# Age-Related Macular Degeneration Surgery

V.A.1.

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## Outline




**Keywords**

Exudative age-related macular degeneration • Vitrectomy • Submacular surgery • Macular translocation • Transplantation • Submacular hematoma surgery • Tissue plasminogen activator


**Electronic supplementary material** Supplementary material is available in the online version of this chapter at 10.1007/978-1-4939-1086-1_32. Videos can also be accessed at http://www.springerimages.com/videos/978-1-4939-1085-4.


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J. Sebag (ed.), *Vitreous: in Health and Disease*,
DOI 10.1007/978-1-4939-1086-1_32, 

**Key Concepts**

1. Submacular surgery was introduced in the early 1990s as innovative treatment for subfoveal neovascularization. The submacular surgery trial demonstrated no benefit for eyes with subfoveal neovascularization related to AMD and only modest benefit for selected eyes with hemorrhagic subfoveal CNV in AMD. Today this technique is used very rarely.
2. Submacular surgery is effective for large hematomas of recent onset with dramatic results in a minority. Recurrent hematomas are the most frequent complication.
3. Macular translocation was developed to support the fovea with healthier pigment epithelium and thus restore or maintain vision. Results today are very good, indeed superior to PDT in a prospective randomized trial. The introduction of anti-VEGF therapy restricts surgical intervention to a second-line treatment for eyes not responding to therapy.
4. Retinal pigment epithelial transplantation has been supplanted by anti-VEGF injections, but may in the future find renewed interest because of stem cell therapies and viral or nonviral transfection of retinal cells to enhance survival. Thus, the expertise gained in the initial experience could be transferred to future applications.

# I. Submacular Surgery

## A. History

### 1. Trauma and PVR

For many years subretinal surgery has been performed in eyes with retinal detachments related to proliferative vitreoretinopathy (PVR) and severe trauma [1, 2]. Several techniques have been developed to achieve relaxation of the retina and prevent complications like subretinal silicone oil or perfluorocarbon displacement, enlargement of the retinotomy into the retinal center, as well as choroidal hemorrhage. Routine vitrectomy instruments were used at this time, which made subretinal strand removal quite adventurous, and enlargement of the retinotomy was often created due to mechanical manipulations. Large retinectomies were feared and only more frequently used in the late 1980s when Zivonovic actually showed that the retina could be purposefully cut to remove subretinal tissue and relax the retina [3]. With the introduction of liquid perfluorocarbons in 1986 to facilitate treatment of retinal detachments arising from giant retinal tears, these manipulations became easier to execute in PVR and other surgeries [4].

### 2. Choroidal Neovascular Membranes in AMD

Removal of a choroidal neovascular membrane (CNV) together with extensive hemorrhage in AMD patients was first described in 1988 by Machemer and Steinhost [5], who considered this as a last attempt in hopeless cases. The removal of the subretinal membrane occurring in eyes with inflammatory disease, like presumed ocular histoplasmosis syndrome, was successfully performed by Thomas and Kaplan in 1991 [6]. Visual results were encouraging, and recurrences rare compared to other treatment modalities at that time. For several years subretinal techniques have been refined and special instrumentation designed allowing a much less traumatic and safer access to the subretinal space. Thus, submacular membrane removal in AMD patients evolved in an attempt to offer patients with subfoveal CNV an alternative treatment to observation or laser photocoagulation. In spite of this, visual results were generally disappointing when this surgery was performed in AMD patients.

## B. Instrumentation for Submacular Surgery

As already mentioned special instruments are mandatory to perform subretinal surgery in the least traumatic way. The most important is a set of 70–90° angled instruments designed by Matthew Thomas in 1991 [7] which have a longer tip to firmly grasp a subfoveal membrane from an extrafoveal location. The microsurgical set consists of a vertical and horizontal forceps as well as a vertical and horizontal scissors and spatulas of different lengths. A tapered fluid needle with a long silicone end tip reaching under the retina to aspirate fluid actively or passively is helpful as well as a silicone tip forceps for gentle manipulation of the retina if it needs to be grasped.

## C. Indications for Submacular Surgery

Current indications for subretinal surgery are large subretinal hematomas in AMD (below) and subretinal strands due to trauma and PVR, although most are managed by large retinectomies to allow direct access, better view, and more complete removal of this pathologic tissue [see chapter V.B.6. Retinectomy in recalcitrant retinal detachments]. Although small extrafoveal membranes are easy to remove and might do very well as far as visual acuity and recurrences are concerned, anti-VEGF injections, laser therapy, and PDT are the first treatments of choice for neovascularization of different origins, and surgery is considered as a last resort. Currently, subretinal surgery is a technique that augments the armamentarium of vitreous surgery allowing access and manipulations in the subretinal space to remove scar tissue, many types of CNV, and/or large hemorrhages. Whether subreti-

nal surgery for juxtafoveal membranes or juxtapapillary membranes is more successful than anti-VEGF treatment has never been compared. Still, there are small case series showing good results with subretinal membranectomy if the membrane itself has not yet grown under the fovea. However, due to the disappointing visual results of membrane excision in eyes with submacular involvement, anti-VEGF treatments are now preferentially administered in these patients [8]. On the other hand, knowledge about this technique might prove to become very useful for future treatment options in retinal degenerative disease amenable to subfoveal transplantation of retinal cells either as suspensions or sheets or retinal implants. Moreover, during the performance of this procedure for submacular CNV, there were important observations made regarding the frequency of an attached vitreous to the macula in these elderly patients. This led to studies that demonstrate a probable role for the vitreous in the pathophysiology of exudative AMD [see chapter III.G. Vitreous in age-related macular degeneration].

