Vitrectomy in phakic patients is a procedure intrinsically complicated by vitreous incarceration. In phakic patients complete removal of vitreous near the sclerotomies without touching the lens is difficult to perform. Vitreous incarcerated in sclerotomies may give rise to sclerotomy related complications such as recurrent hemorrhage due to anterior hyaloid fibrovascular proliferation in diabetic patient, and postoperative recurrent retinal detachment due to anterior loop contraction. This may be one the explanations why surgical outcome of retinal detachment in phakic patients was shown to be better with buckle surgery compared to vitrectomy [1].

There are several situations, however, where it would be of clinical benefit to be able to perform a complete vitrectomy in phakic patients: in pediatric patients to increase chances to prevent amblyopia; in younger adult patients to preserve an accommodating lens as long as possible; preserving the natural lens during silicone oil tamponade to obtain a more effective tamponade by silicone oil [2].

We describe a new method to shallow the anterior chamber and deepen the vitreous space effectively during surgery. This intentional continuous shallowing of the anterior chamber carries the acronym ICSAC.

Method

We insert a wedge (cut out with scissors from a silicone tube or a 30 gauge polyamide canula) in a paracentesis after injecting some curls of a dispersive viscoelastic to protect the endothelium [figure A, B]. Though easily observable through the microscope, we documented the shallowing of the anterior chamber by axial immersion ultrasonography in four patients [Table 1]. The anterior chamber shallowed by a mean of 1.84 mm and the vitreous cavity axis was elongated by a mean of 1.79 mm.

With the shallowed anterior chamber, we are able shave vitreous over the pars plana and remove incarcerated vitreous from the canula [figure C, D]. We only apply ICSAC when working on the vitreous base, rarely longer than 20 minutes.

Comment

Other methods have been suggested for shaving the vitreous base in a phakic patient. By deep indentation and shaving or manipulating from the ipsilateral side, instruments do not cross the posterior pole of the lens and thus avoid lens touch [3]. However, a crossing instrument has a more effective angle of approach to the contralateral vitreous base. Another (unpublished) method is to place the sclerotomies as far posterior as possible onto the ora serrata and then use deep indentation. This manoeuver is most acceptable in patients with a giant retinal tear when cleaning the contralateral vitreous base. The latter approach would certainly not be possible in pediatric ROP vitrectomy, where the pars plana is not yet formed.

Although the ICSAC technique has obvious practical benefits, shallowing of the anterior chamber during vitrectomy may be potentially harmful to endothelial cells due to iris apposition. The corneal endothelium is a monolayer of specialized cells lining the posterior surface of the cornea and facing the anterior chamber of the eye and is required for optical transparency. Progressive endothelial cell loss is a physiological phenomenon of aging that continues throughout life. The normal rate of endothelial cell loss is 0.5-0.6% per year. Any corneal insult, whether surgical or nonsurgical, can increase the rate of cell loss. In most cases, a trauma of the cornea (caused for example by intraocular surgery) will increase the loss of endothelial cells in 2 stages: a rapid loss of endothelial cells in the first weeks after surgery followed by a gradual long-term (often life-long) decline of endothelial cell density (ECD) exceeding the physiological cell loss.

Increased endothelial cell loss has been described after cataract surgery [4], corneal transplant surgery, phakic IOL implantation and glaucoma surgery[5]. Most studies measured ECD after 1, 3 and 6 months postop to assess whether it was significantly decreased compared to preop or not; a few studies describe a follow up of 10 years [4]. After shallowing of the anterior chamber in trabeculectomy (generally for considerably longer duration than during ICSAC) no endothelial damage has been reported [5]. Very few publications have addressed endothelial cell loss after vitreoretinal surgery [6-9].

We started a prospective trial in which patients undergoing vitrectomy were randomized to intentional continuous shallowing of the anterior chamber (ICSAC) in combination with an ophthalmic viscoelastic device (OVD)or not(NTR 3046). To have a predictable and comparable difficulty of surgical intervention, we restricted the inclusion to phakic patients undergoing vitrectomy for vitreous floaters, macular pucker and macular hole. Pre- and post-operative ECD at 6 weeks and 6 months were evaluated [table 2].

Unfortunately, inclusion of patients proved to be much slower than anticipated and we had to abort the study after inclusion of only 11 patients.
In these patients, endothelial cell loss was limited and not noticeably different between patients with or without ICSAC [Table 2].
Therefore, with the caveats associated with conclusions drawn from small datasets, but with our own clinical experience over 10 years of having no corneal decompensation after ICSAC, we conclude that when clinical circumstances warrant the preservation of the patients' lens, intentional shallowing of the anterior chamber is a feasible option.

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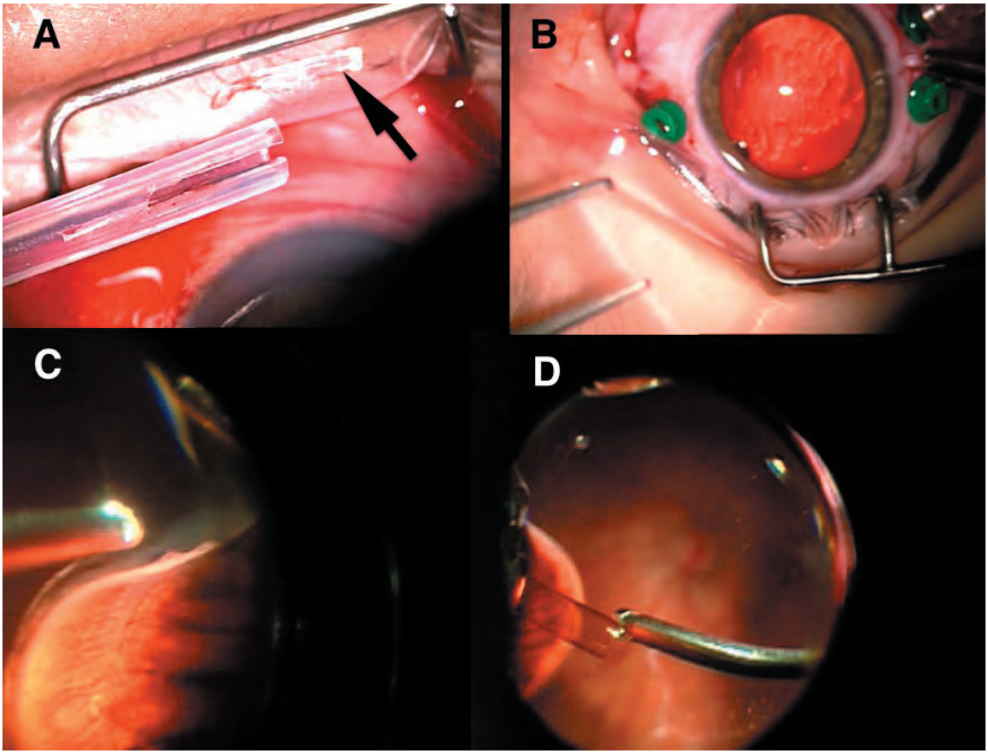

Figure A: wedge (black arrow) cut out of silicone tube. B: curls of viscoelastic in the not yet shallowed anterior chamber with wedge in paracentesis. C: Shaving of vitreous over the pars plana. D: Pars plana canula being cleaned.

Axial biometry (mean of 4 patients)

	before ICSAC	**after ICSAC**	
AC	3.21	1.37	Δ 1.84
Lens	5.13	5.07	
VC	14.76	16.55	Δ 1.79

Table 1. Axial biometry data in mm. ICSAC: intentional continuous shallowing of the anterior chamber; AC: anterior chamber; VC: vitreous cavity

nr	Age (years)	Gender	Indication	ICSAC	duration ICSAC (minutes)	ECD baseline (cells/mm2)	ECD 6 weeks (cells/mm2)	ECD 6 months (cells/mm2)	Difference 6months - baseline (cells/mm2)	cataract at 6 months
1	75	F	Macular hole	no	-	2529	2601	2647	118	yes
2	66	F	Macular Pucker	no	-	2367	2360	2389	22	yes
3	69	F	Macular hole	no	-	2372	2345	2419	47	yes
4	60	M	Macular Pucker	yes	21	2840	2821	2817	-23	yes
5*	67	F	Macular hole	yes	9	2662	2615	2703	41	yes
6	63	F	Floaters	yes	6	2259	2188	2275	15	no
7	61	M	Macular hole	yes	9	2756	2903	2903	147	no
8	64	F	Macular hole	yes	5	2429	2383	2408	-21	no
9	63	F	Macular hole	yes	11	2325	2235	2279	-46	yes
10	46	F	Floaters	yes	7	2664	2606	2599	-65	no
11	64	F	Floaters	yes	15	2428	2412	2420	-9	yes

Table 2. Mean Endothelial cell densities (ECD) in patients with and without ICSAC. ECD was measured five times per visit and averaged(Tomey EM 3000 specular microscope). One patient (*) was reoperated 6 weeks after initial surgery due to persistent macular hole and retinal detachment.

Deferred laser photocoagulation of relaxing retinotomies under silicone oil tamponade to reduce recurrent macular detachment in severe proliferative vitreoretinopathy

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Abstract
Purpose This study sought to investigate whether, in patients with retinal detachment complicated by proliferative vitreoretinopathy, we can re-attach the retina with a posterior relaxing retinotomy and silicone oil tamponade while postponing laser retinopexy for several months.
Methods In 13 consecutive patients we applied laser coagulation of the retinotomy edge 15±12 weeks after surgery. Silicone oil was removed 9±6 weeks after laser application.
Results After the retinotomy without laser, some degree of central shifting was seen in all patients, followed by obvious curling in 10 patients. The total follow-up was 24±7 months after retinotomy and 13±9 months after oil removal. The retina was attached in 12 patients at the last visit, with the oil still in situ in three patients. Seven patients, however, required additional surgery. Function remained stable with a mean preoperative and postoperative Snellen visual acuity of 0.09.
Conclusions Not anchoring retinotomy edges with a laser at the time of surgery allows inward curling and central slippage of retinal edges under silicone oil. This appears to compensate for the retinal fibrosis occurring in the weeks following surgery and may result in less macula-off re-detachments under oil, and potentially, in better visual outcome.

Keywords Inferior retinotomy · Laser photocoagulation · Retinal detachment · Vitreoretinopathy

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Introduction

Proliferative vitreoretinopathy (PVR) can be defined as vitreoretinal wound healing in response to a retinal break and consists of inflammation, cellular proliferation, and extracellular matrix remodeling. Following breakdown of the blood-retina barrier, a proinflammatory and fibrotic milieu (cells, cytokines, and growth factors) develops in the vitreous cavity and the subretinal fluid that ultimately may lead to epiretinal, intra-retinal, and subretinal fibrosis, causing (recurrent) retinal detachment (RD) [1]. Therapeutic strategies to prevent PVR or to temper its severity include pharmacological agents and endotamponades [2–8]. Endotamponades, apart from closing retinal breaks, can compartmentalize the hydrophilic PVR milieu away from the wound healing site [9].

In established PVR, surgery remains the mainstay of treatment, with meticulous surgical removal of epiretinal (and sometimes subretinal) tissue, relaxing retinotomies with or without a broad buckle in the case of retinal shortening due to peri- and intra-retinal fibrosis, and the closure of retinal breaks by an endotamponade. Endolaser photocoagulation would be applied around retinal tears and retinotomy edges. A recurrent retinal detachment, however, may develop in some patients after relaxing retinotomies under silicone oil, necessitating a series of repeat surgeries.

The application of a laser or cryocoagulation to the edges of retinal breaks is an important ingredient of successful treatment of uncomplicated rhegmatogenous retinal detachment (RRD) surgery. The scars seal the retinal breaks effectively, closing off the subretinal space and thereby preventing re-detachment. In cases of RRD complicated by PVR, however, the effect of immediate retinopexy may not be unequivocally beneficial. In inferior re-detachments that necessitate relaxing retinotomies, the retina is usually diffusely thickened and tense, even after meticulous membrane peeling. This is demonstrated by the often quite marked central displacement of the retina that can be observed immediately after performing the retinotomy. Inspection of the edge of the retinotomy usually shows a tense and shortened inner retinal surface, while the outer surface appears corrugated and redundant, resulting in a poor apposition between the outer retina and the retinal pigment epithelium (RPE), even under heavy (perfluoro carbon) liquids. Consequently, inducing laser burns at the retinotomy edge usually requires high energy. Extensive use of a laser can cause increased breakdown of the blood-retinal barrier and activate cell proliferation [10, 11]. The resulting scars could, rather than seal the retinotomy, increase epi- and/or intra-retinal fibrosis, promoting secondary shortening and traction. Traditional intraoperative laser application performed simultaneously with the retinotomies may then be a factor in the subsequent recurrent RD under silicone oil. We hypothesized that postponing laser photocoagulation along the retinotomy edges could allow central slippage of the remaining retina as well as inward curling of its edges, avoiding traction over the laser scars and limiting consequent recurrent retinal detachment. Once PVR fibrosis would have run its course and the retina is relocated to an unchallenged position, the postoperative laser would create retinochoroidal adhesion in that position and allow a relatively safe silicone oil removal.

We report here the results on the first case series of patients treated in this manner.

Patient and methods

A retrospective analysis of a series of 13 patients (13 eyes) was performed at the Rotterdam Eye Hospital, in whom we did not apply intra-operative laser retinopexy along the retinotomy edge ("the retinotomy procedure"). The first patient was operated on in January 2011, and the censoring date was January 2014. Patients were eligible if they previously underwent one or more vitreoretinal surgeries for retinal detachment repair, after which they developed a re-detachment of the inferior retina that was related to obvious PVR. The nature of the procedure and the need for additional laser application later was discussed with the patient by the surgeon and all patients consented to this treatment. Patients in whom we removed the silicone oil and performed laser surgery of the retinotomy edges in combination with a gas tamponade were excluded.

Preoperative data collected for each patient included age, gender, visual acuity (VA), intraocular pressure (IOP), lens status, and number and indication of previous vitreoretinal surgeries. Variables noted during surgery were the position and clock-hours of the retinotomy. Postoperatively, we analyzed the interval between the retinotomy procedure and slit lamp laser retinopexy, and between the slit lamp laser and silicone oil removal. In addition, postoperative VA, IOP, retinal status, number and indication of re-operations and presence of oil at the last visit were recorded.

Surgery

We used a 23-gauge standard three-port pars plana Baush & Lomb Stellaris vitrectomy system (Bausch & Lomb, Rochester, NY, US), a chandelier illumination, as well as a hand-held light pipe and intraocular forceps (Dutch Ophthalmic Research Center (DORC), Zuidland, the Netherlands). After the removal of the silicone oil, surgery entailed the removal of the inner limiting membrane (ILM) (if not previously removed) and all visible and/or graspable epiretinal tissue, identification of which was facilitated by Membrane Blue-Dual® vital staining (DORC). A relaxing retinotomy without intra-operative laser retinopexy followed by a silicone oil tamponade was performed in all patients. The vitreous cutter was used to create the retinotomy and to remove the retina peripheral to the retinotomy site (retinectomy). Injection of oil was preceded by a fluid-air exchange in all cases. Lensectomy and insertion of an intraocular lens was performed at time of the silicone oil removal in phakic patients. All surgeries were performed by one surgeon (JvM).

Laser coagulation along the retinotomy edge was applied postoperatively with a slit-lamp laser before eventual silicone oil removal.

Results

Baseline characteristics

The age of the patients (four females and nine males) was 63± 17 (mean±SD) years (range 19–84) (Table 1). The number of previous vitreoretinal surgeries ranged from one to four (mean 2). All patients had one or more vitrectomies before the retinotomy procedure. Three patients also underwent one scleral buckle procedure.

The original diagnosis was a rhegmatogenous retinal detachment in 12 patients (two of them after a blunt trauma and another patient also had a history of a central retina vein occlusion). One patient had an RPE-tear after intravitreal anti-VEGF injections for exudative age-related macular degeneration. This patient was treated with an autologous RPE-choroid graft translocation that was subsequently complicated by an inferior retinal detachment due to PVR. In seven patients the macula was attached before the retinotomy procedure, but in all but one (the patient with a preoperative VA of 0.6) had been detached at least once before. In the other six patients the macula was detached. Eight patients were pseudophakic and two aphakic at time of the retinotomy procedure.

Table 1 Patient demographics

Patient	Age (years)	Previous surgery (number)	Preoperative macula on/off	Preoperative VA	Last VA	Follow-up (months)	Postoperative re-detachment surgery (number)
1	66	2 ppv	off	2/300	0.5	11	–
2	51	2 ppv	off	1/60	2/60	28	2
3	19	2 ppv/ 1 sb	on	0.05	0.05	34	3
4	61	3 ppv	on	0.1	0.05	36	–
5	67	1 ppv/ 1 sb	on	0.2	0.05	13	2
6	81	3 ppv	off	0.05	0.05	24	–
7	69	1 ppv/ 1 sb	off	1/300	0.5/60	25	–
8	65	1 ppv	off	1/300	1/60	25	–
9	77	1 ppv	off	1/300	0.1	23	1
10	73	4 ppv	on	0.6	0.3	27	–
11	84	1 ppv	on	0.05	1/60	27	1
12	49	2 ppv	on	0.05	1/60	16	1
13	51	1 ppv	on	1/300	0.05	19	2

Sb scleral buckling, ppv pars plana vitrectomy, VA visual acuity, preoperative means before the retinotomy procedure without peroperative laser retinopexy

At the time of analysis, the patients had a total follow-up of 24±7 months (range 11–36) after the retinotomy procedure. The follow-up after oil removal was 13±9 months (range 2.5-31 months).

Surgery and postoperative laser slit-lamp retinopexy

The ILM was still present and peeled in three patients. We performed epiretinal membranectomy in 12 patients and the removal of subretinal membranes in two. Perfluoro carbon liquid to flatten the retina was additionally used in two patients. The total retinotomy size was 5.2±1.4 clock hours (range 3–8) and always located in the inferior quadrants. In all patients, a fluid-air exchange preceded the insertion of the silicone oil tamponade. There were no significant complications encountered during surgery.

The interval between the retinotomy procedure and slit-lamp laser retinopexy was 15±12 weeks (range 4–46). Subsequently, we removed the oil 9±6 weeks (range 3–24) after the laser in all patients. Curling of the retinotomy edge was left intact during silicone oil removal.

Anatomical and functional results

Mean VA was 0.09 (range 1/300 to 0.6) before the retinotomy procedure and remained unchanged upon the last examination (mean 0.09 with a range of 1/300 to 0.5). Five patients showed an increased intraocular pressure (≥ 25 mmHg). Four of them could be medically controlled and one patient needed transscleral cyclophotocoagulation to normalize the intraocular pressure. No cases of hypotony (< 7 mmHg) were recorded.

Initial retinal re-attachment after the retinotomy procedure was achieved in all patients (Table 1).

In most patients, a central shifting of the retina adjacent to the retinotomy site could already be observed at 1 day after surgery (Fig. 1). Curling of the retinotomy edge took more time to develop (Fig. 2).