## D. Technique of Submacular Surgery

Submacular surgery starts with a standard pars plana vitrectomy. Sclerotomy locations are chosen to enable easy access to the submacular pathology by the more dexterous hand of the surgeon. Small incision, trocar-guided systems can be used for vitreous removal, but in order to introduce the angled subretinal instruments for submacular manipulation, at least one self-retaining cannula needs to be removed and the incision enlarged. After core vitrectomy, the posterior vitreous cortex is lifted and removed if a posterior vitreous detachment is not present. Although AMD patients are elderly patients and thus one would expect that the posterior vitreous cortex is already detached, in more than 80 % of cases with neovascular AMD, the posterior vitreous is still attached [9]. Complete removal of the posterior vitreous cortex is mandatory in these cases.

The retinotomy site is chosen to be as far away from the foveola as possible, yet still allows the surgeon to reach the membrane with the 90° angled subretinal instruments. The retinotomy is best done by using a 130° angled pick to perforate the neurosensory retina. Endodiathermy can be used to facilitate perforation and will additionally improve visibility of a small retinotomy during later manipulations. Subretinal bleeding should be avoided as much as possible. If this occurs, intraocular pressure can be raised temporarily or a small liquid perfluorocarbon bubble can be placed over the posterior retina to stop or avoid bleeding.

> *Of paramount importance is that subretinal manipulations should be done with slow movements in a rather soft eye to avoid incarceration of tissue. –Professor Susanne Binder, 2013*

A controlled retinal detachment is created to allow a working space for subretinal manipulation. With a bent cannula that is introduced through the retinotomy, balanced salt solution is slowly injected into the subretinal space. A bullous configuration of the retinal detachment should be avoided because it reduces visibility of the subsequent subretinal maneuvers. The cannula is also used to gently loosen connective tissue around the membrane and to test for adhesions. If some hemorrhage becomes visible under the membrane, gentle pressure can be applied on the membrane with the cannula for some time to achieve hemostasis. If an extrafoveal retinal angiomatous proliferation is present with a vascular connection to the sensory retina, it must be treated with careful diathermy and then cut with horizontal subretinal scissors. The membrane must be completely separated from the retina to avoid tearing and hole formation during removal, and its edges should be freed to avoid unnecessary removal of adjacent RPE. Then, subretinal forceps are introduced, and an edge of the membrane is grasped and slowly removed in a rather horizontal or oblique direction but never in a vertical direction. Again, if bleeding occurs while the tissue is extracted, pressure increases, and perfluorocarbon will help to stop it. Since larger diffuse bleedings can occur after the tissue is removed from the eye and the sclerotomy is open, it is wiser to hold the membrane in the vitreous cavity or let it fall back on the retina for some time until bleeding has ceased. Then the membrane can be grasped again and safely removed from the eye, while the posterior retina is covered with perfluorocarbon liquid. As there is much elasticity of tissue, quite large membranes can be removed via a small retinotomy, if it is performed slowly. However if larger fibrotic choroidal neovascular membranes and organized blood complexes should be removed with the cutter, the size of the retinotomy needs to be adapted and sealed either with diathermy before removal or with laser after removal when the retina is reattached. Again the vitreous is cleaned from blood and tissue particles to reduce postoperative inflammation. The peripheral retina is indented to look for possible tear formation or tissue incarceration that can easily occur close to the sclerotomy site during tissue removal. The perfluorocarbon liquid is removed, and the surgery is completed with fluid gas exchange. If a large fibrohemorrhagic complex had to be removed via a large retinectomy, a silicone oil tamponade is preferable.

In elderly patients with some cataract, vitrectomy is usually preceded by phacoemulsification of the lens in combination with a posterior chamber lens implant.

### 1. Complications of Submacular Surgery

As with all types of vitreous surgery, there is a small chance of endophthalmitis, retinal detachment, and retinal tear formation in about 2–5 % of cases. In phakic eyes, cataracts will develop in more than 80 % of patients over 50 years of age. Related to the submacular surgery and retinotomy is insufficient closure of the retinotomy or a higher incidence of hemorrhage postoperatively which might clear within 1–3 weeks. While small retinotomies usually close even if not treated with laser coagulation, large retinotomies require careful laser treatment and a sufficient internal tamponade to permanently close [10]. The most common complication

during membrane removal in AMD is recurrent choroidal neovascularization that occurs in up to 32 % of cases [7].

### E. Functional Results of Submacular Surgery

In younger patients with inflammatory neovascularization, the CNV is usually a classic type, i.e., well circumscribed (focal) and located anterior to the RPE, while in elderly patients with AMD, these membranes can be either classic, as described for younger patients, or occult, i.e., diffuse (non-focal) and located posterior to the RPE. Don Gass described classic membranes as type 2 membranes and the occult membranes as type 1 in his report about the rationale of subfoveal membrane excision [11]. In large studies of membrane excision in AMD patients, visual acuity improvement was reported between 0 and 33 % of patients [12–14]. This was much lower than the primary results in young patients with inflammatory disease, who attained postoperative visual acuity of 20/40 in 30–40 % [6]. The reason for this difference can be explained by two facts:

- Type one, occult, membranes located under the retinal pigment epithelium have worse outcomes because the overlying pigment epithelium is removed simultaneously during membrane excision leaving a larger defect of the RPE in comparison to type two classic membranes located anterior to the pigment epithelium where the membrane can be removed with much lesser mechanical damage to the RPE.
- In diffuse disease like AMD, the pigment epithelial defect created at surgery tends to enlarge over time, while in focal disease and young patients, the defect remains either stable or become smaller due to cell migration from its edges and a healthier Bruch's membrane/choriocapillaris complex than in elderly patients [15–17].

In a retrospective meta-analysis evaluating 26 different studies and a total of 647 cases of subretinal membrane excision in AMD patients, it was shown that improvement was achieved in about 33 %, but there was also deterioration in 27 %. Additionally, recurrence of CNV occurred in 25 % (0–55 %), which added to further visual loss in initially successful cases [18]. In a prospective multicenter study comparing submacular surgery with laser photocoagulation, the two treatment options were found to be equivalent. After 2 years, 65 % of laser-treated cases versus 50 % of surgically treated eyes had a visual acuity that was better than or no more than one line worse than baseline [19]. While in the early years of submacular surgery for AMD, small, classic membranes were removed surgically, but with the introduction of photodynamic therapy for small classic CNV this became the standard of care (later replaced by intravitreal anti-VEGF injections). Surgery was only performed for large occult hemorrhagic membranes with the worst prognosis [20].

## II. Macular Translocation in AMD

The basic concept of macular translocation is to improve vision in patients with subfoveal choroidal neovascularization by relocating the macula away from the neovascular complex so that it enables the macula to receive nourishment from a healthier underlying RPE and choroid. For macular displacement an iatrogenic retinal detachment is created either partially or totally, and the retina is reattached by a tamponade.

### A. History

The first who explored translocation of the retina experimentally was Linsey in 1983 [21]. In 1985 Tiedemann published their proposal for retinal translocation [22], and in 1993 Machemer and Steinhorst published their results in the first human surgical cases suffering from AMD [23]. Over the years the procedure has gone though multiple evolutionary iterations with major developments by Eckardt et al., Toth et al., and Tano et al. [24–26].

In 1996 translocation with partial retinotomy was described mainly to reduce surgical complications like PVR [27], and in 1998 de Juan invented a limited translocation technique combined with scleral infolding for smaller submacular membranes [28].

### B. Surgical Technique

#### 1. Limited Translocation

The original technique of limited translocation included primarily a crescent-shaped partial scleral resection which was subsequently followed by scleral infolding performed with 4–6 mattress sutures to reduce the complexity of the surgery [28]. A modified technique was to achieve scleral shortening by scleral outfolding with clips [29].

Essentially, the surgical procedure consists of four major steps:

1. Pars plana vitrectomy with posterior vitreous cortex removal
2. Iatrogenic retinal detachment
3. Scleral shortening
4. Partial fluid–air exchange

##### a. Scleral Infolding

In scleral infolding, rectus muscle traction sutures are placed first and 5–6 mattress sutures preplaced through partial-thickness sclera starting 2 mm behind the temporal rectus muscle insertion and reaching upwards to the superior rectus muscle. Then, a standard 3-port pars plana vitrectomy is performed. By slowly injecting balanced saline solution into the subretinal space via a 39 or 41 gauge needle, a retinal detachment is created from the optic nerve to the ora serrata in

the temporal 180° of the globe. Following this, the scleral mattress sutures are secured to shorten the sclera, and the surgery is completed with a partial fluid–air exchange. Postoperatively the patient is positioned to attain a shift of the central retina away from the choroidal neovascular membrane.

#### b. Outfolding Technique

In the outfolding technique a pars plana vitrectomy is performed, and a retinal detachment is created. Then, titanium clips are applied to the sclera 2–2.5 mm wide and 10 mm long between the temporal lateral muscle and the oblique superior muscle. A fluid–air exchange and positioning are performed in a similar way to the aforementioned infolding technique [30].

### 2. Full Macular Translocation (MTS 360)

In this surgery phakic eyes undergo cataract surgery with implantation of a posterior chamber intraocular lens at the beginning of the procedure. After complete pars plana vitrectomy including posterior vitreous cortex removal and peripheral vitreous shaving under scleral depression, the retina is detached completely via a peripherally placed retinotomy and subretinal fluid injection. Then the retina is cut circumferentially as anterior as possible, while posteriorly placed perfluorocarbon liquid can help to stabilize the retina during this procedure for a short while. The retina is then reflected after the perfluorocarbon liquid is removed, and the subretinal membranous complex, if present, is carefully removed. Then the retina is gently translocated (mostly upwards) to cover the fovea with healthier retina using perfluorocarbon liquid placed on the posterior pole. When enough displacement is achieved (35–45°), the retina is completely reattached with additional perfluorocarbon liquid, and endolaser is applied at the edges of the retina. The perfluorocarbon liquid is immediately replaced by a silicone oil tamponade. To prevent visual distortion, extraocular muscle surgery needs to be performed in these eyes either simultaneously [24] or a few weeks after translocation surgery [25].