In 11 patients, a postoperative slit-lamp laser could be applied to the attached retina just central to the curled retinotomy edge (Fig. 3). In one patient, the slit-lamp laser was incomplete due to poor visualization of the anterior retina and the laser surgery was completed at the time of oil removal using scleral depression. In two patients, the retina detached in the inferior quadrants under oil before the slit-lamp laser procedure could be performed, while their macula remained attached (Fig. 4). Re-detachment occurred in five more patients after the oil had been removed, with the macula off in three. Re-detachment occurred in total in 54 % of eyes (n=7).

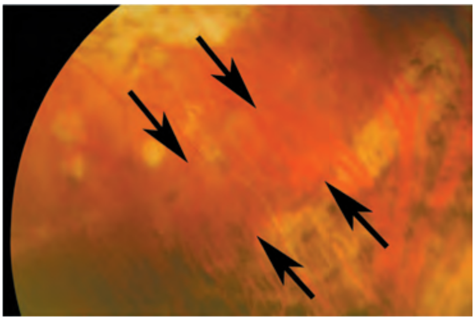

Fig. 1 Central shift of the retinotomy edge without curling (arrows) observed at 1 day after surgery (patient 5)

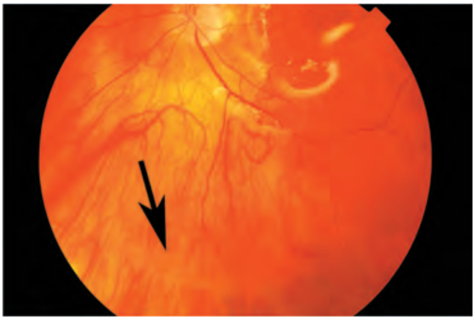

Fig. 2 Inward curling of the retinotomy edge (arrow) at 6 weeks after surgery (patient 1)

Four patients of the re-detachment group needed 2–3 additional surgeries. The retina was attached in 12 patients at the last visit with the oil still in situ in three patients. Figure 5 shows a case of a curled retinotomy edge intact 8 months after silicone oil removal.

Discussion

In PVR surgery, epiretinal tissue is recognized as an important cause of re-detachment, much more often than subretinal membranes. Stiffness of the retina itself, persisting after membrane peeling, is clinically recognized and retinectomy was introduced as a means of treating this. This approach to established PVR has remained largely unchanged since it was popularized in the early 1980s by Zivojnovic [12]. Although this surgical technique meant a major breakthrough for previously intractable cases, the overall anatomical and functional outcome of RRD complicated by PVR remains disappointing, particularly when disease severity necessitates a relaxing retinotomy. A review of the literature by de Silva et al. revealed an ultimate anatomical success rate ranging between 52 and 93 %, whereas mean functional outcome was worse than 20/400 in 26 % of eyes [13].

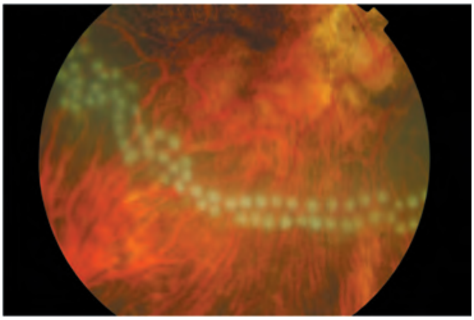

Fig. 3 Fresh postoperative laser applied at the slit lamp through oil to the flat retina near the retinotomy edge, 8 weeks after retinotomy (patient 8)

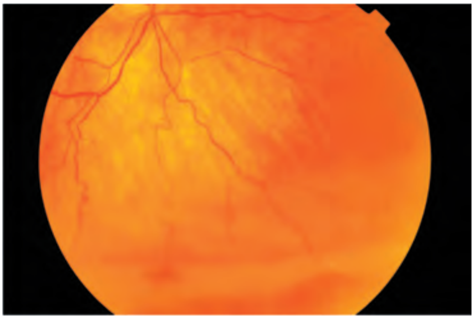

Fig. 4 Curling with significant re-detachment under oil, making laser surgery impossible. Therefore, a reoperation was needed in this patient before the oil was removed (patient 11)

Recent insights through imaging and histology have prompted us to modify our surgical approach of cases with a particularly high risk of re-detachment.

Histopathological confirmation of intra-retinal fibrosis was obtained from excised retinectomy tissue, showing a predominantly glial cell activation and proliferation replacing the neuronal elements [14]. Retinal curling in the absence of obvious PVR, as can be seen at the edge of a horseshoe tear or along a giant retinal tear, is probably caused by a combination of the inherent stiffness of the inner retinal surface on one hand, and by some degree of swelling of the outer retina that occurs after detachment as seen on OCT [15, 16]. Contraction of epiretinal membranes in PVR can add to this phenomenon, causing extreme folding of the inferior retina after retinotomy [17]. Consequently, the position where the posterior retina settles immediately after the retinotomy, under perfluoro carbon liquid, should not be

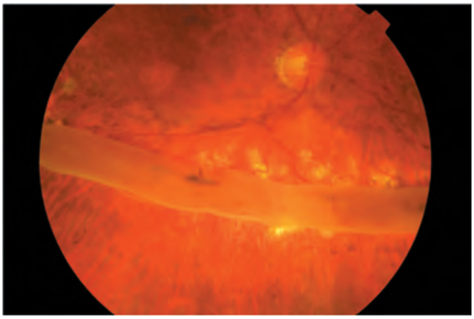

Fig. 5 Eighteen months after retinotomy under oil, 10 months after laser use at the slit lamp and 8 months after oil removal: pronounced curling of the retinotomy edge is seen, but with a completely flat central retina (patient 4)

considered unchallenged and thus, intra-operative anchoring of the retina in this position may not be optimal. Several issues may have bearing on this.

1. The time course of PVR remains unpredictable and identification of the phase of the disease based on clinical signs is almost impossible. The timing of surgery is usually based on (impending) macular detachment. A retinotomy may thus be performed when the PVR response is not in a quiescent phase [18].
2. The trauma of cutting the retina, although immediately releasing traction, may (re-)activate the scarring process.
3. Re-attaching the retina, while essential for functional recovery and ultimately inhibiting the PVR response may, according to the feline model, initially activates Muller cell outgrowth [19].
4. Intra-operative (often heavy) laser burns increase the blood-ocular breakdown and cellular proliferation [10, 11].

We hypothesized that intra-operative anchoring of retinotomy edges would not only prevent settling of the shortening retina into an unchallenged position, but would also promote further traction and detachment through reactive fibrosis. The end result would be either an anterior relocation of the retina central to the retinectomy when sufficiently elastic, or in retinal re-detachment in the case that it was not elastic.

It is unknown for how long a period PVR changes occur, but clinically, 2–16 (median 8) weeks are thought to be a reasonable estimate [18]. Typically, recurrent retinal detachment after retinectomies are slow to develop, suggesting that retinal fibrosis becomes manifest after the laser scars have healed and have reconstituted chorioretinal adhesion at the laser site, a much faster process than the spontaneously occurring slow recovery of adhesion elsewhere [20].

Patients included in this series were judged to be at high risk of recurrent retinal shortening and re-detachment. In comparison, in patients where this risk is estimated to be low, we usually choose a gas tamponade even when a retinotomy is performed and rely in these cases on laser scar adhesion to form while the breaks are temporarily closed by the gas bubble. The 13 patients in this series were given lighter-than-water silicone oil, rather than a gas tamponade. Avoiding retinopexy could theoretically increase the likelihood of re-detachment, as fluid could gain access to the subretinal space that is not occluded by laser scars. We have previously demonstrated that a buckle without intra-operative retinopexy can sufficiently occlude the retinal breaks, leading to successful re-attachment in conventional buckling surgery [21]. Similarly, an intra-ocular tamponade can displace fluid away from a retinal break, allowing the retina to re-attach as can be observed in pneumatic retinopexy. Postponing laser surgery under silicone oil has been described before the era of routine availability of endolaser procedures. It has also been suggested as a strategy to reduce reproliferation in inflamed eyes [22]. In this series, the silicone oil bubble in itself seemed to sufficiently tamponade the retinotomy and prevented residual vitreous fluid from gaining access to the subretinal space. Lighter-than-water silicone oil does not provide an actual closure of inferior retinotomies but would decrease the risk of recurrent retinal detachment by decreasing fluid currents around the retinotomy edge [23]. Recurrent RD is thought to be more common in the inferior quadrants because cells gravitate there in a watery milieu, which also contains the hydrophilic growth factors and cytokines. The use of heavy silicone oil was thought to result in a lower tendency for PVR by shifting this PVR milieu away from the inferior retina. This hypothesis, however, was not fully realized in practice in two clinical studies. In an observational study, 39 patients with a lighter-than-water silicone oil tamponade with an inferior chorioretinal wound in contact with the watery milieu did not develop PVR more frequently than 170 patients with a similar wound in the superior quadrants tamponaded by the same silicone oil [24].

In the HSO (heavy silicone oil) study, heavier-than-water silicone oil was compared to lighter-than-water silicone oil, but no difference in the rate of recurrent retinal detachment was found. However, recurrent retinal detachment did develop in the quadrants where an aqueous compartment was left [8]. A large inferior retinotomy without retinopexy may therefore be an interesting indication for HSO tamponade, as it may prevent the excessive curling we have seen in some of our patients (Fig. 5) and may reduce the re-detachment rate under oil. We intend to investigate whether HSO tamponade could indeed reduce the recurrence rate under such circumstances.

Scleral buckling in addition to vitrectomy is another well-accepted technique for dealing inferior retinal shortening and possibly reducing the need for relaxing retinotomies. Initial experience with combined vitrectomy and external scleral buckle for proliferative vitreoretinopathy often had modest anatomical outcomes, but no comparative trials of the two techniques have been undertaken, however, and the choice of technique remains governed by surgeon personal preference [25–27]. The added value of a buckle was not investigated in this study.

To allow central relocation of the shortening retina, we delayed laser surgery until several weeks after the procedure. We performed slit-lamp laser photocoagulation of the retinotomy edges, central to the curled areas, and assumed that the retina would by then be in a position no longer under contraction. In addition, some recovery of the physiological adhesion between the retina and RPE would have occurred and the retinal swelling subsided, reducing the need for extensive and heavy laser use. This modified surgical approach to PVR could theoretically improve functional outcomes by a reduced incidence of macula-off re-detachments under oil.

In 10 patients we have observed signs of curling or central slippage, confirming our assessment of residual fibrosis. In two patients, with their macula still on, we did not apply deferred laser use, as the recurrent detachment was too extensive, but proceeded to surgery, again with deferred lasering. Eventually, postponed lasering allowed oil removal in all 13 patients. Recurrent detachment, however, developed in five (three with their macula off) after some weeks.

Hence, the overall anatomical outcome is not significantly superior to previous reports. Nevertheless, as we only included challenging cases with poor prognosis in this series, the hypothesized mechanism of recurrent RD after relaxing retinotomy in relation to intra-operative laser photocoagulation may be realistic, and postponing laser use may merit consideration in selected patients suspected of future inferior recurrent RD under silicone oil.

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Novel 'heavy' dyes for retinal membrane staining during macular surgery: multicenter clinical assessment

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ABSTRACT.

Purpose: **To evaluate the feasibility of two novel 'heavy' dye solutions for staining the internal limiting membrane (ILM) and epiretinal membranes (ERMs), without the need for a prior fluid-air exchange, during macular surgery.**

Methods: **In this prospective nonrandomized multicenter cohort study, the high molecular weight dyes ILM-Blue™ [0.025% brilliant blue G, 4% polyethylene glycol (PEG)] and MembraneBlue-Dual™ (0.15% trypan blue, 0.025% brilliant blue G, 4% PEG) were randomly used in vitrectomy surgeries for macular disease in 127 eyes of 127 patients. Dye enhanced membrane visualization of the ILM and ERMs, 'ease of membrane peeling', visually detectable perioperative retinal damage, postoperative best-corrected visual acuity (BCVA), dye remnants and other unexpected clinical events were documented by 21 surgeons.**

Results: **All surgeries were uneventful, and a clear bluish staining, facilitating the identification, delineation and removal of the ILM and ERMs, was reported in all but five cases. None of the surgeries required a fluid-air exchange to assist the dye application. BCVA at 1 month after surgery improved in 83% of the eyes in the MembraneBlue-Dual™ group and in 88% in the ILM-Blue™ group. No dye remnants were detected by ophthalmoscopy, and no retinal adverse effects related to the surgery or use of the dyes were observed.**

Conclusion: **The 'heavy' dye solutions ILM-Blue™ and MembraneBlue-Dual™ can be injected into a fluid-filled vitreous cavity and may facilitate staining and removal of the ILM and/or ERMs in macular surgery without an additional fluid-air exchange.**

Key words: brilliant blue G – epiretinal membrane – internal limiting membrane – macular surgery – polyethylene glycol (PEG) – trypan blue

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Introduction

As epiretinal membranes (ERMs), the internal limiting membrane (ILM) and the vitreous cortex are essentially transparent tissues, nontraumatic removal may be challenging in various types of macular surgery. In 1998, Melles et al. introduced the use of vital dyes for staining (the capsulorhexis and) epiretinal membranes, allowing for better visualization of these tissues during vitrectomy, and selective 'membrane peeling' from the underlying retina (Melles 1999; Melles et al. 1999).

Veckeneer, Feron, Stalmans and Teba et al. pioneered the use of trypan blue (TB) for selective staining of ERMs and the ILM (Feron et al. 2002; Teba et al. 2003; Veckeneer et al. 2001). However, while awaiting FDA approval for trypan blue for use in 'chromovitrectomy', surgeons started using off-label indocyanine green (ICG) in macular hole surgery, indicating the demand for tissue staining in removal of the ILM (Burk et al. 2000; Da Mata et al.

2001; Gandorfer et al. 2001a; Kadonosono et al. 2000; Kusaka et al. 2001; Kwok et al. 2001; Stalmans et al. 2001). Clinical observation showed that ICG was more effective in staining the ILM than TB, while TB had better affinity for epiretinal membranes (Teba et al. 2003; Enaida et al. 2006a,b). Alternative dyes such as brilliant blue G (BBG) were later preferred over ICG because of the potential toxicity of the latter dye (Engelbrecht et al. 2002; Gandorfer et al. 2001b; Sippy et al. 2001; Weinberger et al. 2001). To further improve the staining effect of TB and BBG, a fluid-air exchange is commonly performed. This limits swirling of the dye within the fluid-filled vitreous cavity and achieves a more concentrated dye near the target tissue. However, a fluid-air exchange may jeopardize subsequent visualization of the macula during peeling due to clouding of the posterior lens capsule and may relate to postoperative visual field defects (Hasumura et al. 2000; Hirata et al. 2000; Yang et al. 2006).

To overcome these problems, sequential 'double' staining (Stalmans et al. 2003) and addition of glucose (Lesnik Oberstein et al. 2007) or deuterium oxide (D_2O) (Gerding et al. 2011) to increase the viscosity and/or density of the dye solution have been evaluated. Preferably, these combined, 'heavy' dyes should come as premixed, 'ready-to-use' dye solutions with acceptable shelf-life, good biocompatibility and CE and/or FDA approval. Recently, extensive laboratory studies have yielded two novel commercially available and CE-approved dye solutions, MembraneBlue-Dual™ and ILM-Blue™, that may have a higher efficacy as a result of the synergenic effect through the use of two dyes within the same sample, combined with polyethylene glycol (PEG) to increase the molecular weight and viscosity, potentially eliminating the need for fluid-air exchange. The purpose of our study was to prospectively evaluate whether these novel, polyethylene glycol (PEG)-enriched, 'heavy' dye solutions (Membrane Blue-Dual™ and ILM-Blue™) effectively stained ERM's as well as ILM without prior fluid-air exchange.

Materials and Methods

A total of 127 eyes of 127 patients enrolled in this prospective study and were randomly assigned into two groups: Group I had macular surgery performed with the intra-operative use of MembraneBlue-Dual™, a solution with 0.15% trypan blue + 0.025% brilliant blue G + 4% polyethylene glycol (D.O.R.C. International, Zuidland, the Netherlands) (63 eyes, 35 male and 28 female, mean patient age 68 ± 1.3 years); and Group II with ILM-Blue™, a solution with 0.025% brilliant blue G + 4% polyethylene glycol (D.O.R.C. International) (64 eyes, 35 male and 29 female, mean age 68 ± 1.3 years) (Table 1). The study protocol was subjected to IRB review and all patients signed an IRB-approved informed consent. Patients consented to prospective data collection, and the study was conducted according to the declaration of Helsinki.

Vitrectomy surgeries were performed by 21 surgeons in 20 centres (Fig. 1). In all cases, a 23- or 25-Gauge valved cannula 3-port pars plana vitrectomy was performed, during which a posterior vitreous detachment was created when needed. Without performing a prior fluid-air exchange, either 0.1 ml of MembraneBlue-Dual™ (Fig. 2A) or of ILM-Blue™ (Fig. 2B) was applied onto the macula (while the vitreous cavity was completely filled with fluid), and all excess dye was immediately aspirated with a blunt back-flush instrument. In all cases, the intention was to completely remove epiretinal membranes as well as ILM in the central macular area. The stained ILM/ERMs were removed using routine surgical techniques, by engaging the tissue with a pick or hooked needle, peeling the tissue from the underlying retina, and removing it from the eye with an intraocular forceps (Fig. 2C,D). In eyes with a macular hole, the surgery was completed by gas tamponade (C3F8 or SF6). Simultaneous phacoemulsification with intraocular lens implantation was performed in eyes that also had a cataract (Group I: $n = 9$, Group II: $n = 20$).

To evaluate the efficacy of both dyes in the visualization of the ILM and/or ERMs, and the 'ease of membrane removal' after staining, these parameters were graded on a scale of 1 (poor) to 10 (excellent), by each surgeon for each individual intervention. Patients were examined before surgery, at the first postoperative day, and 1, 6 and 12 months after surgery. At each visit, the best-corrected visual acuity (BCVA), intraocular pressure (IOP), slit-lamp biomicroscopy and funduscopy details were documented. Particular attention was given to postoperative dye remnants, and/or unexpected clinical events possibly related to the use of dye. Surgeons were requested to report any signs of mechanical trauma such as 'pinch' haemorrhages and local retinal tears. The clinical outcome at 1 month was used for comparison with the pre-

Table 1. Patient data.