## C. Complications

A large study cohort of 153 cases undergoing limited macular translocation showed at least one complication in 35 % of cases [31] including retinal tears, retinal detachments, macular holes, retinal folds affecting the fovea, neovascularization at the injection site, and subretinal and choroidal hemorrhages. The main problem with this surgery, however, was that the amount of translocation was small and insufficient for larger choroidal neovascular membranes, the amount of retinal shift was not predictable, and recurrences were frequent [32]. For MT360, retinal detachment was among the most common complications ranging from 7.8 % from reports by Cynthia Toth and her group [33] to 42.8 % in a comparative study between different techniques by Ohji and coworkers [34]. Recurrent neovascularization was the second most common complication ranging from 3.3 % after an extremely long observation period of 90 months in a German study [35] to 27.8 % with a 36-month observation time in the comparative Japanese study [34]. Other complications were cystoid macular edema, preretinal membrane formation, macular hole or tear, hypotony, and keratopathy [36]. As frequently observed with complex surgery, the highest complication rates were reported with earlier cases than later because the learning curve is long.

Because of the large rotation performed in MTS 360, binocular vision is often not recovered, and extraocular muscle surgery is needed [37].

## D. Functional Results

Functional assessment after limited macular translocation showed that after 6 months 48 % of patients gained two or more lines of visual acuity, and at 1 year 40 % gained two or more lines of visual acuity, while 31 % lost two or more lines [31, 32]. For MTS 360 the percentage of patients with improvement in distance visual acuity ranges between 43 and 66 % [24, 38], and gains of more than three lines range from 13 to 36 %. In contrast, the number of patients who were losing three or more lines after surgery is described between 6.6 and 56.2 % [24, 25]. Even more interesting, however, are the results in reading vision that have been reported to be larger than distance vision in two studies [39]. When compared with PDT in a prospective randomized trial, it was shown that macular translocation produced better visual results over 2-year observation [40].

# III. RPE Transplantation

## A. Rationale

The transplantation of RPE seemed to be a logical approach in restoring vision in patients with AMD. The disappointing visual results after membrane excision alone were explained by the mechanical removal of the RPE together with the membrane as well as the primary dysfunction of the RPE in these cases. Consequently, restoring RPE became an objective. Retinal rotation techniques (see above) have actually provided us with the proof of principle that this kind of *autotransplantation* can in fact restore useful vision and that reading visual acuity can be regained from an extrafoveal location. Thus, reconstituting central RPE structure and function via transplantation became a priority.

Following the path of successful experimental neuronal transplantation [41, 42], transplantation of retinal cells has been performed in animal and human eyes during the last

two decades. Despite evidence that transplantation was somewhat effective in animal models, efficacy in humans has been confounded by various difficulties. Indeed, successful transplantation requires the following:

- A viable source of cells
- A technique for safe delivery
- Survival of the transplanted cells within the host
- No transdifferentiation of the grafted cells from their normal RPE phenotype (i.e., ideally restoration of the retinal pigment epithelium monolayer)
- A restoration of normal retinal architecture
- A permanent stabilization or improvement in vision

## B. History

Options for patients with exudative AMD and subfoveal choroidal neovascularization were subretinal membrane excision only, laser treatment, or observation. With the introduction of photodynamic therapy for classic choroidal neovascularization and limited lesion sizes, submacular surgery was only indicated for large or mainly occult lesions complicated by bleeding. With the introduction of anti-VEGF therapy as the first line of treatment in exudative AMD, retinal cell therapy came almost to a halt. It is only with several years of experience with anti-VEGF treatment that we have learned that this treatment delays but does not prevent further visual loss because of retinal atrophy. Consequently, there is and will continue to be a resurgence of interest in cell transplantation.

### 1. Transplantation of Ocular Tissues

The first experiments detailing the behavior of transplanted neural tissue were performed in 1946 by Tansley, who transplanted embryonic eyes into rat brains [43]. Although the use of the anterior chamber as a tissue culture chamber to observe the behavior and growth of various transplanted tissues had already been reported previously, the first transplantation of fetal retina into the anterior chamber of maternal eyes in rats was performed in 1959 by Royo and Quay [44]. No further experiments were reported for more than 20 years.

### 2. Retinal Pigment Epithelial Transplantation

The concept of retinal pigment epithelial (RPE) transplantation evolved from the successful culturing of RPE from donor eyes by Flood et al. in 1980 [45]. In 1984 and 1985, cultured human retinal cells were transplanted in the eyes of monkeys, first by open sky techniques and later with closed eye methods by Gouras and others [46–48]. Finally, the therapeutic potential of RPE transplantation was demonstrated in the Royal College of Surgeons (RCS) rat model when radiolabeled RPE suspension grafts delivered through a bleb detachment were fully capable of phagocytosing host outer segments [49, 50]. The retinal atrophy that occurred in the RCS rat within 2 months after birth as a result of the inherited phagocytosis defect of the photoreceptor outer segment was therefore prevented [51–53].

The RPE is known to produce a variety of cytokines both *in vivo* and *in vitro* [54]. In addition to the expected rescue effects observed over areas with transplanted RPE cells, fine cellular processes extending from the transplanted RPE over long distances were observed with electron microscopy. This suggested that trophic factors secreted from the graft may be involved in rescue of the overlying retina as well [49]. It is well known that experimental debridement of Bruch's membrane in normal pigmented rabbits will lead to atrophy of the underlying choriocapillaris and the overlying neural retina [55, 56]. Interestingly, intravitreal administration of basic fibroblast growth factors (bFGF) in RCS rats also led to a transient effect of photoreceptor rescue, which therefore may support such a trophic factor interaction [57, 58].