	MembraneBlue-Dual™	ILM-Blue™	p
Number of patients included	63	64	
Age (mean ± SD) (years)	68 ± 1.3	68 ± 1.3	0.83
Male/female	35/28	35/29	0.92
OD/OS	29/34	37/27	
Lens status before surgery			
Phakic	34	27	
Pseudophakic	18	15	
Cataract	9	20	
Unknown	2	2	
Indication			0.26
Macular hole	9	25	
Macular pucker	45	28	
Macular oedema	3	3	
Retinal detachment	2	4	
Proliferative vitreoretinopathy	1	0	
Vitreomacular traction syndrome	0	4	
ERM with central vein occlusion	3	0	

Fig. 1. World map of participating surgeons and their location. (1) Marc Veckeneer, M.D., Oog ziekenhuis Rotterdam, the Netherlands; (2) Andreas Mohr, M.D., St. Joseph Stift, Bremen, Germany; (3) Essam Alharthi, M.D., Alhokama Eye Specialist Centre, Riyadh, Saudi Arabia; (4) Rajvardhan Azad, M.D., FRCSed., Dr. Rajendra Prasad Centre for Ophthalmic Sciences, All India Institute of Medical Sciences, Ansari Nagar, New Delhi, India; (5) Ziad F. Bashshur, M.D., American University of Beirut, Lebanon; (6) Enrico Bertelli, M.D., Div. Oculistica, Azienda Sanitaria dell'Alto Adige-Südtirol, Bolzano, Italy; (7) Riad A. Bejjani, M.D., Lebanese American University, Lebanon and Saint Joseph University, Beirut, Lebanon; (8) Brahim Bouassida, M.D., Clinique Ophthalmologique et O.R.L. De Tunis, Tunesia; (9) Dan Bourla, M.D., Rabin Medical Centre, Petah Tikva, Israel; (10) Iñigo Corcóstegui Crespo, M.D., Instituto Clínico Quirúrgico de Oftalmología, Bilbao, Spain; (11) Charbel Fahed, M.D., Lebanese American University of Beirut, Lebanon; (12) Faisal Fayyad, M.D., Jordan Hospital, Amman, Jordan; (13) Marco Mura M.D., Academic Medical Centre, University of Amsterdam, the Netherlands and Oogziekenhuis Zonnestraal, Hilversum, the Netherlands; (14) Jerzy Nawrocki, M.D., Ph.D., Klinika Okulistyczna, Okulistyczna 'Jasne Blonia', Lodz, Poland; (15) Kelvin Rivett, M.D., Medivision, Beacon Bay, South Africa; (16) Gabor B. Scharioth, M.D., Ph.D., Aurelios Augenzentrum, Recklinghausen, Germany; (17) Dmitry O. Shkvorchenko, M.D., S. Fyodorov Eye Microsurgery State Institution, Moscow, Russia; (18) Peter Szurman, M.D., Ph.D., Knappschafts krankenhaus Sulzbach, Sulzbach, Germany; (19) Hein Van Wijck, M.D., Keravision, Johannesburg, South Africa; (20) Ian Y. Wong, FHKAM and David S.H. Wong, FRCOphth., University of Hong Kong, China; (21) Johannes Frank, Ph.D., Delft University of Technology, the Netherlands; (22) Silke Oellerich, Ph.D., Marieke Bruinsma, Ph.D. and Gerrit R.J. Melles, M.D. Ph.D., Netherlands Institute for Innovative Ocular Surgery (NIIOS), Rotterdam, the Netherlands.

operative data, because the use of gas tamponade in macular hole cases did not allow for reliable visual acuity measurements on the first postoperative day.

Statistical analysis

A total of 21 patients with incomplete follow-up or data collection were excluded from the study.

For statistical analysis, a *t*-test was conducted to detect differences regarding age, gender, indication for surgery, and pre-operative and postoperative BCVA, between Group I and II. Pearson correlation analysis was performed to assess the correlation between the efficacy of tissue staining and the 'ease of membrane peeling', the indication for surgery and efficacy of staining, and the indication for surgery and the 'ease of membrane peeling'. Linear regression analysis was conducted to evaluate whether the dye-choice or the indication for surgery related to the postoperative visual acuity. $p < 0.05$ was considered significant.

Results

Efficacy of staining and 'ease of membrane peeling'

In Group I (MembraneBlue-Dual™), efficacy of tissue staining was graded 8 (±2), and membrane removal 7 (±2), and in Group II, (ILM-Blue™) were graded 6 (±3) for both parameters (Table 2). Hence, the 'ease of membrane peeling' correlated with the density of staining achieved (Pearson correlation analysis; $p < 0.001$).

In both Group I and II, no correlation was found between the indication for surgery (Table 1) and the efficacy of staining ($p = 0.35$), or between the indication for surgery (Table 1) and 'ease of peeling' ($p = 0.72$). A second dye application was required in 25 (40%) cases in Group I and 21 (33%) cases in Group II (Table 2). In one centre, a secondary ICG application was performed after unsatisfactory staining with MembraneBlue-Dual™ (two cases) or ILM-Blue™ (three cases). After surgery, none of the eyes showed residual staining or dye remnants. No side-effects related to the intra-operative use of the dyes were observed. No signs of mechanical trauma related to membrane peeling were reported.

BCVA and IOP

In Group I, BCVA averaged 0.2 (±0.4) before, and 0.4 (±0.5) at 1 month after surgery (Table 3): BCVA improved in 52 eyes (83%) was stable in nine eyes (14%) and worsened one line in two eyes (3%). In Group II, BCVA averaged 0.15 (±0.5) pre-operatively, and 0.3 (±0.5) at 1 month (Table 3): BCVA improved in 55 eyes (88%) was stable in six eyes (9%), and worsened one line in three eyes (3%).

All patients had a normal IOP (Table 3), except for two eyes in Group I and one eye in Group II (Table 3), which showed a transient rise in IOP that returned to normal after topical treatment.

Between Group I and II, no differences were found in pre-operative BCVA ($p = 0.94$), postoperative BCVA ($p = 0.4$), pre-operative IOP ($p = 0.64$), postoperative IOP ($p = 0.32$), age ($p = 0.83$), gender ($p = 0.92$) or indication for surgery ($p = 0.26$). Postoperative BCVA did not correlate with the dye-choice or the indication for surgery.

Complete data files were available of 35 eyes reaching 6 months of follow-up and 28 eyes with 12 months follow-up. No complications or side-effects related to the intra-operative use of the dye solutions were found.

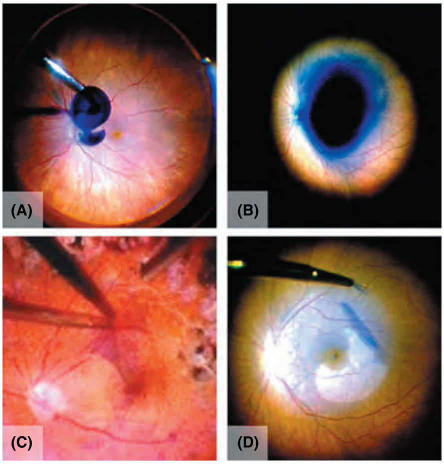

Fig. 2. Intra-operative images of (A) MembraneBlue-Dual™ and (B) ILM-Blue™ staining of the ERM and/or ILM. Before staining, the epiretinal tissue can hardly be visualized. After a core vitrectomy, a posterior vitreous detachment was induced. With the vitreous cavity filled with fluid, MembraneBlue-Dual™ (A) or ILM-Blue™ (B) was gently injected into the fluid-filled vitreous cavity, over the macular area. Note that these dyes immediately sink to the posterior pole without dispersing throughout the vitreous cavity. After the excess dye is aspirated, the size and extent of the ERM and ILM are clearly visible, following staining with MembraneBlue-Dual™ (C) or ILM-Blue™ (D).

Table 2. Staining and injection characteristics.

	MembraneBlue-Dual™ (n = 63)	ILM-Blue™ (n = 64)
Scoring 1–10: poor-excellent		
Staining result		
Mean ± SD	8 ± 2	6 ± 3
Range	4–10	1–10
Ease of membrane peeling		
Mean ± SD	7 ± 2	6 ± 3
Range	3–10	1–10
Second dye application	25	21

(Fig. 1). Our study showed that these solutions met a first objective, as none of the surgeries required a fluid-air exchange to obtain effective staining of the targeted area. If so, these 'heavy' dyes may be easier to use during vitrectomy than earlier solutions, while fluid-air exchange-related complications are avoided.

So far, the dyes commercially available were dissolved in balanced salt solution resulting in a density of the dye solutions similar to that in the infusion system. To facilitate the application, and to obtain sufficient intensity of staining, 'swirling' of the dye throughout the vitreous cavity was commonly avoided by performing a fluid-air exchange before injecting the dye (Engelbrecht et al. 2002; Gandorfer et al. 2001a; Sippy et al. 2001; Weinberger et al. 2001). However, because a fluid-air exchange may interfere with media clarity and may hold the risk of postoperative visual field defects, surgeons would want to avoid this manoeuvre (Hasumura et al. 2000; Hirata et al. 2000; Yang et al. 2006).

To increase viscosity and density of the dye solution, glucose (Lesnik Oberstein et al. 2007) or deuterium oxide (D_2O) (Gerding et al. 2011) has been added to the dye solution, to promote immediate settling of the dye onto the macula and to minimize dispersion throughout the vitreous cavity. With D_2O, the density of the dye solution is increased, but not its viscosity, so that the dye is dispersed throughout the vitreous cavity when the infusion line is opened. Alternatively, the addition of glucose to the dye solution improves both the viscosity and the density of the solution but the osmolarity may be increased to toxic levels (Costa et al. 2009). Also, most 'short-chain sugars' (glucose, maltose, etc.) show poor stability of the solution, rendering them less suitable for 'ready-to-use' dye solutions (Frank et al., unpublished).

From a panel of high molecular weight compounds, PEG was chosen as an additive to the dye solution to obtain effective tissue staining, but without the need for a prior fluid-air exchange. A good biocompatibility and chemical stability (for acceptable shelf-life) of the PEG enriched dyes should make them suitable as 'ready-to-use' product, as PEG is an additive

Discussion

In the past decade, the use of vital dyes during vitrectomy has become standard practice for most surgeons. The currently available dye solutions, however, require application 'under air', show variable staining capacities and may sometimes have a questionable safety record. We therefore conducted extensive laboratory studies to determine which dyes can be combined to broaden the staining profile without the risk of chemical interaction between the dyes (NIIOS, unpublished). Furthermore, we investigated which high molecular weight additives would be most suitable for use in such a combined dye solution, to facilitate the application of the dye in balanced salt solution, that is, without performing a fluid-air exchange. Finally, it would be preferable that a solution is subjected to CE and/or FDA approval, to avoid variation in shelf-life and/or contamination of the dye solution, as has been reported with off-label use products (Centres for Disease Control and Prevention 2012).

In the current study, two 'novel' compound 'heavy' dye solutions, MembraneBlue-Dual™ and ILM-Blue™, were evaluated by a panel of experienced vitreo-retinal surgeons

Table 3. Pre-operative and 1 month postoperative evaluation results.

	MembraneBlue-Dual™ (n = 63)	ILM-Blue™ (n = 64)	p
BCVA pre-op			
Mean ± SD	20/100 (0.2 ± 0.4)	20/100 (0.15 ± 0.5)	0.94
Range	HM -20/25 (HM-0.7)	HM -20/40 (HM-0.5)	—
BCVA 1 month postop			
Mean ± SD	20/50 (0.4 ± 0.5)	20/60 (0.3 ± 0.5)	0.40
Range	CF -20/25 (CF-0.8)	20/200-20/20 (0.1–1)	—
AT pre-op			
Mean ± SD	15 ± 3.5	15 ± 3.4	0.64
Range	9–24	8–22	—
AT 1 month postop			
Mean ± SD	15 ± 3.7	14 ± 2.8	0.32
Range	8–24	11–24	—
Changes in BCVA			
Improved	52	55	
Stable	9	6	
Worsened	2	3	

CF = Counting fingers, HM = Hand movements.

commonly used in human pharmacology products. PEG 3350 (as used in MembraneBlue-Dual™ and ILM-Blue™) has a molecular weight of 3350 Dalton resulting in an osmolarity of 0.012Osm for a 4% solution, 18 times lower than the osmolarity of a 4% glucose solution (0.22Osm). Thus, adding PEG 3350 increases the viscosity and density of the solution without significant impact on its osmolarity (Money 1989).

PEG also has several other advantages. First, PEG reduces the potential toxicity of a dye solution (Awad et al. 2011). A recent study on cytotoxicity in retinal pigment epithelial cell culture reported that dye solutions containing 4% PEG 3350 showed lower toxicity than those without PEG. Furthermore, using electrophysiological evaluation, good biocompatibility of MembraneBlue-Dual™ and ILM-Blue™ has been found with application times up to 5 min (Januschowski et al. 2012).

Our study showed that both dyes investigated effectively stained (epi)retinal membranes during surgery in all eyes, except for five all operated on by the same surgeon, who used ICG as a back-up stain in these cases. Most surgeons reported that both dyes showed effective staining within approximately 15 seconds (although some cases required repeated injections) and that they could be injected into and aspirated from the fluid-filled vitreous cavity while the infusion line remained open. Swirling of the dye may also have been limited by the use of the valved cannula system.

As the tissue composition of various ocular structures such as the vitreous cortex, epiretinal membranes or the ILM may differ greatly, it may be expected that staining patterns also differ among these tissues, and between disease entities, severity and stage. With regard to PVR, the cellularity of the membrane as compared to the fibrous extracellular matrix components depends on the phase of the wound healing and with the progression of the disease, the affinity of a specific dye will also vary. Oberstein et al. (2011) reported that cellularity and active proliferation is particularly pronounced in 'fresh' PVR, whereas 'older' membranes are much less active. Intra-operative application of trypan blue selectively stains degenerating cells which are usually present in PVR membranes but particularly common in 'older' membranes. This agrees with the fact that TB usually stains these membranes more intensely at the time of oil removal (Feron et al. 2002). However, the efficacy of TB may vary with the fibrotic component of ERM, showing less intense staining with less cellular or reactive tissue elements. Hence, the 'naked' ILM, essentially an a-cellular matrix, is better visualized with ICG or BBG. In most macular diseases, however, ILM contains some degree of ERM as was demonstrated by Kenawy et al. (2010), and Gandorfer et al. (2005, 2012). These observations have added to the debate about whether a 'naked' ILM that does not contain any ERM (and would stain poorly with TB) should be removed to begin with.

To improve the overall staining effect, a combination of several dyes has been suggested. Stalmans et al. (2003) reported the technique of sequential 'double' staining using TB for ERM peeling, followed by ICG to visualize ILM. More recently, the combination of TB with BBG has been investigated (Awad et al. 2011). The aim of the current study was to expand on a mixed dye solution that would provide a broader range of tissue staining, while allowing discrimination between the various tissues. Although overlapping to some extent, both dye solutions investigated may have a different use in application. ILM-Blue™ may be primarily indicated for retinal disease with a minor fibrotic component, such as ILM removal in macular hole surgery. MembraneBlue-Dual™ was found to have a broader scope of application, rendering it suitable for more complex retinal disease, with either variable disease stages, different types of (fibrotic) membranes or a more extensive surface area of pathology. However, our study also showed that MembraneBlue-Dual™ may better facilitate macular membrane peeling. Owing to the addition of trypan blue, the area of ILM covered with ERM does not demonstrate the 'negative' staining as is usually seen with the use of ICG or BBG alone (Park et al. 2008; Schumann et al. 2010).

Although the long-term studies are warranted to determine the safety of the dyes investigated, no intra- or postoperative complications or side-effects related to the use of the dyes were reported up to 12 months after surgery. With an improved BCVA at 1 month after surgery in 80–90% of cases, both novel dyes solutions appeared effective and user-friendly in vitreo-retinal macular surgery.

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Conflict of interest

Dr Melles is a consultant for D.O.R.C. International/Dutch Ophthalmic USA; Dr Mohr has obtained reimbursement for travel expenses connected to products of D.O.R.C. No conflicting relationship exists for any other author.

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Vital Stains for Vitreoretinal Surgery

Since the introduction of vital dyes in posterior segment surgery, our capacity to comfortably and completely remove tissues that were previously difficult to visualize, such as the vitreous cortex, the epiretinal membranes, and the internal limiting membrane (ILM), has increased radically, as has our inclination to do so.

However, what has been gained through all of the membrane staining and peeling in the macular area? A large amount of research and publications? Most certainly. Better anatomical results? Very likely. Better functional results? Unfortunately, even after 12 years of the staining era, the jury is still out on this question.

Hence, before we discuss the issue of staining, we must ask why and when we should really peel a membrane. After the introduction of indocyanine green (ICG) for ILM staining by Kadonosono et al[1] in 2000, the focus of the debate on this unresolved matter unfortunately shifted from "to peel or not to peel" toward "which is the most effective and safe dye."

How effective is membrane peeling, truly? When we consider the surgical repair of a rhegmatogenous retinal detachment complicated by proliferative vitreoretinopathy, the foremost goal of our intervention is anatomical success. To achieve this goal, the meticulous removal of epiretinal and, sometimes, subretinal membranes (which should be as atraumatic as possible and followed by relaxing retinotomy, if necessary) allows us to reattach the retina. Using a dye, such as trypan blue, in these cases, undeniably increases the visualization of the membrane and, more importantly, of its full extent. In addition, peeling all of the epiretinal membranes made visible by the dye application at the time of silicone oil removal has been reported to reduce the incidence of redetachment.[2]

However, our main indication for membrane peeling is not traction related to proliferative vitreoretinopathy but traction at the vitreomacular interface. The goal of surgery in these macular diseases is typically to improve function. Patients can present with good visual acuity, complaining only of metamorphopsia. As a result, the margin for error in these cases is minimal, and our decision to peel a membrane in the macular area should be based on a very high likelihood that the membrane peeling will resolve the symptoms with a very low risk of adverse effects.

Internal limiting membrane peeling has been studied for macular edema in diseases such as Irvine-Gass syndrome, uveitis, vascular occlusions, diabetes, and retinitis pigmentosa and for idiopathic or secondary epimacular membranes, vitreomacular traction, and full-thickness macular holes.[3–6] Although numerous studies have demonstrated an improved anatomical outcome (often highly significant) after ILM peeling, only one study, on macular hole surgery, found a significantly greater mean improvement in vision in the peel versus no peel group. No functional benefit of ILM peeling has been demonstrated in cases of macular pucker or macular edema related to diabetes or vein occlusion. An important common result in the majority of reports is the absence of epiretinal membrane recurrence in the area where the ILM was peeled. This finding in conjunction with the fact that no prospective comparative study has shown an inferior functional outcome after ILM peeling may be considered a strong argument in favor as was suggested by Almony et al[7] in a recent review article on the rationale for ILM peeling. An overview of the studies that have prospectively compared peeling versus no peeling are listed in Table 1.[8–13]

Complications associated with the peeling itself, phototrauma, or dye-related toxicity have been reported abundantly.[14–16] A crucial issue in the discussion on safety of ILM peeling (with or without dye) is the choice of outcome measures and how they are studied. We know that anatomical success, as measured by optical coherence tomography, correlates poorly with distance visual acuity. In addition, distance visual acuity may not be the best outcome measure for macular visual function. Tadayoni et al[17] recently reported absolute paracentral microscotomas as measured with scanning laser ophthalmoscopy (SLO) microperimerty in five of eight cases after ILM peeling compared with zero of eight without peeling.[17] Yet another concern is whether improved visual function in the operated eye of a patient with

Table 1. Published Prospective Studies Comparing Peel Versus No Peel

Author	Indication	Intervention	Adjuvant	Study Design	Anatomical Results (%)	Functional Results
Lois et al[8]	Macular hole	Peel (67) vs. no peel (64)	TB	Prospective + randomized	Hole closure 84 (peel), 48 (no peel); $P < 0.001$	No significant difference
Christensen et al[10]	Macular hole	Peel ICG (35) vs. Peel TB (18) vs. no peel (25)	ICG, TB	Prospective + randomized	Hole closure 94 (ICG peel), 89 (TB peel), 44 (no peel); $P < 0.001$	No significant difference
Kwok et al[9]	Macular hole	Peel (26) vs. no peel (25)	ICG	Prospective + randomized	Hole closure 92.3 (peel), 32 (no peel); $P < 0.001$	Mean BCVA lines gained 3.7 (peel), 1.5 (no peel); $P = 0.002$
Shimada et al[11]	Macular pucker	Peel ERM only (104) vs. peel ERM+ILM (142)	ICG, TB, BBG, TA	Prospective nonrandom	ERM recurrence 16.3 (ERM only), 0 (ERM+ILM); $P < 0.001$	No significant difference
Odrobina et al[12]	PVR	Peel (33) vs. no peel (51)	TB	Prospective nonrandom	Macular ERM recurrence 0 (peel), 17.6 (no peel); $P = 0.008$	No significant difference
Patel et al[13]	DME	Peel (10) vs. no peel (8)	Not disclosed	Prospective nonrandom	No significant difference	No significant difference

TB, trypan blue; TA, triamcinolone acetonide; ERM, epiretinal membrane; PVR, proliferative vitreoretinopathy.

another good eye is a good outcome measure for quality of life. Ternent et al,[18] in a prospective randomized trial, found no statistically significant difference in either costs or quality-adjusted life years between macular hole surgery with or without ILM peeling.[18]

The question of whether to peel should consequently be raised in each separate case. However, once we have decided that we really must peel a membrane, a technique to improve the visibility of that membrane would significantly facilitate the procedure. Indeed, most surgeons will agree that peeling an unstained (semi)transparent membrane, particularly the ILM, is challenging, often incomplete and seldom atraumatic. To be applicable on a large scale, such a technique should be certified, safe and highly effective in the majority of cases, and easy to use.

At present, how far have we progressed in developing such a technique, and does it comply with all of our demands?

We have been aware of the possibility of staining the ILM using ICG since 2000. Although this dye is highly effective in staining the ILM, early publications reported damage to the retinal pigment epithelium (RPE) after its use.[19] This observation urged the introduction of other, safer alternatives. In the past 12 years, trypan blue, brilliant blue green, and (even though not a dye, as such, but rather a light-reflecting and light-scattering granule) triamcinolone acetonide have been widely used. Preservative-free triamcinolone (Triesence, Alcon Laboratories Inc., Fort Worth, TX) is registered for use in vitrectomy in the United States, whereas FDA-approved trypan blue (Membrane-Blue, Dutch Ophthalmic Research Center [DORC], Zuidland, The Netherlands) and brilliant blue green (Brilliant Peel, Geuder AG, Heidelberg, Germany, and ILM-Blue, Dutch Ophthalmic Research Center) are commercially available in Europe for the staining of fibrotic tissue and the ILM, respectively. More recently, a combined dye has become available (MembraneBlue-Dual®).

Nevertheless, a number of concerns regarding chromovitrectomy remain.

Safety

Much research has focused on the aspect of dye-related toxicity. One of the reasons that considerable debate still exists on this subject is the fact that a myriad of different analyses are used to investigate this issue, which range from (many different types of) cell culture, tissue culture, and in vivo animal models to clinical trials in patients.[20–23] Unfortunately, most of the work is performed by different research groups, each with its own focus on one type of analysis, rather than working according to a systematic, step-by-step approach to the evaluation of intraocular dyes, with preliminary ex vivo safety testing before animal and then human studies. The results are often contradictory and should be interpreted with care. Let us attempt to distinguish the facts that this research has demonstrated from the further questions that it has raised.

Publications on the toxic potential of ICG demonstrate the previous point adequately. ICG was suspected early on to be the cause of poor postoperative visual recovery, visual field defects, and RPE atrophy in patients treated for macular holes.[15,19,24] Increasing toxicity with exposure time was later confirmed in cell culture studies. In contrast, infracyanine green, although it uses the exact same chromophore as ICG, involves different additives (iodine in ICG) and a different solvent (water in ICG and glucose in infracyanine green) and was not toxic in RPE culture compared with ICG.[25] More recently, infracyanine green was reported to be the least toxic dye compared with brilliant blue G (BBG), bromophenol blue, and ICG when tested in RPE and retinal ganglion cell cultures.[20] This finding indicates that different aspects of the dye, such as the osmolarity, additives, and solvent, require optimization. The use of a solvent with minimal impact on osmolarity, such as polyethylene glycol, can reduce the toxic potential of a dye, as a recent study on cytotoxicity in RPE culture has shown.[26]

Another strongly debated topic is the cleavage plane of the membrane peel. In particular, ICG seems to alter the surgical plane, thereby potentially causing significant sub-ILM damage.[27] The tissue-modifying abilities of ICG in relation to the photosensitization-dependent crosslinking of collagen could have a bearing on this effect. Conversely, Kenawy et al[28] have shown that rather than the dye, the type of disease and thus the membrane that is peeled determine the cleavage plane and the associated collateral damage.[28]

Yet another source of potential dye-related toxicity is the use of off-label products. These products can be purchased as powders and need to be dissolved (without granules remaining in the fluid), diluted to the correct concentration, and continuously maintained under sterile conditions. Apart from the purity of the powder (presence of the active substance in the raw compound can range from 60% to 95% between batches and is mentioned on the certificate of analysis) (internal communication, Thomas De Rijdt, Pharmacy UZLeuven, 2006), the manipulations needed to compound the product are susceptible to error, potentially leading to incorrect (hence toxic) concentrations or endophthalmitis.

Effectiveness

Ideally, one dye should stain all of the different tissues that we want to target during our surgical intervention. Unfortunately, different dyes have different affinities toward our target tissues. If we want to stain the vitreous cortex and an epiretinal membrane and the ILM, we will need to apply more than one dye, as has been described by Stalmans et al.[29]

Both color contrast and luminance are major factors in the visualization of the ILM. In this issue, Kadonosono et al demonstrate that the color contrast between the stained and nonstained areas of the ILM was significantly higher when stained with ICG compared with BBG.

We recently conducted a multicenter trial evaluating the staining efficacy of two novel polyethylene glycol-enriched dye preparations and found a strong correlation between the recorded density of staining and the reported "ease of membrane peeling" (Veckeneer M, Mohr A, Alharti E, et al. Novel 'heavy' dyes for retinal membrane staining during macular surgery: multicenter clinical assessment. Submitted to Acta Ophthalmologica.). The mixture of trypan blue with BBG was not shown to be superior to the preparation of BBG alone with respect to its ability to stain the ILM.

User-Friendliness

Ready-to-use, prefilled syringes containing trypan blue (MembraneBlue) and BBG (Brilliant Peel) have been available in Europe for some time, and MembraneBlue has more recently been marketed in the United States (FDA approved as drug).

So far, the available dyes were dissolved in balanced salt solutions, resulting in a density and viscosity similar to that of the infusion fluid used during surgery. To optimize the intensity of staining and to avoid "swirling" of the dye throughout the vitreous cavity, a fluid-air exchange needs to be performed before injecting the dye. This procedure also increases the contact between the staining agent and the tissue. Because a fluid-air exchange may interfere with medium clarity and to limit the risk of postoperative visual field defects, several authors have experimented with dye formulas with increased density (glucose and deuterium).[30,31] Cooling the dye has also been recommended.[32] More recently, solutions of trypan blue and/or BBG dissolved in polyethylene glycol to increase the specific gravity and cohesivity of the substance became commercially available with CE-approval (MembraneBlue-Dual and ILM-Blue, respectively). In a recent trial investigating the staining efficacy of these polyethylene glycol-enriched dyes straight from the syringe at room temperature, satisfactory staining was obtained in 125 of 127 patients without fluid-air exchange (Veckeneer M, Mohr A, Alharti E, et al. Novel 'heavy' dyes for retinal membrane staining during macular surgery: multicenter clinical assessment. Submitted to Ophthalmology.).

Conclusion

Approximately 12 years ago, chromovitrectomy started with the off-label use of ICG. Several subsequent improvements have led to the availability of better, safer, user-friendlier on-label products, bringing safe and reliable membrane and ILM removal within the reach of every vitreoretinal surgeon. Eventually, resolving the dye safety issue can bring us back to where we left off: why and when should we peel and when should we stop? What is the true pathophysiological effect of ILM peeling? Should we only remove the ILM when there is clear evidence that it plays a role in the disease for which we are operating? Or should we even consider the prophylactic removal of the ILM (if such a procedure would be absolutely harmless) when there is a chance that this procedure may be beneficial for the future course of the disease, as in diabetic retinopathy, or in surgery for retinal detachment to prevent pucker formation after surgery? Research trials that will try to answer these questions should be performed in accordance to the CONSORT guidelines and the outcome measures should preferably also include quality-adjusted life years and cost effectiveness. In the mean time, outside of the trials and research, our decision on whether to peel should be made with caution, and clinical results should always be studied with great diligence.

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Subretinal Lavage to Prevent Persistent Subretinal Fluid after Rhegmatogenous Retinal Detachment Surgery: A Study of Feasibility and Safety

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Abstract

Purpose: To report the proof of concept of a surgical innovation.

Background: Optical coherence tomography often identifies persistent subretinal fluid (PSF) after apparently successful retinal detachment repair surgery. Based on the literature, we hypothesised that highly viscous PSF, which interferes with the normal function of the retinal pigment epithelium, can lead to these persistent blebs. We therefore devised a novel surgical manoeuvre of subretinal lavage to dilute the subretinal fluid (SRF) during surgery. We expected that this would reduce the incidence of PSF.

Methods: We report our experience with a modified surgical drainage technique carried out in 12 eyes of 12 patients with long standing retinal detachments. We implemented subretinal lavage combined with vitrectomy and gas.

Results: None of the patients developed PSF.

Conclusion: We concluded that the novel technique of subretinal lavage was safe and feasible. We propose that a controlled trial would be worthwhile.

Keywords: Persistent submacular fluid; Rhegmatogenous retinal detachment

Abbreviations: PSF: Persistent Submacular Fluid; SRF: Subretinal Fluid; RRD: Rhegmatogenous Retinal Detachment; OCT: Optical Coherence Tomography; MV: Marc Veckeneer

Introduction

After surgery for rhegmatogenous retinal detachment (RRD), although the retina appears fully attached by ophthalmoscopy, some subretinal fluid (SRF) may persist. The introduction of optical coherence tomography (OCT) resulted in multiple reports of persistent subretinal fluid (PSF) after RRD surgery [1-4].

It is currently difficult to link the incidence of PSF to any particular clinical characteristics. Both Wolfensberger and Benson et al. reported that PSF occurred more frequently after buckling than after vitrectomy [5-7]. They suggested that scleral buckling might disturb the choroidal circulation and, consequently, impair SRF absorption [8]. Others suggested that cryotherapy might break down the blood-ocular barrier. However, this seems unlikely, because various vitrectomy cases used cryotherapy and reported no blebs; but, in contrast, we avoided cryotherapy in scleral buckling surgery and, nevertheless, observed PSF in several cases. Finally, it is possible that intraocular gas bubbles might displace any SRF away from the macula; however, neither Wolfensberger nor Benson found any relationship between postoperative posturing and incidence of PSF.

We generated a new hypotheses based on the observation that PSF tended to occur in patients with long-standing retinal detachment and viscous SRF. Upon examining these SRF samples by immunohistochemistry and electron microscopy, we found high levels of cellular debris, particularly photoreceptor outer segments [9]. We therefore hypothesised that the viscous nature of the SRF interfered with its spontaneous, complete absorption by the retinal pigment epithelium, and this could lead to postoperative blebs. The aim of this interventional study was to test this hypothesis by determining whether subretinal lavage could prevent persistent subretinal blebs, and to establish the feasibility and safety of this novel technique.

Materials and Methods

This study included non-consecutive patients with primary macula-off RRD that were scheduled for vitrectomy surgery. Selection criteria included cases of RRD that arose from retinal breaks situated away from the deepest SRF, with estimated retinal detachment (RD) duration of at least 1 week. In these cases, SRF can be highly viscous and impossible to drain completely through the existing breaks. Rather than creating an extra retinal break near the posterior pole to complete the drainage of residual fluid, transscleral drainage was performed. Patients with previous ocular history, including cataract surgery, were excluded. This study was approved by the Institutional Research Board of the Rotterdam Eye Hospital. In accordance with the IDEAL recommendations on the stages of development of surgical innovation [10], this study was defined as stage 1. Although the combination of surgical techniques was not reported before, we had previous experience with this approach. No new instruments or pharmacological aids of an experimental nature were used. All surgical procedures were performed by one surgeon (MV).

All patients underwent full ophthalmologic assessment,

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preoperatively and 4 weeks after surgery. The assessment included best-corrected visual acuity, anterior segment examination, fundoscopy with indirect ophthalmoscopy, and slit-lamp biomicroscopy with a Volk Super Quad contact lens. The extent of RD was expressed as the number of retinal quadrants that showed detachment. At the 4-week postoperative visit, we performed a Stratus OCT scan with a 6×6 mm radial line scan protocol.

The surgical procedure comprised a 23-gauge 3-port pars plana vitrectomy. Bimanual manipulation was facilitated by chandelier illumination. Rather than flattening the retina with perfluorocarbon liquids, we performed modified transscleral drainage. Briefly, a 27 gauge needle, fitted with an insertion tool (normally used for fluid drainage during conventional sclera buckling surgery) (Figure 1), was connected by tubing to a 3-way stopcock with two 5cc syringes, one filled with balanced salt solution . The needle was introduced into the subretinal space in the area of highest retinal elevation (Figure 2). The subretinal space was then inflated with BSS in order to dilute the viscous SRF. The intra-ocular pressure was normalised by venting vitreous fluid via a flute needle positioned in the mid-vitreous cavity (Figure 3). Then, after turning the stopcock, SRF was aspirated into the second syringe; this resulted in partial flattening of the RRD. At least 2 cycles of inflation and aspiration were performed. Finally, the needle was removed from the subretinal space as the retina re-attached itself. The evacuation of

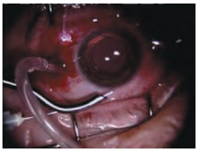

Figure 1: The insertion tool for introduction of the needle during transscleral drainage is the same as used during buckling surgery.

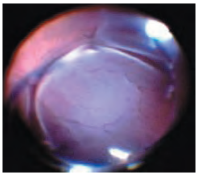

Figure 2: Lavage is performed through a 27 gauge needle inserted transsclerally into the subretinal space in the area of highest retinal elevation.

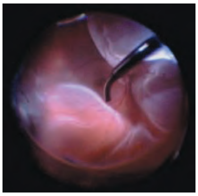

Figure 3: Maintaining stable intraocular pressure by venting vitreous fluid via a flute needle positioned in the mid-vitreous cavity.

Age (yrs)	68(54-80)
Gender (female, male)	3, 9
Eye (right, left)	10, 2
Duration of detachment (days)	12(7-60)
Type of detachment (round hole, horseshoe tear)	3, 9
Number of breaks	1(1-3)
Clock hours detachment	6(4-12)
BCVA, pre-op	0.033(0.003-0.16)
BCVA, post-op	0.16(0.05-0.6)
Follow up (wks)	14(6-28)

Table 1: Demographic data and outcome of 12 Patients.

any residual peripheral SRF was accelerated by raising the infusion bottle to increase the hydrostatic pressure in the vitreous cavity. For the surgeon not accustomed to transscleral drainage, alternatively, diluting the subretinal fluid could be performed by infusing fluid through a dual bore needle inserted into an existing break. The procedure is demonstrated in Video 1. The vitreous base was shaved as previously described [11].

Results

Twelve patients were recruited from March through July 2008. Demographic data and functional outcome are shown in Table 1. In two cases, minor subretinal haemorrhages (not clinically elevated) occurred at the transscleral needle introduction site. The procedure was otherwise straightforward and uncomplicated in all cases. Four weeks after surgery, ophthalmoscopy showed re-attached retinas in all twelve patients. No patients exhibited subretinal blebs or subclinical detachment on the OCT.

The values are the median(range) unless otherwise stated; BCVA: best corrected visual acuity, as tested on the Snellen chart (logMar converted); post-op: 4 weeks after surgery.

Discussion

Delayed or incomplete visual recovery after RD surgery remains an important problem involving many factors [12,13]. With OCT-facilitated diagnostics, PSF has become recognised as an additional factor. Although some visual improvement typically occurs with the disappearance of PSF, spontaneous resolution can take many months [4,6,7,16]. It is unknown whether a better outcome might be achieved by rapid fluid absorption. However, longstanding fluid between the RPE and photoreceptor layer whether it be hyaluronic acid as in experimental RD or fluid originating from the choriocapillaris as in chronic central serous chorioretinopathy causes the photoreceptor layer to progressively atrophy over time [17].

In fresh detachments, when all retinal breaks are closed, an oncotic pressure gradient and an active retinal pigment epithelium pump favour rapid fluid absorption [18]. Similarly, after a fresh bullous detachment, pneumatic retinopexy can result in complete re-attachment within 24 hours.

Longstanding detachments have a different pathophysiology. They frequently occur in phakic eyes with small breaks, particularly at inferior locations [2,19]. Non-syneretic vitreous may slow the progression of RD by tamponading the retinal breaks. Similarly, these characteristics of “young” vitreous may play a role in PSF. The highly viscous, protein- rich SRF may show enhanced adherence to retinal pigment epithelium after the excess SRF is drained.

Interestingly, the oncotic pressure in SRF increases with the duration of detachment [20,21]. After detachment, the loss of microvilli and the presence of hyaluronic acid can inhibit the ability of the retinal pigment epithelium to phagocytose rod outer segments; this increases the concentration of large molecules and cellular debris in the SRF [22-24].

During RRD repair, subretinal lavage may effectively lower oncotic pressure by removing most of the cellular debris and large molecules from the subretinal space. In this series, we demonstrated that subretinal lavage was feasible and safe. Also, transscleral drainage during vitrectomy allows remote SRF to be evacuated without creating an additional, often inferior, retinal break. This study improves our understanding of the pathogenesis of this relatively common condition and provides clues for improving surgical outcome. Further development of surgical technique is necessary. Lavage should preferably be isovolemic. A prototype of a dual bore cannula system to be used in non-vitrectomizing RRD repair is under development. This is particularly important since patients prone to develop PSF are mostly non-presbyopic and therefore cataract formation as a complication of RRD repair should be avoided.