### 3. RPE Transplantation in Human Eyes

RPE transplantation in humans was first performed by Peyman et al. in 1991 in two cases of terminal AMD [59]. Photoreceptor transplantation was attempted in human eyes in patients with retinitis pigmentosa by two groups: del Cerro and Das [60, 61]. Kaplan and his group treated two patients who were NLP preoperatively with outer retinal sheet transplants derived from adult cadaver eyes with no complications; however, no visual improvement was reported [62]. In 1994 Algvere and Gouras transplanted small patches as well as cell suspensions of previously cultured human fetal RPE into the foveal area after membrane excision [63]. Because of disappointing visual results, immune reaction to the homologous cells was considered as the main culprit in all the aforementioned experiments.

An interesting strategy to eliminate rejection has been the use of autografts of iris pigment epithelium (IPE) to replace defective RPE [64, 65]. Iris pigment epithelium cells have been used by groups in Japan and Germany [66, 67]. This concept is intriguing due to the ease by which the IPE can be harvested. The surgery can be performed in a one-step procedure or in two steps where iridectomy is performed in combination with cataract surgery and the IPE thereafter expanded in cell culture or transfected. Several investigators have shown the ability of IPE to phagocytose outer segments *in vitro* [68, 69]. However, when compared to the RPE, the IPE has been demonstrated to digest outer segments much more slowly and thus not as well as RPE [70]. It was thus reasonable to search for a safe way to harvest autologous RPE cells to transplant them subfoveally in eyes with subfoveal neovascularization related to AMD [71].

## C. Surgical Techniques

### 1. Cell Suspensions (See Video V.A.1-1)

The technique we used was experimentally tested [72] and then used in a pilot study in humans and in a subsequent trial

comparing membrane excision with and without RPE transplantation [73, 74]. The procedure is as follows:

- After pars plana vitrectomy and careful removal of the posterior vitreous cortex, a bleb retinal detachment is created nasally from the optic disc via a small retinotomy.
- With a special instrument the RPE is gently harvested and aspirated in a tube and a microsyringe over an area of approximately 4–5 disc diameters.
- While these cells are counted and centrifuged by a surgical assistant, the subfoveal choroidal neovascular membrane is removed by the surgeon via a second retinotomy created away from the fovea but close enough to the lesion to grasp it with subretinal forceps (see above).
- A perfluorocarbon liquid bubble is used to cover the posterior pole and prevent bleeding.
- Now the RPE cell suspension prepared by the assistant is slowly injected into the subretinal space via a small cannula connected to a tuberculin syringe with the perfluorocarbon liquid still in place to avoid reflux of cells into the vitreous.
- The retinotomies are sealed with endolaser photocoagulation.
- PFCL is aspirated after some minutes to allow cells to settle and the vitreous cleaned from cellular debris.
- The retinal periphery is inspected carefully for retinal tears or vitreous incarceration.
- A fluid–air exchange is performed.
- The sclerotomy wounds are closed.

Postoperatively, the patient is asked to maintain a supine position for 1 h to further allow the cells to settle in the subretinal space and is then turned into a prone position until the next day. Complications with cell suspension transplantation were rather low and mainly related to vitrectomy. In a pilot study and in a trial, we reported about 8.7 % retinal detachment, all treatable [73, 74]. No recurrence of CNV was observed during the observation period of 17 months but reached 5–8 % after 2 years.

While the suspension technique bears the advantages of being technically easy and has complication rates close to standard vitrectomy, it bears the disadvantage that the cells are irregularly distributed on a defective or diseased Bruch's membrane which makes their survival difficult. This limitation is being addressed by experiments that are underway to create artificial basal lamina to provide better survival of these cells by improving this *cell culture* milieu from its diseased environment and by approaches using artificial laminas rather than cell suspensions.

### 2. RPE/Bruch's Membrane/Choroid Patch

Another strategy using autologous material is the transplantation of a full-thickness RPE–choroidal patch or sheet taken from the periphery of the same eye to cover the foveal defect. The first who performed full-thickness RPE patch transplantation that was taken from adjacent areas of the CNV in nine patients was Bill Awylard 1998 to 1999. Unfortunately these flaps demonstrated sequestration after an observation period of 1–2 years [75], although some remaining functions were demonstrated by microperimetry [76]. As with retinal rotation, bleeding and inflammation need to be kept to a minimum to provide a basis for success with this surgery.

Over the following years full-thickness patch transplantation has gone some technical changes with large contributions by Jan van Meurs and Drs. Pertile and Parolini [77–79]. As with full retinal rotation surgery, phakic patients undergo cataract surgery with lens implantation at the beginning of surgery. The classic transplantation consists of the following steps:

- A complete 3-port pars plana vitrectomy including anterior vitrectomy and removal of the posterior vitreous cortex.
- A retinotomy temporal from the lesion is created, and the fibromembranous complex is carefully removed under perfluorocarbon liquid.
- An area for the patch is identified nasal to the optic disc or inferior to the vascular arcade.
- Diathermy and/or laser is performed at the borders of the transplant which was chosen as large as possible, but in general $4 \times 5$ mm.
- With horizontal scissors the full-thickness patch is cut 90 % with the overlying retina left as long as possible to prevent damage to the RPE with instruments. If bleeding occurs from the choroid during cutting, this must be managed immediately with diathermy and transient intraocular pressure rise; otherwise, all manipulations are performed in a soft eye.
- Now some fluid is injected into the subretinal space to allow easier access with the patch.
- After the patch is freed completely and the overlying retina removed, it is grasped carefully at the edge and slowly transferred into the subfoveal space.
- Now the anterior vitreous is excised and the vitreous filled with perfluorocarbon liquid anterior from the equator.
- Addition laser treatment is applied to the retinotomies.
- A direct perfluorocarbon liquid–silicone oil exchange is performed, and the sclerotomy wounds are closed.