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Persistent subretinal fluid after surgery for rhegmatogenous retinal detachment: hypothesis and review

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Abstract
Background Persistent subretinal fluid after rhegmatogenous retinal detachment (RRD) surgery is responsible for delayed recovery, and may affect the final visual outcome. Cause, consequences, and treatment remain elusive.
Design Literature review and case series.
Methods We reviewed the pathophysiological principles and therapeutic options from the literature, and we report the results from a subretinal fluid cytology study. Nine eyes from nine patients with macula-involving RRD underwent surgical repair. The cellular content of subretinal fluid (SRF) was studied by electron microscopy and anti-rhodopsin immunostaining. All eyes were assessed postoperatively with optical coherence tomography for the detection of persistent submacular fluid (PSF) (Ethics Committee Ghent University Hospital, registration number B6702006169).
Results Certain patient characteristics as well as surgical methods were implicated. PSF appears to occur more frequently in patients with longstanding detachments treated with buckling surgery. Several therapeutic options have been suggested but safety and efficacy remain unclear. We found PSF in three eyes on postoperative OCT scans, which corresponded to the three cell-rich subretinal samples.
Conclusions PSF after successful RRD repair seems to be related to fluid composition. We hypothesize, in the absence of an effective treatment, that a modified surgical drainage, including a washout of the subretinal space, could evacuate the subretinal fluid more completely, and may prevent this complication.

Keywords Rhegmatogenous retinal detachment · Subretinal fluid composition · Persistent subretinal fluid · Photoreceptors

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Introduction

After RRD surgery, shallow subretinal fluid (SRF) may persist even when the retina appears fully attached on ophthalmoscopy. Machemer was probably the first to report this entity when he described small collections of subretinal fluid after resolution of experimental retinal detachment in owl monkeys [1]. In 1978 Robertson [2], later Lobes Jr and Grand [3] and Avins and Hilton [4] described subretinal precipitates occurring after delayed absorption of subretinal fluid following scleral buckling procedures. The lesions were reported to be not evident on fluorescein angiography (FA). The introduction of optical coherence tomography (OCT) resulted in multiple reports of persistent fluid after RRD surgery. OCT images show shallow subretinal fluid remnants, even when all retinal breaks are closed and the retina appears fully attached on ophthalmoscopy [5–8]. PSF seems to occur frequently but the incidence of PSF varies widely depending on the reported series. In a recent study, Ricker et al. found PSF in 94% of cases 1 month postoperatively. [9]

PSF may slow visual recovery, with poor central vision, metamorphopsia, and loss of depth perception. It remains unclear whether the final outcome is affected [8–12].

Based on selected case series, several authors have suggested possible causes for persistent subretinal fluid, without, however, conclusive evidence for either vitrectomy versus buckling surgery, cryotherapy, the use of or omission of tamponades, or completeness of subretinal fluid drainage.

Studying patient characteristics from reported case series as well as from our observations, we speculated that the higher incidence of PSF after buckling may be related to selection bias. Patients with the common characteristic of having long-standing retinal detachment and viscous subretinal fluid are more likely to be treated with a buckle . Moreover, using immunohistochemistry and electron microscopy we found an increased cellularity, photoreceptor (PR) outer segment (fragments) in particular, in the SRF from patients with long-standing RRD and PSF on OCT postoperatively.

We hypothesize that SRF composition combined with RPE dysfunction may predispose to fluid persistence in longstanding retinal detachments, and that decreasing fluid cellularity and viscosity during drainage may reduce the incidence of PSF.

Subretinal fluid cytology: materials and methods

Between September and December 2007, nine samples of SRF were collected from nine eyes from nine consecutive patients with macula-involving RD. Patients with a previous ocular history other than cataract surgery were excluded. All interventions were performed by one surgeon (Marc Veckeneer).

Surgical technique

A sharp 27-gauge needle connected to a 3 cm^3 syringe without a plunger was used to drain SRF transsclerally during buckle surgery or 20-G pars plana vitrectomy. All collected samples were immediately stored at minus 20°C. Consent was covered by the opt-out procedure “Onderzoek met uw medische gegevens of restmateriaal” that was implemented at the Rotterdam Eye Hospital. This procedure is based on the Code for Proper Secondary Use of Human Tissue in the Netherlands (Federation of Medical Scientific Societies; Federa).

Immunocytochemistry

SRF samples were thawed at 4°C overnight before use. Then, the sample (150 μl) was spun down on a coated glass plate using a cytospin for 10 min at 1,500 rpm. Weri-Rb1 retinoblastoma cells (250,000 cells) were spun down as a positive control. Slides were fixed in cold methanol for 15 minutes followed by washing with Tris-buffered saline (TBS) for 5 minutes. Non-specific binding of the primary antibody was blocked by incubation with 5%BSA/TBS for 30 minutes; subsequently, SRF samples were incubated with anti-rhodopsin (1/100) (Sigma Aldrich) for 1 hour at room temperature. An Envision + HRP (DAB) kit was used (DAKO) to visualize the antibody binding. Slides were mounted in aqueous medium and evaluated with a microscope (Dialux 20, Leica, Germany), and photographs were taken using a digital camera (Leica).

Electron microscopy

Another 150-μl sample was fixed in 2% glutaraldehyde buffered at pH 7.4 and subsequently post-fixed in 1% osmium tetroxide (OsO_4) in phosphate buffer (Merck, Darmstadt, Germany), dehydrated, and embedded in epoxy resin. Ultra-thin 60 nm sections were cut and examined with a Jeol 1200 EX-II transmission electron microscope at 80 keV (Jeol, Zaventem, Belgium).

Optical coherence tomography

All patients were assessed 6 weeks after surgery using a 6× 6-mm radial line scan protocol with the Stratus OCT Model 3000 (Zeiss Humphrey Instruments, Dublin, CA, USA).

Results

Nine SRF samples, obtained during surgery from nine patients with macula-involving RRD, were analyzed. Demographic data and patient characteristics are summarized in Table 1. Eight patients had RRD associated with horseshoe tears, and one patient presented with round holes and no posterior vitreous detachment. Three patients underwent 20-G PPV, and six patients underwent scleral buckling surgery. The samples were classified clinically by the surgeon at the time of surgery as highly viscous when the consistency resembled a visco-elastic material, or as serous when it resembled balanced salt solution. Immunocytochemical analysis and electron microscopy was performed in a blinded manner on all samples. Analysis revealed rhodopsin immunopositive cells and cell fragments, and rhodopsin immunonegative cells

Table 1 Patient characteristics

Sample	Age (years)	Gender	Eye	Duration detachment	PVD	Lens	Surgery	SRF consis-tency	Pre-op BCVA	Post-op BCVA	Rh cells/mm2	PSF
1	88	Female	Right	6	yes	Ps	PPV	Serous	2.48	2.48	<1500	No
2	52	Female	Right	21	yes	Ph	Buckle	Viscous	0.80	0.52	9092	Yes
3	49	Male	Right	4	yes	Ph	PPV	Viscous	1.30	1.0	7304	Yes
4	78	Male	Left	7	yes	Ps	PPV	Serous	2.47	1.0	<1500	No
5	62	Female	Left	3	yes	Ph	Buckle	Serous	1.0	0.80	<1500	No
6	77	Male	Right	5	yes	Ph	Buckle	Serous	1.30	0.52	<1500	No
7	67	Female	Right	1	yes	Ph	Buckle	Serous	1.30	0.70	<1500	No
8	70	Male	Left	1	yes	Ph	Buckle	Serous	1.30	0.52	<1500	No
9	43	Male	Left	16	no	Ph	Buckle	Viscous	0.80	0.70	20270	Yes

BCVA: best-corrected visual acuity in LogMar duration of detachment (days); Ph: phakic eye Ps: pseudo phakic eye; Rh: rhodopsin immunopositive cells; PPV: pars plana vitrectomy; PVD: posterior vitreous detachment assessed by slit-lamp-assisted ophthalmoscopy; PSF: persistent submacular fluid on OCT

such as retinal pigment epithelial cells and red blood cells in all samples (Figs. 1 and 2). The number of rhodopsin immunopositive cells was calculated for each sample, and was high in three samples (9,092, 7,304, and 20,270 cells/mm^2) and low (<1,500 cells/mm^2) in the other six samples. All three cell-rich samples originated from cases graded highly viscous during drainage, and the OCT images showed PSF in the macula postoperatively.

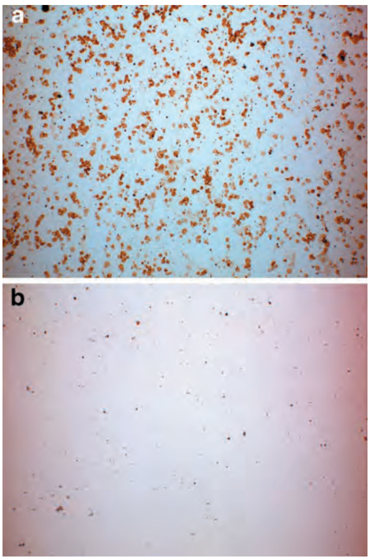

Fig. 1 Cytospin and anti-rhodopsin immunostaining of submacular fluid samples. **a** Cell-rich sample (sample 9) and **b** a scantily cellular sample (sample 4)

Discussion

Delayed or incomplete visual recovery after RRD surgery remains an important problem. While most authors report good or very good primary anatomical success rates (up to 91%), depending on the series functional results are often disappointing, with only between 28 and 42% of macula-off patients achieving 20/50 or better [13–16].

Many factors are involved in visual recovery. Preoperative visual acuity, duration of macular detachment and height of the macular detachment have been shown to be of importance. Postoperative cystoid macular edema, epiretinal membranes, macular holes and retinal folds are obvious and easily diagnosed causes of poor function after the retina has been reattached. More recently, with the introduction of OCT technology, PSF has been added to the list.

The pathophysiology of PSF remains poorly understood. Research [17] as well as clinical practice demonstrates that fluid absorption is favored by strong forces including oncotic pressure gradients, hydrostatic pressure, and an active retinal pigment epithelial (RPE) pump. In many cases of RRD, fluid absorption proceeds very rapidly when the retinal breaks are closed, even without drainage of fluid, as in pneumatic retinopexy. Why then would small fluid remnants take months to reabsorb?

Possible causes of PSF

More frequent after buckling surgery than after vitrectomy?

Wolfensberger [18] studied the macular recovery in 33 patients after RRD surgery, (24 patients treated with vitrectomy and nine with scleral buckling). He noted subfoveal fluid in six of the scleral buckling cases but in none of the vitrectomy cases, and concluded that surgical technique

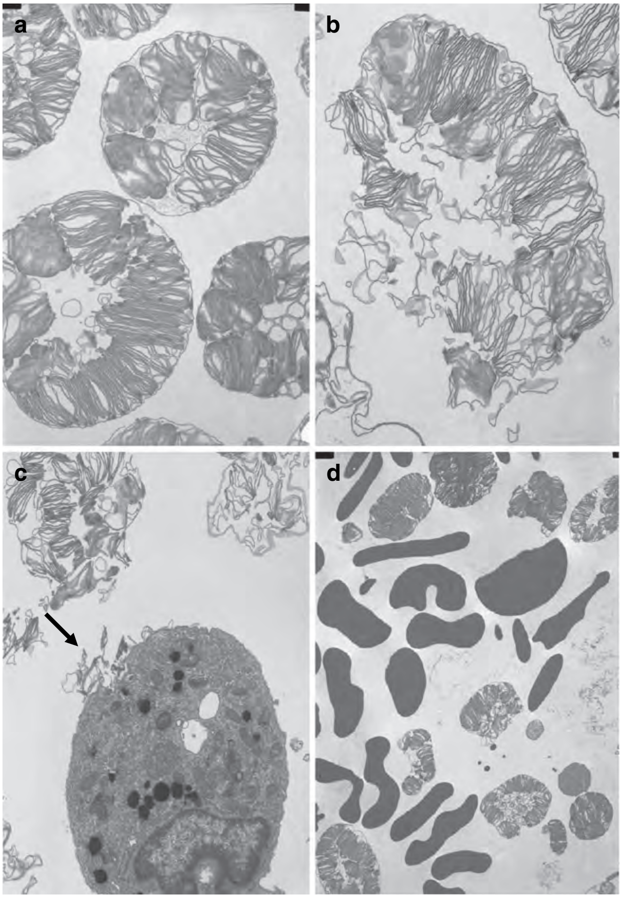

Fig. 2 Transmission electron micrographs of submacular fluid samples. **a** Well-preserved photoreceptor outer segments in sample 9 (magnification × 8,000). **b** Photoreceptor outer segment with fragmented saccules and ruptured cytoplasmic membrane in sample 2 (magnification × 12,000). **c** In-progress phagocytosis of a photoreceptor outer segment by a macrophage-like cell containing pigment in sample 2 (magnification × 5,000). **d** Sample 3 contaminated with red blood cells, most likely a consequence of transscleral drainage (magnification × 2,500)

could contribute to PSF formation. Benson et al. [10, 11] reported that in 98 patients treated with a scleral buckle, 54 (55%) had PSF on OCT 6 weeks after surgery, as compared to 15 out of 100 (15%) patients treated with vitrectomy.

Ischaemia caused by buckles?

It is unknown how a particular surgical procedure could predispose to PSF occurring. Encircling elements could potentially cause choroidal ischemia, with subsequent fluid leakage [19]. No leakage is seen on FA in any of the reported cases, however, and persistent SRF can occur without the use of any buckling element.

Cryocoagulation?

Breakdown of the blood–ocular barrier by cryotherapy has also been implicated [19, 20]. This is unlikely, as Wolfensberger used cryotherapy in all his vitrectomy cases and no PSF were found, whereas we avoid cryotherapy even during buckling surgery by performing laser postoperative retinopexy [21, 22], with PSF occurring nevertheless.

Tamponade?

A gas bubble, particularly in vitrectomized eyes, could displace subfoveal fluid. We have observed multiple cases of PSF after vitrectomy with gas and postoperative posturing. In the study by Wolfensberger, foveal reattachment was independent of whether the fovea was compressed with the gas bubble (in case of complete fluid–air exchange) or not (in case of partial exchange). Moreover, Theodossiades et al. [23] found fluid under the fovea postoperatively on OCT in patients with an attached macula preoperatively, without the use of a tamponade.

Drainage of SRF?

Incomplete drainage of SRF is another factor to be considered. Pars plana vitrectomy and fluid–air exchange probably result in a more complete drainage of SRF. Conversely, in scleral buckle series, Benson et al. found no influence of drainage of fluid on the incidence of PSF.

Physical and biochemical properties of subretinal fluid?

Most reported patients in the buckling groups were phakic (Wolfensberger: all nine as compared to seven out of 24 in vitrectomy group), retinal breaks were often inferior and a large number were round holes or oral dialysis (Benson et al. series: 79 out of 98) as compared to the vitrectomy group (two out of 100). In practice, many surgeons will buckle small breaks in phakic patients, particularly in the absence of an obvious posterior vitreous detachment (PVD).

Retinal detachments in phakic eyes with small breaks, particularly when located inferiorly, can be slowly progressive and the detachment can be longstanding, becoming symptomatic only when the macula is detached or threatened. This delay in symptoms could explain why no relationship between duration of detachment and incidence of postoperative SRF was found in Benson's series. Hagimura et al. [6] noted the absence of clinical PVD in their patients with PSF, and Abouzeid et al. [24] have recently reported that younger age and longer standing detachments were predisposing factors.

In fresh detachments, oncotic pressure gradient and an active RPE pump favor rapid fluid absorption when all retinal breaks are closed. Experiments with cynomolgus monkeys have demonstrated that RPE can pump up to 100 μl/h, 2.4 ml/day [25]. This is consistent with the observation that pneumatic retinopexy for a fresh bullous detachment can result in complete re-attachment within 24 hours. Negi and Marmor [17] demonstrated that breakdown of the blood–retinal barrier, caused by RPE damage, facilitates SRF absorption due to the greater oncotic pressure in the choroid.

The pathophysiology of longstanding detachments, however, is very different. Non-syneretic vitreous may slow the progression of RD by tamponading retinal breaks. The same characteristics of the composition of "young" vitreous suggest that slow progression detachment may be of importance in the persistence of SRF once the retina has been re-attached.

The high viscosity of the SRF may cause it to stick to the RPE when the SRF is drained. Furthermore, higher hyaluronic acid levels in the vitreous, and consequently in the SRF, would slow fluid absorption. Hyaluronic acid is a preferred substance for experimental RD, because it maintains the detachment over long periods of time, possibly by inhibiting RPE phagocytotic activity [26, 27].

In addition, in longstanding detachments the higher oncotic pressure of the fluid remnants may act against fluid absorption. Indeed, it has been shown that oncotic pressure of the SRF increases with duration of detachment [28, 29].

RPE malfunction?

A recent report of three patients with PSF treated with selective retina therapy (SRT) laser highlights the role of RPE [30]. It was noted that in the first days after laser treatment the SRF increased on OCT, followed by a gradual decrease after 1 or more months. Histopathological findings of the effect of SRT on RPE have been reported by Roider et al. [31]. The early effect from SRT laser is to destroy RPE. This would cause a breakdown of brain–ophthalmic barrier (B-O B) and allow passive fluid movement guided by oncotic pressure, as was demonstrated by Negi and Marmor [32]. In the weeks following the laser application, RPE reproliferation occurs, reconstituting the B-OB as well as the RPE's phagocytic capacity.

Decreased phagocytotic activity of the RPE in chronic detachments may be a contributing factor in the slowed absorption of SRF. Immel et al. [33] demonstrated a progressive loss of microvilli in RPE after detachment. Experiments by Gregory et al. [27] showed that glycosaminoglycans (GAG), such as hyaluronic acid, strongly inhibit the ability of RPE to phagocytose rod outer segments. Indirect evidence indicating an accumulation of shed outer segments in persistent SRF comes from studies on autofluorescence that show hyperautofluorescent material in the subretinal space [34]. We have found highly reflective material in cases with PSF using spectral domain OCT (Fig. 3) (Heidelberg Spectralis, Heidelberg Engineering, Germany). Biochemical and histological analyses have furthermore shown that large molecules such as proteins and GAG, as well as cells and cellular debris, are concentrated in longstanding SRF [35, 36]. These compounds cannot be removed through ion or water channels, resulting in an imbalance between the decreased capability of and the increased need for phagocytosis by RPE cells. We studied SRF samples collected during RD repair surgery, and found photoreceptors, photoreceptor

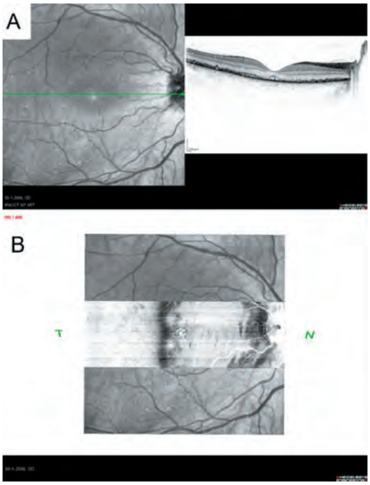

Fig. 3 SD-OCT image acquired 6 weeks after surgery for macula-involving RRD. **a** Horizontal cut through the fovea showing foveal PSF and disturbance of the photoreceptor-RPE interface throughout the macula. **b** C-scan image suggesting the presence of photoreceptor debris

fragments, retinal pigment epithelial cells, and red blood cells. Three cytospin samples were particularly cell-rich, which correlated with the highly viscous samples during surgery and the PSF on postoperative OCT.

Similarly, Matsuo [37] described a syndrome where RRD is complicated by glaucoma. He found PR outer segments in the aqueous humor of patients with longstanding detachment caused by oral dialysis and proposed a clogging of the trabecular meshwork to be the cause of elevated intraocular pressure.

Consequences of PSF

Although most reports agree that persistent fluid may slow visual recovery, with resolution of fluid usually coinciding with an improved visual acuity, final outcome may not be affected [8–12]. Patients suffering from persistent foveal detachment, however, can complain bitterly about poor central vision. Metamorphopsia and loss of depth perception can persevere for more than 1 year after "successful" RD surgery.

In addition, further damage to PR is very well possible when fluid persists under the macula. As shown in chronic central serous chorioretinopathy (CSC), irreversible loss of vision can occur due to progressive atrophy of the PR layer [38]. The fluid in CSC originates from the choroid, and thus contains a high concentration of substrates, allowing for a long survival of PR [39]. Thus, atrophic changes in CSC can take several months to develop [40]. In contrast, in experimental detachments using hyaluronic acid, photoreceptor apoptosis is observed within weeks [41]. Irreversible PR damage could consequently occur sooner in persistent SRF after RD.

Therapeutic options

Several interventions have been considered for this condition.

Laser?

Koinzer et al. [30] experimented with laser therapy that selectively affected RPE cells. A frequency-doubled Q-switched Nd:YLF laser emitting at a wavelength of 527 nm in a 100-Hz pulsed mode appeared to be effective in three cases.

Stimulate RPE pump?

Sheldon Miller (Invest Ophthalmol Vis Sci 2002 43: E-Abstract 4541) showed rapid clearance of experimentally induced subretinal space blebs in rats treated with somatostatin (SST14). Somatostatin analogs have been delivered systemically in patients with uveitis and cystoid macular edema and in patients with diabetic macular edema [42, 43]. An effect on PSF after longstanding RRD is unlikely, since somatostatin would not promote phagocystosis of macromolecules and cellular debris. Similarly, PSF does not respond to acetazolamide administration.

Surgery?

Surgical re-intervention with drainage of the submacular fluid through a small-gauge cannula, although technically conceivable, seems overly invasive for a relatively benign condition.

In the absence of a safe and effective treatment, prevention should be considered. We have shown that SRF from patients with PSF on post-operative OCT contains high levels of photoreceptor fragments. These findings may suggest a clogging phenomenon of the RPE and blood–retinal barrier as a contributing factor in the development of PSF. Therefore, we speculate that altering the composition of SRF by rinsing the SR space before draining the fluid may achieve a more complete removal of subretinal fluid and earlier re-apposition of photoreceptor outer segments to the RPE. In a recent pilot study, we demonstrated that a subretinal space washout with basic salt solution is feasible and appears safe. In 12 eyes of 12 patients, subretinal lavage was carried out in combination with pars plana vitrectomy. None of the patients developed PSF, as demonstrated by OCT 4 weeks after surgery [44].

In conclusion, PSF after RD surgery is seen more often after buckling than vitrectomy. This seems related to selection bias. Case characteristics such as phakic lens status, absence of PVD, and small breaks predispose a patient to be treated with a buckle rather than vitrectomy. The same characteristics are known to slow the progression of a retinal detachment. We hypothesize that patients with longstanding detachments are at increased risk of PSF and are most likely to benefit from a modified surgical drainage technique aimed at preventing this complication. Since these patients are often phakic patients with no PVD, further research will be aimed at investigating the possibility of combining subretinal lavage with non-vitrectomizing surgery.

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A case-control study of beneficial and adverse effects of 2-octyl cyanoacrylate tissue adhesive for episcleral explants in retinal detachment surgery

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Dear Editor

Despite the recent trend towards primary vitrectomy, scleral buckling, either alone or in combination with vitrectomy, remains a successful technique in the repair of retinal detachment. Suturing an encircling band, however, can cause a scleral perforation, with possible complications including hypotony, retinal incarceration, and subretinal, or choroidal hemorrhage at the perforation site [1].

An alternative and safer method for securing encircling bands and local episcleral explants would be desirable.

Given the reports on the use of butyl-cyanoacrylate (Histoacryl®) to secure scleral explants, and the reported advantages of octyl-cyanoacrylate (Dermabond®) (better elasticity and less tissue reaction, both in animals and patient studies) over its butyl sibling, we decided to use octyl-cyanoacrylate in a pilot study in patients undergoing external buckling retinal detachment surgery [2–9].

When we used 2-octyl cyanoacrylate, we were pleased with its relative ease of application, the resulting fixation of the encircling band and the uneventful postoperative findings. We were not aware at that time, however, that butyl-cyanoacrylate carried an ophthalmic use approval, whereas 2-octyl cyanoacrylate, the newer formulation with advantageous properties, did not have this approval. Therefore, on learning this, we decided to recall our patients to study their longer-term results, to ensure that no untoward late effect would be observed after this off-label use of 2-octyl cyanoacrylate.

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From December 2005 to March 2006, one surgeon (JvM) used 2-octyl cyanoacrylate for securing encircling bands in a consecutive cohort of 25 patients (26 eyes) with a primary rhegmatogenous retinal detachment.

Forty-eight control patients were randomly chosen from patients undergoing retinal detachment surgery by other surgeons in the same period.

Two-year appraisal:

All patients were evaluated by an investigator (RR), who was masked for the type of encircling band fixation.

Major outcome criteria were position of the explant (pre-equatorial, equatorial or post-equatorial) and whether or not the explant was covered by the conjunctiva (yes or no).

Minor outcome criteria were visual acuity, intraocular pressure, conjunctival redness using a standard grading series of pictures of conjunctival redness [10], number of post operative visits, foreign body sensation (subjective analogue scale) and whether the retina was attached or not. SPS Software 15 (SPSS Inc., Chicago, IL, USA) was used to analyse the data.

The 2-octyl cyanoacrylate group consisted of 25 patients (26 eyes). In 19 eyes an encircling band had been placed followed by conventional retinal detachment surgery with a segmental buckle. In seven eyes, a primary vitrectomy with a gas tamponade was performed.

Of these 25 patients, two patients were lost to follow-up: one died, one moved to Norway.

The control group consisted of 48 patients (48 eyes) with a primary rhegmatogenous retinal detachment. (Table 1)

We could not detect any difference in most of the outcome measures between 2-octyl cyanoacrylate-treated patients and controls. However, conjunctival redness was significantly more marked in 2-octyl cyanoacrylate-treated patients ($p=0.005$).

Table 1 Groups and type of procedure

Type of procedure	Dermabond	Control	Total
EB+buckle	19	37	56
EB+PPV+gas	7	10	17
EB+PPV+oil	0	1	1
Totals	26	48	74

(EB: encircling band; PPV: pars plana vitrectomy)

As there were only slightly more reoperations in the 2-octyl cyanoacrylate group, it cannot be excluded that there is a relation to toxicity of 2-octyl cyanoacrylate, or its breakdown product formaldehyde. The effect did not appear to be clinically harmful, though.

Although our study does not have sufficient power to prove non-inferiority of 2-octyl cyanoacrylate to scleral sutures, it documents the feasibility of using 2-octyl cyanoacrylate when surgeons consider the use of glue instead of suture in a patient with a thin sclera.

Conflict of interest R. Reyniers MD : Competing interest: none to declare.

S. Boekhoorn MD. PhD : Competing interest: none to declare.

M. Veckeneer MD : Competing interest: none to declare

J. van Meurs MD. PhD: Competing interest: none to declare

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The effect of a preoperative subconjuntival injection of dexamethasone on blood–retinal barrier breakdown following scleral buckling retinal detachment surgery: a prospective randomized placebo-controlled double blind clinical trial

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Abstract
Background Blood–retinal barrier breakdown secondary to retinal detachment and retinal detachment repair is a factor in the pathogenesis of proliferative vitreoretinopathy (PVR). We wished to investigate whether an estimated 700 to 1000 ng/ml subretinal dexamethasone concentration at the time of surgery would decrease the blood–retinal barrier breakdown postoperatively.
Methods Prospective, placebo-controlled, double blind clinical trial. In 34 patients with rhegmatogenous retinal detachment scheduled for conventional scleral buckling retinal detachment surgery, a subconjunctival injection of 0.5 ml dexamethasone diphosphate (10 mg) or 0.5 ml placebo was given 5–6 hours before surgery. Differences in laser flare photometry (KOWA) measurements taken 1, 3 and 6 weeks after randomisation between dexamethasone and placebo were analysed using mixed model ANOVA, while correcting for the preoperative flare measurement.
Results Six patients did not complete the study, one because of recurrent detachment within 1 week, and five because they missed their postoperative laser flare visits. The use of dexamethasone resulted in a statistically significant decrease in laser flare measurements at the 1-week postoperative visit.
Conclusion The use of a preoperative subconjunctival injection of dexamethasone decreased 1-week postoperative blood–retina barrier breakdown in patients undergoing conventional scleral buckling retinal detachment surgery. This steroid priming could be useful as a part of a peri-operative regime that would aim at decreasing the incidence of PVR.

Keywords Preoperative · Subconjuctival injection · Dexamethasone · PVR · Blood–retina barrier · Breakdown

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Clinical Trials registration reference number: ISRCTN (International System of Randomized Controlled Trials Number) 31308983

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Introduction

Proliferative vitreoretinopathy (PVR) remains the major cause of ultimate surgical failure in patients with rhegmatogenous retinal detachment [9, 19]. Retinal pigment epithelium (RPE) cell dispersion and inflammatory changes secondary to breakdown of the blood–retinal barrier (BRB) have been implicated as important pathogenetic mechanisms in the development of PVR [4, 6, 7, 17].

Studies in animals [5, 18] have reported that intravitreal corticosteroids may be useful in the prevention of proliferative vitreoretinopathy. Clinical reports have suggested the same effect using either systemic [15] or intravitreal [31] steroids. This was mainly attributed to their attenuating effect on blood–retinal barrier breakdown and their inhibiting effect on proliferation of RPE cells and fibroblasts, which are thought to be transformed RPE cells, and as myofibroblasts responsible for the contractile properties of PVR membranes.

Studies in animals have suggested that pretreating with steroids was more effective in PVR prevention than treatment started at the time of injury or later [5]. Adequate intraocular concentrations of corticosteroids at the time of surgery might reduce the blood–retina barrier breakdown induced by the surgical trauma during cryotherapy, drainage of subretinal fluid, or intravitreal gas injection, and thereby decrease the incidence of PVR.

Weijtens et al. showed in patients that among external routes of administration, a subconjunctival injection of dexamethasone resulted in the highest intravitreal and subretinal fluid concentrations [25, 26, 28–30].

Therefore we wished to study, in patients undergoing conventional scleral buckling retinal detachment surgery, whether a subconjunctival injection of dexamethasone prior to surgery would decrease postoperative blood–retinal barrier breakdown as measured by laser flare photometry.

Materials and methods

Consecutive patients admitted to the Rotterdam Eye Hospital with a rhegmatogenous retinal detachment scheduled for scleral buckling were included in the study.

Exclusion criteria were therapy with systemic or local steroids, glaucoma, diabetes, and other vascular retinopathies. This prospective, randomized, placebo-controlled, double blind study had been approved by the Institutional Review Board (NRT 194, ISRCTN31308983).

Preoperative investigation All patients underwent a comprehensive ophthalmological examination, including best-corrected visual acuity tested with an EDTRS chart. Specific items were noted and entered into a database: lens status (phakic or pseudophakic), the presence of vitreous blood, number of quadrants of detached retina, presence and number of horseshoe tears, presence of PVR according to 1983 classification [1], as well as aqueous laser flare meter measurements (Kowa Company, Ltd, Tokyo, Japan). Patients were examined 30 minutes after mydriasis with 5% phenylephrine and 1% tropicamide, and always before the application of fluorescein for intraocular pressure measurement. For each eye, five measurements were averaged.

Surgical Technique Six hours before the planned surgery, all patients received under topical anaesthesia (cocaine and oxybuprocaine eye drops) a subconjunctival injection 0.5 ml placebo NaCl (Delftse Apotheek, Apotheek Westblaak), or 0.5 ml dexamethasone diphosfate 20 mg/ml (Delftse Apotheek, Apotheek Westblaak). A 30-gauge needle was used, 4 mm from the limbus, with closure of the injection site by a cottonwool tip for 10 seconds. Randomization had been performed by opening an envelope with study medication that contained either verum or placebo, of which our trial-pharmacist held the code; therefore, surgeons and technicians alike were blinded to the nature of the subconjunctival injection. All patients underwent a standard scleral buckling procedure as described before [22, 23]. A silicone band was placed under the four rectus muscles at the presumed area of the vitreous base, and the sclera under retinal tears and breaks was indented with either a circumferential (278, 277, 287 Mira Silastic) or radial (7.5 mm sponge) buckle. Subretinal fluid was drained in all patients. Retinopexy of the tears or breaks was done by cryocoagulation during surgery, or with an argon laser mounted on a slit lamp between 2 and 6 weeks after the surgery, according to the surgeons' preference. In some patients, an air or gas (air/SF6) tamponade was used. All patients received a 2 mg dexamethasone and 1 mg gentamycin subconjunctival injection at the end of the surgery.

Follow-up All patients received the same postoperative treatment, prednisolone acetate 1% eyedrops in a tapering dose over 6 weeks. ETDRS vision, a fundus exam and laser flare measurements were taken at 1, 3 and 6 weeks.

The treatment effects of dexamethasone versus placebo on flare were analyzed after logarithmic transformation of flare (photon counts/ms). Hence, effects were specified as percentage differences in photon counts/ms. Mixed model ANOVA was used to estimate and test for statistical significance the effects on flare of week (weeks 1, 3 and 6), treatment (dexamethasone, placebo), and their interaction. The baseline measurement of flare at week 0 was entered as covariable in the model, along with its interaction with week. No structure was imposed on the (co)variances of the three repeated measurement of flare.

Results

A total of 34 patients (19 males/ 15 females) were included from 1 February 2003 to 1 February 2004. The age of the patients ranged from 18 to 76 years (mean 54 years). Follow-up ranged from 6 to 8 months. Six patients did not complete the study as planned. One patient had a redetachment due to an undetected tear within the first weeks, and five patients missed two or more of their laser flare follow-up visits; none of these five patients suffered new breaks or a redetachment.

Of the remaining patients, 15 were in the placebo group and 13 in the dexamethasone group. The various baseline characteristics, such as preop vision, macula on or off, quadrants involved, type of breaks, or variables depending on the surgical procedure such as cryocoagulation or postoperative laser, were equally distributed between the dexamethasone-treated patients and the placebo group (Table 1). At the last examination, two patients given placebo and two patients given dexamethasone had an intraocular pressure between 20 and 25 mmHg.

In the placebo group, laser flare measurements on average increased during the first week and decreased thereafter. In the dexamethasone group, there was a steady decrease as from week 0 (Table 2, summary raw data). The mixed model ANOVA yielded the following results. The treatment effect on flare of dexamethasone versus placebo differed significantly between the three weeks (P=0.007).

Table 1 Baseline characteristics of the two groups

	Age	Refr	IOL	Preop vision	Preop PVR	Macula	Quadrants	Holes	Horseshoe tears	Surgeon	Laser	Cryo
Dexa patients												
1	65	plan		0.016		off	3		1	E	x	
2	21	plan		1.6		on	2	1		C	x	
3	44	nn		0.1		off	2		2	B		x
4	72	plan		0.003		off	2		2	C	x	
5	60	-5		0.25		off	1		1	D		
6	56	-5		0.016		off	2	1		D	x	
7	66	plan		0.016		off	2	1		D		x
8	40	-3		0.016		off	2	2		C	x	
9	47	-10		1.0		on	1	1		D	x	
10	71	-3	+	0.003		off	3		2	B		x
11	49	-9		0.15		off	1	1		E		x
12	65	nn		0.25		off	2		1	D	x	
13	81	plan		0.7	A	on	2	1		C	x	
Placebo patients												
1	77	-2		0.003		off	3			E		x
2	55	plan		0.016		off	3		1	C	x	
3	61	-4		1.0		on	1		1	D	x	
4	47	-6		1.0		on	1	1		E		x
5	29	-3		0.25	A	off	1	2		C	x	
6	59	-8		1.0		on	1		1	B		x
7	40	-.7		0.7		part	2	1		D	x	
8	64	plan		0.003	C1	off	2		1	B		x
9	56	-5		0.003		off	2		1	C	x	
10	62	-6		0.003		off	2		1	C	x	
11	17	plan		0.6		part	1		dialysis	D		x
12	30	+2		0.5		part	1		1	B		x
13	59	-7		1.0		on	1		1	B		x
14	71	nn		0.1		off	2	2			x	
15	22	-6		1.0		on	1	1		A	x	

refr: refractive error

plan: plano refraction

IOL: intraocular lens

nn: not noted

part: partially off/partially attached

Table 2 Laser flare measurements (counts per seconds) at four visits, and their relative percentage in patients treated with dexamethasone when compared to patients treated with placebo

Week	Treatment	Summary raw data				Mixed model ANOVA estimates		
		N	Median	Min.	Max.	% dexa vs placebo	95% CI	*P*-value
0	Placebo	16	10.2	2.4	94.0			
	Dexa	13	10.4	7.7	95.6			
1	Placebo	16	16.7	3.1	56.9			
	Dexa	12	8.1	1.0	58.6	-48.3%	-72.1% to -4.4%	0.017
3	Placebo	15	9.6	2.2	16.1			
	Dexa	12	7.1	3.1	48.9	+2%	-37.8% to +67.2%	0.94
6	Placebo	15	5.7	0.9	14.0			
	Dexa	12	6.2	1.6	12.4	+17.6%	-35.1% to +113%	0.58

The effect of baseline flare on flare during treatment also decreased significantly across the 3 weeks (P=0.019). Only at week 1 was a significant reduction of dexamethasone relatively to placebo seen: flare was 48.3% lower under dexamethasone, adjusted for baseline flare (95% CI: 72.1% lower to 4.4% lower; P=0.037); see the mixed model ANOVA estimates in Table 2.

Discussion

Intravitreal dexamethasone has been shown to reduce the number of tractional detachments in experimental animal models of PVR by cell-injection [18, 20]. Studies in animals and patient have suggested that pretreating with steroids was more effective in PVR prevention than treatment started at the time of injury or later [5]. It was speculated that the decrease of BRB breakdown and inhibition of the proliferation of RPE cells accounted for this effect. Dexamethasone has a biphasic effect on RPE cell proliferation in vitro, i.e. rather a stimulatory effect with lower concentrations (ng per ml) [12, 32, 33], and an inhibitory effect on proliferation of RPE in vitro at relatively high concentrations (mg per ml, not reached by peribulbar or systemic administration, only by intravitreal injection).