A variation mainly performed by Drs. Pertile and others is the following:

- After vitrectomy, a 180° retinotomy is created in the temporal periphery of the fundus, and the retina is detached and flapped nasally.
- PFCL is used to hold the retina in place when the neovascular complex and blood are removed.
- Bleeding vessels are treated with diathermy.
- The patch is prepared under perfluorocarbon liquid in a similar way as with the classic technique and then gently translocated over the foveal defect.
- A perfluorocarbon liquid "rock and roll" technique is used to allow this. The subretinal perfluorocarbon liquid is gently removed and the retina unrolled with new perfluorocarbon liquid.

- Laser photocoagulation is applied at the edges of the retinotomy.
- A direct perfluorocarbon liquid–silicone oil exchange is performed.

This technique has the clear advantage that it minimizes bleeding and provides better access to the neovascular lesion which tends to be quite large to justify surgical intervention and easier preparation of the patch. Whether a residual film of perfluorocarbon liquid around the transplant might reduce cell function has never been separately evaluated.

Complications with patch transplants were higher than cell suspension techniques, especially with the occurrence of proliferative vitreo-retinopathy in up to 45 % [76–80]. As already pointed out with MTS 360, complication rates were lower in reports from those groups who performed the surgery for several years in higher numbers [81–83]. Figures V.A.1-1, V.A.1-2, V.A.1-3, V.A.1-4, V.A.1-5, V.A.1-6, V.A.1-7, V.A.1-8, V.A.1-9, V.A.1-10, V.A.1-11, and V.A.1-12 show two cases of RPE–choroid patch transplantation performed by Dr. Binder. Both are last eye patients. Nr 1 (Case 2) turned out to be less successful (Figures V.A.1-1, V.A.1-2, V.A.1-3, V.A.1-4, V.A.1-5, V.A.1-6, and V.A.1-7), and Nr 2 (case 5) was indeed a permanent success (Figures V.A.1-8, V.A.1-9, V.A.1-10, V.A.1-11, and V.A.1-12).

## D. Functional Results

While functional results in the pilot study of 14 cases with RPE suspensions were very promising since 57.5 % of cases gained two or more lines after 17 months of observation [73], later results were rather disappointing. When these experiments were started, PDT was not available, and patients with small foveal lesions were candidates for surgery. In the subsequent trial, however, patients who qualified for PDT were excluded from the surgery trial; thus, the patients who underwent surgery had larger lesions and more hemorrhage. In spite of that we saw a trend that was not statistically significant but suggested superiority in visual gain when cell suspension injection was compared with membrane removal alone. A significant difference, however, was observed in clinical tests like multifocal ERG and microperimetry [74]. Similar experiences have been reported also after iris pigment transplantation [67].

With patch transplantation significant improvement in distance and reading vision can be reached in a certain percentage of cases, but unfortunately due to the high number of complications, this advantage is lost (in a study). A mean gain of one line was described by Van Meurs and his group [83]. With the success of anti-VEGF therapy as first-line

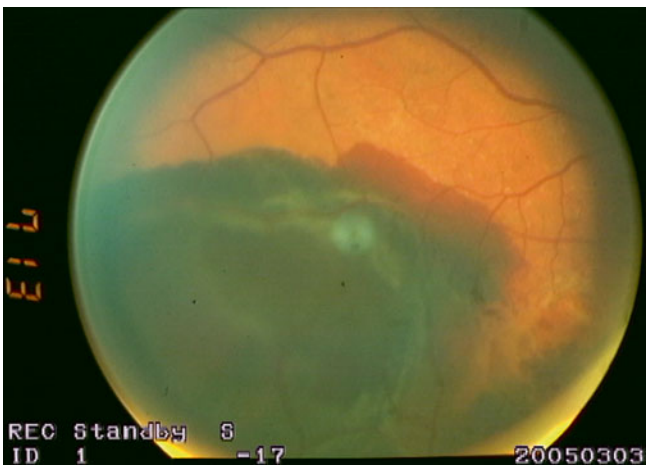


**Figure V.A.1-1** Case Nr 1. Full-thickness RPE/Bruch's membrane choroidal patch transplantation. Case 2. A 76-year-old male. VA on admission = hand motions. History: Status post PDT Jan 2005. Massive subretinal hemorrhage from CNV. Other eye: end-stage AMD, VA = hand motions