Corticosteroids bind to intracellular receptors and act on inflammation by inhibiting the synthesis of immunoregulatory proteins such as cytokines. The magnitude of this response is directly proportional to the number of occupied steroid receptors and is therefore dose-dependant [3]. Given the studies by Weijtens et al. in patients with rhegmatogenous retinal detachments, macular puckers and macular holes, which showed that a subconjunctival dexamethasone injection would result in optimal concentrations in the vitreous (72.5 ng/ml after 2.5 mg dexamethasone [25]) and the subretinal fluid (367 ng/ml after 2.5 mg dexamethasone [27]) between 3 and 6 hours after injection; and assuming that the time interval between binding to the steroid receptor and transcription of effector proteins would take less than 2 hours, we timed the subconjunctival injection 5 to 6 hours before surgery. It may well be that only direct steroid-receptor ligand prevention of nuclear factor kappa B pro-inflammatory effect is acting within this time interval [8]. The estimated dexamethasone concentration levels of 700 to 1000 ng/ml reached with our injection would be effective in decreasing BRB by inducing tight-junction formation [2] and the modulation of cytokine release[11], but not for cell growth inhibition [12, 16, 32, 33].

The disadvantage of using dexamethasone is its short half-life, limiting the time interval in which the drug can be used to minimize the surgically induced inflammation. For clinical purposes, a longer-acting steroid would allow a more flexible preoperative administration treatment moment, as well as a longer treatment effect, but it would be at the price of a higher incidence of raised intraocular pressure and a lower subretinal and vitreous concentration at the time of surgery. To ensure a continuous affective steroid concentration following preoperative priming by a subconjunctival dexamethasone injection, pre-operative intravitreal injection of longer-acting triamcinolone, or a sustained release implant might be an feasible option [14, 34].

A drawback of our study was the small number of patients enrolled. By changes in admission policy right at the start of our study, patients were no longer admitted the day before surgery but were treated on an ambulatory basis. Potential study patients were asked to come in at least 6 hours earlier then the normal admission time, which was a significant inconvenience and reduced the number of patients willing to participate in the study. Therefore, we could only use a quantitative surrogate marker, i.e. laser flare, as a measurement of BRB breakdown, instead of the originally intended rate of PVR.

Laser flare photometry, however, allows precise and non-invasve quantification of the aqueous protein content. Although laser flare photometry has been used mainly to study anterior segment inflammation, it has been shown to be useful in monitoring posterior segment disease [10, 13, 21, 23, 24].

This study showed that a single injection of dexamethasone, injected at an estimated optimized time interval preoperatively, significantly decreased blood–retinal barrier breakdown at 1 week induced by a scleral buckling procedure. We cannot exclude, however, that a similar effect would have been achieved by supplying the same dose at the time of surgery or with a longer interval before surgery. To answer that comprehensively, a four-armed study would have been necessary. Nevertheless, our findings may help in designing a feasible, optimal perioperative steroid regime, which might include a sustained release device or intravitreal injection at the end of conventional surgery or, in the case that vitrectomy is chosen to treat the retinal detachment, steroids in the peroperative intravitreal infusion. However, surgically induced inflammation is only one risk factor among others in the development of PVR. Larger studies including greater numbers of patients, a more sustained dexamethasone regime, and longer follow-up are needed to demonstrate whether pharmacologically decreasing the blood–retina barrier breakdown ultimately may lead to a lower incidence of PVR.

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Visualising vitreous through modified trans-scleral illumination by maximising the Tyndall effect

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ABSTRACT

Background: A new technique for visualisation of the vitreous base is described. It uses a standard lightpipe for scleral indentation and transillumination. Visualisation of the vitreous using low light levels can be achieved by enhancing the Tyndall effect.

Discussion: Perfluorocarbon liquid (PFCL) is used to confine the aqueous environment to the anterior vitreous cavity and triamcinolone is added to increase light scatter. The technique clearly differentiates vitreous from PFCL and infusion fluid, and facilitates trimming of the vitreous base, draining of subretinal fluid and air/fluid exchange.

The vitreous is transparent by design and is normally best seen by light scatter or the Tyndall effect.[1 2] As such, the illumination ideally should come from the side. For the posterior vitreous, we are reliant on a divergent beam emerging from a fibre-optic light pipe. This increases the angle between illumination and viewing. For the anterior vitreous and the vitreous base, visualisation presents further challenges. Even with indirect viewing systems and wide-angle lenses, it is necessary to indent the sclera in order to bring the pre-equatorial retina, ora serrata and the pars plana into view. It is possible for an assistant to perform this indentation, but the control is less than ideal. An additional difficulty is obtaining optimal illumination. This could be from the co-axial illumination from the operating microscope. Because the angle between illumination and viewing is small (virtually co-axial), the vitreous is not well seen, and the view is subjected to interfering specular reflections from the tear film, cornea and lens. Alternatively, one or more 25-gauge (or smaller) light pipes could be secured at the pars plana via extra sclerotomies.[3] With this means, the surgeon can then perform the indentation and carry out the vitrectomy in a bimanual fashion. Despite the small gauge, vitreous incarceration into these ports is inevitable and may give rise to complications.[4–6] Strong chandelier fibre probes have been reported to cause thermal damage.[7] We describe a technique that improves visualisation of the vitreous base using transillumination.

Diaphanoscopy or transillumination is a simple and effective technique for illuminating a body cavity and determining the translucency of its walls. Diaphanoscopy was an important tool to investigate maxillary sinuses before *x* ray invention. Forensic diaphanoscopy is used to determine the presence or absence of subcutaneous invisible haematomas. It is also still considered helpful for breast cancer screening. Transillumination has been used in ophthalmology for fundus examination, diagnosis and treatment of choroidal melanoma delineating tumour for plaque radiotherapy and peroperatively to help locate the posterior border of the ciliary body and to aid sulcus intraocular lens suturing.[8–10]

When the principle of transillumination is applied during vitrectomy, the light that is transmitted through the sclera, choroid and retinal pigment epithelium is used to visualise the vitreous.[11] The transmission of light from a standard 20-gauge light-pipe is, however, substantially reduced by the eye wall. It is most likely because of this limitation that the "diaphanoscopic illuminator" described by Schmidt *et al*[12] for visualisation in pars plana vitrectomy was not widely adopted.

Our technique improves visualisation of the vitreous base by amplifying this low transilluminated light.

METHODS

We have applied the technique on a consecutive series of cases and audited the results of our surgery for the treatment of rhegmatogenous retinal detachment. We also present the experience of a surgeon newly adopting the technique of using triamcinolone.

Description of surgical technique

The method consists of three essential steps:

1. Filling the vitreous cavity with PFCL up to and beyond the retinal breaks.
2. Injecting triamcinolone acetonide crystals at both sclerotomy ports. As the PFCL bubble displaces the remaining vitreous upwards, the crystals are concentrated in the peripheral vitreous. In addition, the PFCL bubble prevents triamcinolone crystals gaining access to the subretinal space and stabilises the retina during vitreous cutting.
3. Scleral indentation using a conventional light pipe. As the crystals settle in the vitreous base, they greatly amplify the light transmitted through the sclera by increasing the Tyndall scattering. An extra refinement is to use a sleeve over the conventional light probe. An example of such a sleeve is that produced by DORC (Zuidland, The Netherlands) (figs 1, 2).

Applying triamcinolone crystals to visualise vitreous during surgery was first suggested by Peyman *et al*.[13] We have found that diluting triamcinolone acetonide (Kenalog) with balanced salt solution by one to one reduces the size of the crystals, and this promotes a more diffuse spread of the triamcinolone throughout the vitreous cortex.

Figure 1 DORC ''Lightindentor''. This device is a disposable sleeve that can be applied over a conventional 20- or 23-gauge light probe (developed by DORC in collaboration with Dr Gabor Scharioth). The smooth surface is designed to reduce the abrasion of conjunctiva and sclera. The sleeve also increases the stiffness of the light pipe to facilitate the indentation process.

Others have also found that dilution can alter steroid particle size.[14 15]

RESULTS

One of us (MV) performs over 500 vitreoretinal interventions annually (fellowship trained 1999). When vitrectomy is performed to treat a rhegmatogenous retinal detachment, the standard approach involves three-port pars plana vitrectomy (PPV) using 20-gauge instruments, heavy liquid to reattach the retina, 360° endolaser, fluid/air exchange and, depending on location, number and size of breaks, SF6 gas tamponade.

The modified transillumination technique was adopted mid 2005. Prior to this, visualisation of the peripheral fundus was routinely done by using the light from the operating microscope and performing a peripheral scleral indentation. From mid 2005 onwards, transillumination using the light pipe to indent the eye as a bimanual technique was combined with the use of triamcinolone to enhance the visualisation of the vitreous base. The fundus was visualised with the indirect wide-angle viewing system (EIBOS, Möller-Wedel, Wedel, Germany)

Figure 2 Maximising the Tyndall effect. The vitreous base with enmeshed triamcinolone can be clearly visualised with the transilluminated light.

With a follow-up of at least 6 months, 5.8% failures occurred in 2007 as compared with 9.8% in 2004. These results seem to indicate that a good anatomical outcome can be achieved using the novel method for vitreous base visualisation and removal.

In our experience, indenting with the lightpipe did not cause any more discomfort than with a standard scleral depressor and can be achieved under general or local anaesthesia. The height of the required indentation to achieve good visualisation is greatly reduced with transillumination when combined with wide-angle viewing. Indentation using the direct viewing through the

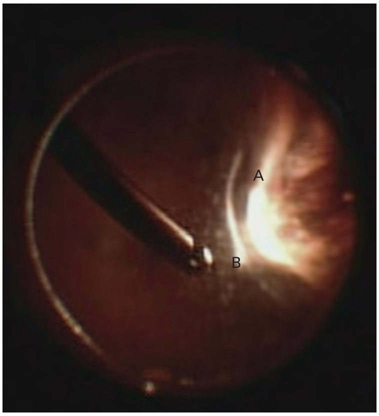

Figure 3 Double light reflexes. This image shows the presence of two strong light reflexes, one from the transilluminated light coming through the full thickness of the eye wall (A) and the other its reflection from the interface between the vitreous and the perfluorocarbon liquid (PFCL) (B). The residual vitreous base occupies the space between the PFCL and the eye wall. The distance between the two light reflexes therefore gave some indication of the extent of vitreous base trimming.

Figure 4 Uncrossed indentation. Indenting near the cutter port allows incarcerated vitreous to be removed without lens touch.

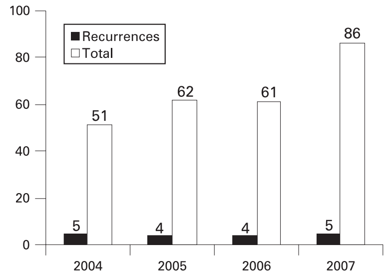

Figure 5 Primary success rate of vitrectomy for rhegmatogenous retinal detachment.

operating microscope and its illumination generally needed to be higher, as the viewing angle was smaller. The cover sleeve "Lightindentor" (fig 1) is designed to provide a smooth and rounded surface to minimise trauma to the conjunctiva and to reduce discomfort. The sleeve also adds stiffness such that indentation can also be achieved using smaller-gauge light pipes.

The coauthor (DW) has been using transillumination with a light pipe for over 10 years. He found that the use of PFCL and triamcinolone significantly enhanced the view of the peripheral vitreous. The adoption of this new technique showed two additional advantages over simple transillumination:

1. A double light reflex (one from transmitted light and one from bubble surface) was often seen, and this increased our perception of depth. The distance between both reflexes gave an idea of the extent of vitreous trimming (fig 3).
2. The movement of the crystals also gave useful feedback. Crystals in the vitreous moved en masse because they were enmeshed in a gel-like structure. Triamcinolone on the surface of the PFCL swirled like debris riding on a current. This information enabled the surgeon to know whether he was using the vitreous cutter to remove vitreous gel or merely to aspirate PFCL or BSS. During the surgical step of air/PFCL exchange, the aim was to completely remove the subretinal fluid through a break in the retina before aspirating the heavy liquid. The presence of the triamcinolone on the surface of the PFCL bubble highlighted the interface between the heavy liquid and preretinal fluid. Aspiration of the PFCL was easily recognised by a rush of the crystals towards the cutter.

The triamcinolone also highlighted the incarcerated vitreous at the slerotomy sites. Even in the phakic eye, using careful indentation (light indenting near the cutter port), we were able to deal with the incarcerated vitreous without lens touch (fig 4).

Between January 2004 and December 2007, a total of 260 cases of rhegmatogenous retinal detachment were treated with vitrectomy. Results from the audit of the anatomical success rate for primary vitrectomy to treat RRD are shown in fig 5.

DISCUSSION

The Tyndall effect allows us to visualise vitreous, which by nature is transparent. The effect is augmented by increasing the angle between illumination and observation axes up to 90°. It is also enhanced by increasing the size of the light-scattering elements within the vitreous, which in this case is achieved by the addition of triamcinolone. The transilluminated light is reflected off the convex upper surface of the PFCL bubble, which acts as a mirror. That means the vitreous is illuminated from different angles maximising the scatter of light.

Our technique involves maximising the low amount of illumination afforded by transillumination not only to identify relatively transparent vitreous tissue, but also to differentiate it from PFCL and infusion fluid. We recommend its use in all cases for which tight trimming of the vitreous base is considered important especially in retinal detachment and proliferative diabetic retinopathy.

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Summary

Until the early 20th century, rhegmatogenous retinal detachment was considered an untreatable condition that almost inevitably blinded the affected eye.

The introduction of the ophthalmoscope by Herman Helmholtz was a pivotal event in the history of RRD repair because it made the in vivo observation of the ocular fundus, and thus the detached retina and the retinal breaks, possible. Aided by this new technology, Jules Gonin would succeed in his relentless endeavour to find an effective cure. By 1920, Gonin had demonstrated convincingly to the ophthalmic society, that closing all the retinal breaks could lastingly re-attach the retina in many cases.

Penetrating thermocautery as introduced by Gonin did not however relieve vitreoretinal traction. Ernst Custodis demonstrated in the fifties that relieving vitreous traction by indenting the sclera with a buckling material in the area corresponding to the retinal breaks, greatly improved the anatomical success rate of rhegmatogenous retinal detachment (RRD) surgery.

In the early seventies, Robert Machemer introduced pars plana vitrectomy, a technique that allowed access to the vitreous face of the retina in a controlled manner. Further developments in technique and equipment would allow surgeon's like Relja Zivojnovic to design a very invasive, but often effective, approach to RRD cases complicated by extensive proliferative vitreoretinopathy (PVR).

Despite further refinements in machine and instrument technology, it remains unclear whether the overall outcome of RRD treatment has changed significantly in the past 30 years. The current results can be summarized as follows: 40% of eyes with macula-off detachments will not achieve reading ability, between 10% to 40% will need more than one surgical procedure (including additional retinopexy or anterior segment surgery), and up to 5% of all RRD eyes will still suffer permanent anatomical failure.

In the frustrating absence of a real solution for poor functional recovery and PVR, the basic approach to RRD is shifting. In the past decade a strong trend can be observed in the surgical practice pattern towards a more aggressive surgical approach that includes vitrectomy and (in phakic patients) primary lens extraction, as standard care for all cases of RRD. This approach, that is paradoxically coined minimally invasive, can not only be accompanied by a multitude of complications, it has so far not been shown to yield higher success rates.

In the past 15 years we have therefore attempted to identify aspects of the disease that are not addressed effectively by current interventions and to modify the surgical approach to better address the critical causes of failure, while eliminating certain elements that can adversely affect the outcome.

Blood-ocular barrier (B-O B) breakdown is an important event in RRD and extensive surgical manipulation seems to increase the B-O B breakdown. Theoretical arguments as well as empirical data suggest that elevated B-O B breakdown may negatively affect functional outcome and serve as a strong promoter for development of PVR. We have shown that pre-operative subconjunctival administration of dexamethasone reduces the breakdown as measured by anterior chamber (AC) flare. In two other studies we demonstrated that avoiding intra-operative retinopexy not only allows for excellent anatomical results but also reduces post-op AC flare and accelerates visual recovery.

Functional recovery as defined by visual acuity and resolution of metamorphopsia can be effected by the persistence of subretinal fluid under the fovea. We have studied potential causes for fluid persistence. Clinical features such as younger age, presence of the natural lens and absence of PVD, slow the progression of the detachment, leading to a particular composition of the SRF that may

slow its absorption and thus promote the persistence of fluid after surgical repair. We reported a correlation between the high content of photoreceptor cell debris in the drained fluid and the presence of fluid on postoperative optical coherence tomography (OCT). A modified surgical drainage technique ("subretinal fluid lavage") was shown to prevent fluid persistence in eyes that presented with high risk features pre-operatively.

In case of RRD complicated by PVR, complete and lasting anatomical success still remains uncertain, even after extensive and often multiple interventions. The original approach of extensive membrane peeling continues to form the basis for successful re-attachment. To improve the efficacy and reproducibility of epiretinal membrane (ERM) peeling, while reducing the surgical trauma, we studied the use of vital dyes to enhance the visibility of membranes on the retinal surface. In an ex vivo study we demonstrated that trypan blue (TB) stains PVR membranes very effectively. We further established the limited toxicity of low concentrations of TB in a rabbit model. In clinical practice, the application of a TB dye can confirm the presence and extent of ERM's more precisely. Using this technique of dye assisted membrane peeling, we reported a low rate of re-detachment following silicone oil removal.

When the retina cannot be re-attached despite optimal membrane peeling, retinotomy is often necessary. PVR can be considered as a fibrotic response in reaction to a retinal break and we consequently consider cutting the retina to be a severe additional trauma. In an attempt to limit the surgical trauma of the retinotomy, we have eliminated intra-operative retinopexy in a series of patients suffering PVR related re-detachments. This modification may allow the ongoing contraction to shorten the retina without promoting re-detachment as long as the oil tamponade is in place.

According to the reported technique, once the fibrotic process has run its course, laser retinopexy to secure the central retinotomy edge can be applied before oil removal.

The treatment of RRD has come a long way in the past century. In order to tackle the remaining obstacles, we should aim to re-define minimally invasive surgery and target the key aspects of the disease without creating additional iatrogenic pathology. Temporary suprachoroidal buckling, optimized immobilization and instant retinopexy techniques deserve further investigation. Developments in pharmacological vitreolysis may lead to new preventive as well as therapeutic strategies to deal with vitreous traction. Identifying patients at high risk for RRD and PVR may help us to better target out approach. And finally, neuroprotective and regenerative agents may promote functional recovery.

The future of RRD therapy looks bright, let's keep our eye on the target.

Samenvatting

Tot aan het begin van de 20e eeuw werd rhegmatogene netvliesloslating (RNLL) beschouwd als een onbehandelbare aandoening die bijna zonder uitzondering tot blindheid van het aangedane oog leidde.

De introductie van de oftalmoscoop door Herman Helmholtz is een scharniermoment in de geschiedenis van de behandeling van RNLL, omdat dit instrument de in vivo waarneming van de oogfundus en dus ook van het losgelaten netvlies en de scheuren mogelijk maakte. Gewapend met deze nieuwe technologie ontwikkelde Jules Gonin een effectieve behandeling voor deze aandoening. Rond 1920 had Gonin de oftalmologische gemeenschap op overtuigende wijze duidelijk gemaakt dat het dichten van alle netvliesgaten de loslating in veel gevallen permanent kan herstellen.