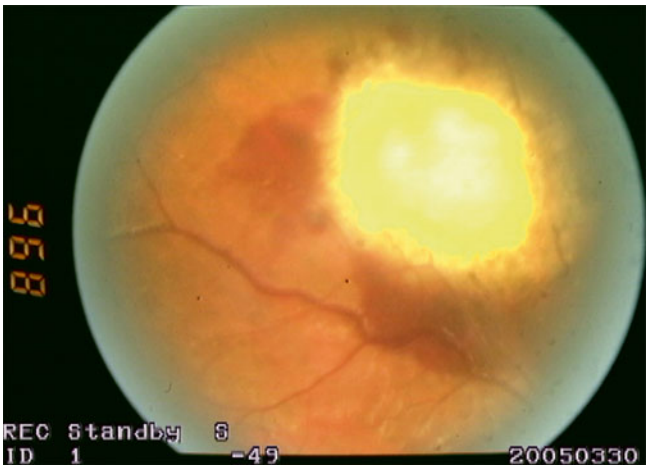


**Figure V.A.1-2** Area where patch has been removed in superior quadrant

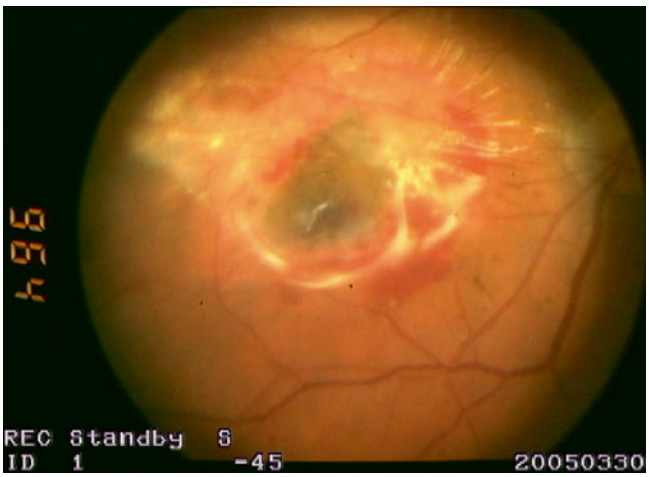


**Figure V.A.1-3** One month postoperatively. Well-centered transplant patch that is perfused on fluorescein angiography. VA = 0.05 (20/400)

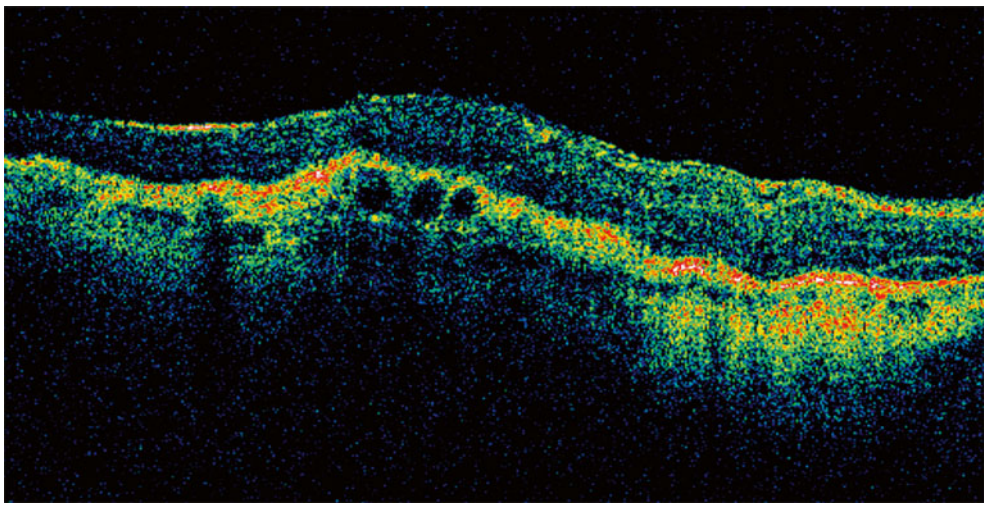

**Figure V.A.1-4** One month postoperatively. OCT of transplant shows cystic changes, intact retinal layers

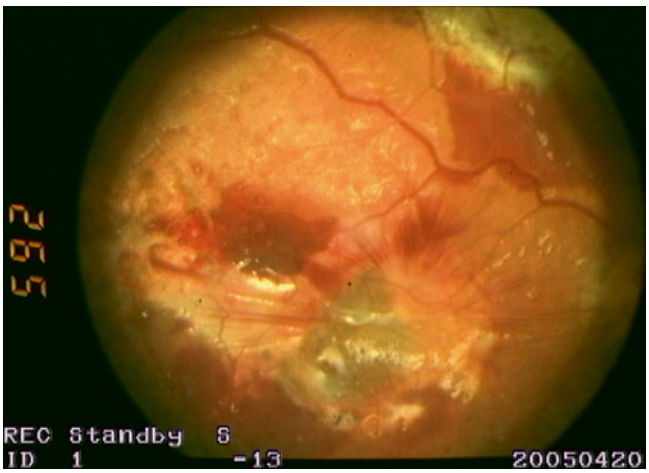


**Figure V.A.1-5** Three months postoperatively. Central patch appears smaller and folded. VA = 0.03 (20/400). Silicone oil removal planned