Tractie vanuit het glasvocht werd echter niet verminderd door de methode van penetrerende thermocauterisatie, zoals ontwikkeld door Gonin. Het succespercentage van de RNLL behandeling zou in de jaren vijftig fors stijgen nadat Ernst Custodis had aangetoond dat de glasvochttractie efficiënt kon worden bestreden met de techniek van sclerale indentatie.

De door Robert Machemer ontworpen methode van pars plana vitrectomie stelde de oogchirurg vanaf de jaren zeventig in staat om het netvlies vanaf de glasvochtzijde te benaderen. Gebruik makend van de verdere vooruitgang van techniek en instrumentarium introduceerde Relja Zivojnovic in de jaren tachtig in het Oogziekenhuis te Rotterdam een erg ingrijpende, maar vaak succesvolle, operatiemethode voor de gecompliceerde gevallen van RNLL met uitgebreide proliferatieve vitreoretinopathie (PVR).

Ondanks vergaande verfijning van de technologie op gebied van onder meer microscoop, vitrectomie machines en randapparatuur, is het onduidelijk of de resultaten van de behandeling in de afgelopen 30 jaar significant verbeterd zijn. Momenteel zien we nog steeds bij ongeveer de helft van alle ogen, waar de macula betrokken is in de loslating, weinig of geen herstel van leeszicht. Bij 10 tot 40% van alle gevallen is er meer dan 1 interventie nodig en bij ongeveer 5% van alle ogen is de loslating onherstelbaar.

Bij gebrek aan een echte oplossing voor de teleurstellende functionele resultaten en het onvermogen om het optreden van PVR te voorkomen, is er in het afgelopen decennium een sterke trend waar te nemen naar een agressievere aanpak. Hierbij worden alle loslatingen behandeld met vitrectomie in combinatie met lensextractie (bij fake patiënten). Deze benadering, die paradoxaal genoeg minimaal invasief wordt genoemd, kent niet alleen een groot aantal mogelijke complicaties, maar heeft tot nu toe ook geen aantoonbaar betere resultaten opgeleverd.

In de afgelopen vijftien jaar zijn we daarom op zoek gegaan naar onderbelichte aspecten van RNLL met als doel het ontwikkelen van een chirurgische techniek die minder agressief is en beter anticipeert op de oorzaken van mislukking.

Afbraak van de bloed-oog barrière (B-O B) is een belangrijk fenomeen bij RNLL en uitgebreide chirurgische manipulatie vergroot dit probleem. Theoretische argumenten en empirische data suggereren dat verhoogde B-O B afbraak niet alleen nadelig is voor het functioneel herstel, maar bovendien de ontwikkeling van PVR stimuleert. Wij hebben aangetoond dat pre-operatieve subconjunctivale dexamethason toediening de B-O B afbraak, gemeten als flare in de voorste oogkamer, remt. Ook vonden wij dat het weglaten van intra-operatieve retinopexie niet alleen uitstekende anatomische resultaten geeft, maar ook de voorkamer flare vermindert en het herstel van het zicht bespoedigt.

Het fenomeen van persisterend subretinaal vocht, dat vaak voorkomt na overigens geslaagde operatie, kan aanleiding geven tot een vertraagd herstel van macula functie. Door patiënten te bestuderen met dit probleem, zijn we tot de hypothese gekomen dat er een verband bestaat tussen klinische presentatie, de samenstelling van subretinaal vocht en het persisteren van het vocht na de operatie. Factoren zoals jonge leeftijd, aanwezigheid van de natuurlijke lens en een aanliggend glasvocht, zorgen ervoor dat de RNLL slechts traag progressief verloopt. Dit gaat gepaard met een verandering in samenstelling van het vocht onder de retina, hetgeen de spontane resorptie vertraagt. Wij rapporteerden een relatie tussen een hoog gehalte van fotoreceptorcel debris in het vocht enerzijds en de aanwezigheid van vocht onder de macula bij postoperatief onderzoek met optisch coherentie tomografie anderzijds. Een aanpassing van onze operatietechniek, die we "subretinaal-vocht-lavage" hebben genoemd, voorkwam het fenomeen van persisterend vocht bij een reeks patiënten die zich presenteerden met hoog risico karakteristieken.

Wanneer een RNLL gecompliceerd is door PVR blijft het bereiken van een volledig anatomisch herstel vaak onzeker zelfs na multipele, vaak uitgebreide, operaties. De oorspronkelijke benadering, waarbij alle littekenmembranen zo volledig mogelijk worden gepeld, blijft de basis vormen voor een goed resultaat. Om de doelmatigheid van membraan pellen te vergroten en tegelijkertijd het chirurgische trauma van deze handeling te reduceren hebben we onderzoek gedaan naar kleurstoffen die de zichtbaarheid van epiretinale membranen verbeteren. In ex vivo experimenten toonden we aan dat trypaan blauw (TB) PVR membranen selectief aankleurt. Daarnaast bleek de toxiciteit van TB in een dierenmodel beperkt. Kleurstof geassisteerde epiretinale membranectomie behoort intussen tot de standaard technieken in de vitreoretinale chirurgie.

Wanneer tijdens de operatie de retina niet aanliggend gemaakt kan worden, ondanks optimale membranectomie, is het doorknippen van het netvlies (retinotomie) vaak de enige uitweg.
Omdat PVR op zich een fibrotische reactie is die ontstaat naar aanleiding van een scheur in het netvlies, beschouwen we de retinotomie als een belangrijk bijkomend trauma. In een poging om het operatietrauma te verkleinen hebben we de intra-operatieve verankering van de pas doorgeknipte netvliesrand door middel van laser, weggelaten. Hierdoor kan het op gang zijnde fibrotische proces weer tot rust komen, terwijl het centrale netvlies krimpt, zonder dat dit aanleiding hoeft te geven tot recidief loslating. Zodra het ziekte proces gestabiliseerd is, kan de netvliesrand vastgezet worden met laser, voordat de olie wordt verwijderd.

In de afgelopen 100 jaar heeft de behandeling van RNLL een enorme vooruitgang doorgemaakt. Om de overgebleven obstakels te kunnen overwinnen zouden we "minimaal invasieve chirurgie" moeten herdefiniëren, daarbij de cruciale aspecten van de aandoening aanpakken, zonder bijkomend iatrogene pathologie te veroorzaken. Tijdelijke suprachoroidale vulling als indentatie, optimaal gebruik maken van de effecten van immobilisatie en instant retinopexie verdienen daarbij verdere studie. Ontwikkelingen op het terrein van de farmacologische vitreolyse kunnen de basis vormen voor nieuwe preventieve en curatieve behandelstrategieën van glasvochttractie. Het identificeren van patiënten met verhoogd risico voor RNLL en PVR zal het mogelijk maken om onze interventies beter te sturen. Neuroprotectieve en regeneratieve middelen zullen ons helpen in ons streven naar een beter functioneel herstel.

De toekomst van RNLL therapie ziet er schitterend uit. Laten we ons doel niet uit het oog verliezen.

List of abbreviations

RPE	retinal pigment epithelium
RRD	rhegmatogenous retinal detachment
RD	retinal detachment
PVR	proliferative vitreoretinopathy
PFCL	perfluorocarbon liquid
PPV	pars plana vitrectomy
SB	scleral buckling
PVD	posterior vitreous detachment
SO	silicone oil
IOL	intraocular lens
AC	anterior chamber
ICSAC	intentional continuous shallowing of the anterior chamber
B-O B	blood-ocular barrier
ERM	epiretinal membrane
HSO	heavy silicone oil
TA	triamcinolone acetonide
TB	trypan blue
ICG	indocyanine green
IfCG	infracyanine green
PEG	polyethylene glycol
ILM	internal limiting membrane
BBG	brilliant blue green
OCT	optical coherence tomography
PSF	persistent of subretinal fluid
GAG	glycosaminoglycan
SRF	subretinal fluid

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Pivotal events, individuals and personal traits

‘87. Laziness. Vice or virtue? Favoring a 3 month summer holiday over a summer of study and entry exam to civil engineering guided me towards medical school.

’92. Luc Missotten. A great lecturer, triggered my interest in ophthalmology.

’94. Ahmed Abu El Asrar. Made me realize early on during my residency in Leuven that it is “normal”, “a duty”, to combine clinical work with research. Triggered my interest in retinal detachment surgery and proliferative vitreoretinopathy.

’94-present. Peter Stalmans. Differences in style and character notwithstanding, our relationship has always been highly amicable, inspiring and fruitful.

’94. Jan Worst. Witnessing his presentation on visualizing vitreous in vitro at a conference in Brussels made me want to become a “vitreous” surgeon.

’96-97. Magdy Nofal. Introduced me to the practice of evidence based medicine during my one year rotation at Torby Hospital, UK.

’96-97. Charley James. Observing him during my stay at Torbay Hosptial(UK) convinced me of the fact that a “surgeon’s factor” variable must be important, as his meticulousness in clinical examination and surgery clearly yielded better results.

’98- present. Eric Feron. Made my VR fellowship in Rotterdam possible. Great teacher and vitreo-retinal soulmate.

’98. Gerrit Melles. My first “buddy” in Rotterdam, genuine out-of-the-box thinker, introduced me to the use of vital dyes in ocular surgery and motivated me to investigate their potential in posterior segment surgery.

’99. Houdijn Beekhuis. Came up to me one day during my VR fellowship in Rotterdam to congratulate me on a diagnosis of an acanthamoeba keratitis, handing me a “green card” (motivating me to stay in Rotterdam).

’99. Peter Ringens and Diane Mertens. Supported my candidacy for staff membership in Rotterdam.

’99. Robert Machemer. Reading the text of his Jackson memorial lecture (’84, AJO) boosted my interest in the pathophysiology of rhegmatogenous retinal detachment.

’98-present. Jan van Meurs. His support over the past 16 years has been paramount. Always demanding high standards, and motivating me to do research and present the results at meetings. As I was trying to dodge my way out of a presentation at the NOG meeting in 2000, Jan would instruct me “you definitely should give a presentation, if need be, just present something about riding your bike to the hospital every day, but please do present”. He introduced me to the international vitreoretinal forum to which he is a major asset.

’99. Seerp Baarsma. Coming from my university hospital setting in Belgium, it was quite an experience to be welcomed to the Eye Hospital in Rotterdam as “equal“ by one so talented and capable.

’99-present. Koen van Overdam. Dear friend and colleague. Great help with the animal experiments in ’99. Multitalented, always ready to get involved in new projects (especially when a game of soccer is included).

’99. An exceptional fellowship with the surgical retina team at OZR (Diana Mertens, Ed Peperkamp, Jan van Meurs, Peter Ringens, Eric Feron). In retrospect it is hard to imagine that I was trained by these giants. I would really love to do it all over!

’99-present. David Wong. Genius and a great inspiration.

’04-present. Lisbeth van Aken. Made a crucial contribution by helping me to bridge the vast gap between clinical work and lab research.

’09-present. Pieter van den Biesen. Always critical about current practice patterns and, based on scrupulous study of his own clinical results, trying to modify his technique. A keen observer of other players in our field.

’12. Relja Zivojnovic. Opened up a world to me that I wish I had been part of: the pioneering days of vitreoretinal surgery.

’98-’14. Medical staff at the Rotterdam Eye Hospital. You guys truly constitute the best mix of professional expertise and social interaction, very difficult to replace.

’91-present. Running outdoors. An activity that allows me to access the more creative areas of my brain and experience inspirational thoughts.

’69-eternity. Mother Denise, father Herman and sister Christel: provided a safe home and carefree childhood. Thanks for the never-ending support and admiration, love always.

’91-eternity. My wife Annik, my children Arno, Victor and Frederik: the best thing that ever happened to me. You are always on my mind, you make every moment of my life more intense. Although our being together, the five of us in the same place at the same time (like in a car!), may not always be completely conflict free, my love and devotion is unstoppable.

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About the author

Marc Veckeneer (1969) received his medical degree from Leuven University (Belgium) in 1994. He performed his specialty training in ophthalmology at the Leuven University Hospital, Torbay Hospital (UK) and the Rotterdam Eye Hospital in the Netherlands. After a one-year fellowship, he joined the medical staff in Rotterdam as a vitreoretinal surgeon in 2000. Marc has combined a strong commitment to patient care and a fascination for complex retinal surgery (www.youtube.com/user/icare4retinasurgery) with a continued research focus. This has resulted in the publication of over 30 peer-reviewed articles in medical journals (www.ncbi.nlm.nih.gov/pubmed?term=veckeneer) as well as presentations at numerous national and international conferences.

As a member of the vitreoretinal surgery department at the Rotterdam Eye Hospital, Marc was deeply involved in the subspecialty training of many vitreoretinal surgery fellows from several countries, including the Netherlands, Belgium, Italy and Rwanda.

As part of his sabbatical leave during the fall of 2013, Marc participated in the establishment of a fully operational retinal surgery department at the Kabgayi Eye Unit in Rwanda. The Retina Repair Foundation (www.retinarepairfoundation.com) was set up in order to improve the availability of surgical retina care in developing countries.

After 15 years in the retina department in Rotterdam, Marc currently works in Middelheim Hospital as a partner in Antwerp Retina Associates.

He lives in Dordrecht, The Netherlands, with his wife Annik and his sons Arno, Victor and Frederik.

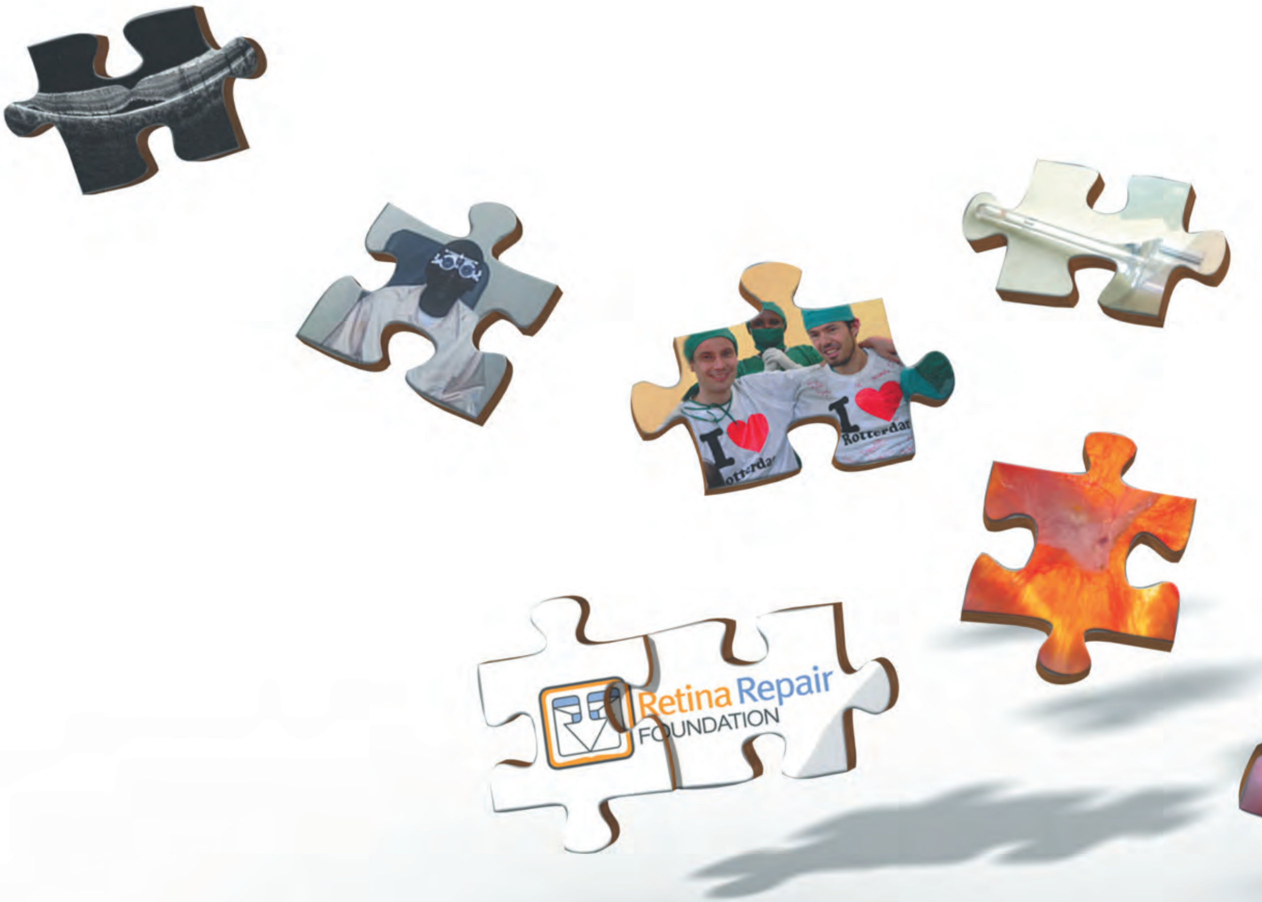
Marc Veckeneer (1969) behaalde zijn diploma geneeskunde aan de Katholieke Universiteit te Leuven in 1994. Tijdens zijn opleiding tot oogarts werkte hij aan de Universiteit te Leuven, in het Torbay Hospital (Engeland) en het Oogziekenhuis Rotterdam waar hij, na een fellowship van 1 jaar (1999), toetrad tot de maatschap als netvlieschirurg.

Marc combineerde (van bij het begin) zijn sterke betrokkenheid bij de patiëntenzorg en zijn fascinatie voor de complexe netvlieschirurgie (www.youtube.com/user/icare4retinasurgery) met een aanhoudende bijdrage aan research, hetgeen resulteerde in meer dan 30 publicaties in 'peer reviewed' medische tijdschriften (www.ncbi.nlm.nih.gov/pubmed?term=veckeneer) en voordrachten op vele nationale en internationale congressen.

Samen met collegae retinachirurgen van het Oogziekenhuis Rotterdam heeft hij in de afgelopen jaren talrijke oogartsen uit diverse landen, waaronder Nederland, België, Italië en Rwanda, opgeleid tot netvlieschirurg.
Tijdens een sabbatical in het najaar van 2013 was Marc nauw betrokken bij het opzetten van een volledig operationele afdeling voor netvlieschirurgie in de Kabgayi Eye Unit te Rwanda. Om de toegankelijkheid tot netvliesvlieschirurgie te vergroten werd de Retina Repair Foundation (www.retinarepairfoundation.com) opgericht.

Na 15 jaar actief te zijn geweest als netvlieschirurg in Rotterdam maakt Marc sinds januari 2014 deel uit van de netvliesspecialisten associatie van het Middelheim Ziekenhuis te Antwerpen.

Marc woont met zijn echtgenote Annik en zonen Arno, Victor en Frederik te Dordrecht, Nederland.



Adding Pieces to the Puzzle