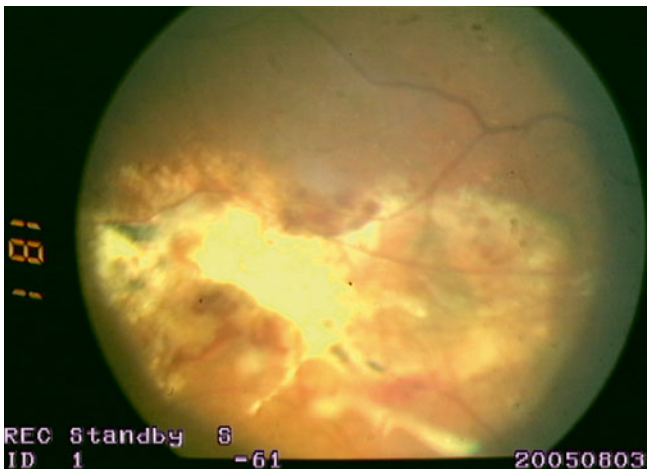


**Figure V.A.1-6** Two months postoperatively. Silicone was removed uneventfully. Patch has lost pigmentation. VA = 0.02 (20/800)

treatment in exudative AMD today, this surgery is only reserved as rescue therapy for isolated cases, but the experience that has been gained techniques that have been developed will be very useful for future therapies.

## IV. Surgical Management of Submacular Hematoma

### A. History

Submacular hematoma may be caused by a number of different conditions including exudative age-related macular degeneration and other causes of choroidal neovascular membrane, ruptured retinal macroaneurysm, complications of scleral buckle surgery, trauma, sickle cell disease, and retinal tears in primary rhegmatogenous retinal detachments. Systemic anticoagulants or antithrombotics may increase the risk of submacular hemorrhage for exudative age-related macular degeneration [84, 85], and long-term anticoagulation or antiplatelet therapy may be associated with larger subretinal hemorrhages [86]. A variant of choroidal neovascular membrane, polypoidal choroidal vasculopathy, is also at increased risk of submacular hemorrhage [87]. Polypoidal choroidal vasculopathy is a common presentation of age-related macular degeneration in Asian patients [88].

Glatt and Machemer observed that in a rabbit model subretinal blood irreversibly damaged the outer retina within 24 h [89]. They hypothesized three mechanisms for this damage: thick subretinal blood created a diffusion barrier between the retinal pigment epithelium choroid and the photoreceptors, contraction of the blood clot caused mechanical damage, and/or iron toxicity. Fibrin was associated with tearing of sheets of photoreceptor inner and outer segments by 7–14 days in a cat model [90] supporting the concept of early therapeutic intervention.

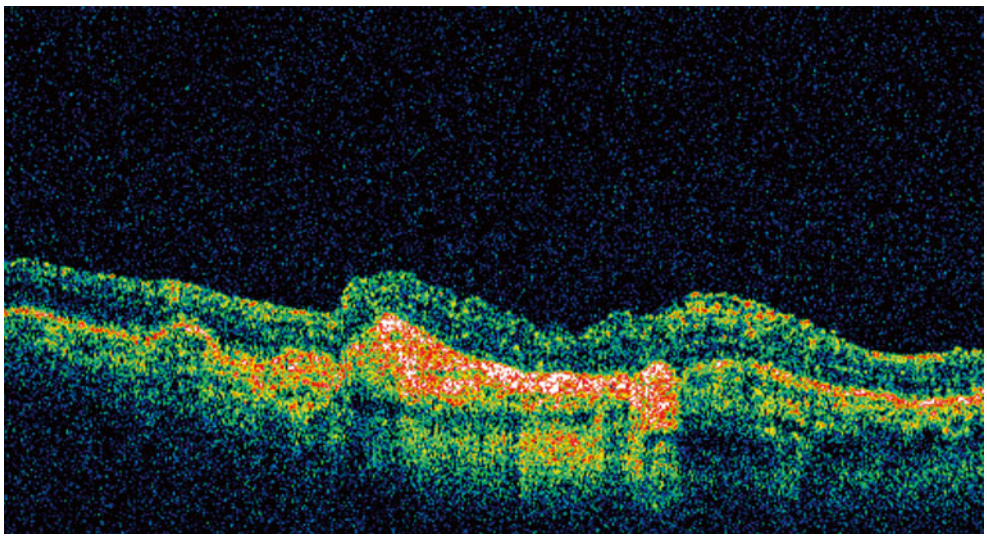

**Figure V.A.1-7** OCT 12 months postoperatively. Loss of intraretinal structure with fibrosis

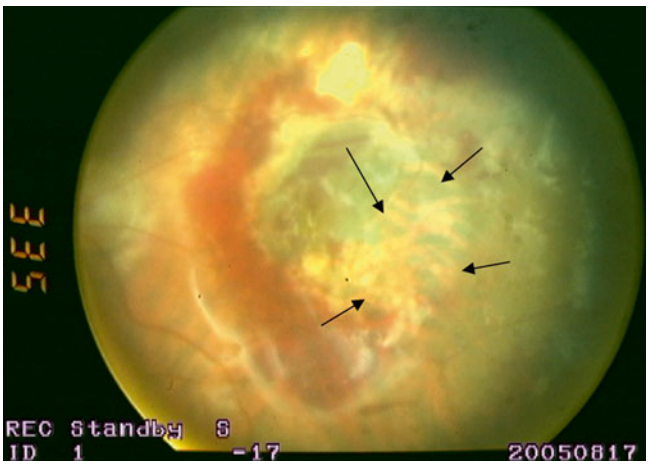


**Figure V.A.1-8** Case Nr 2: 71-year-old female. History. Massive hemorrhage after PDT. VA = LP+, other eye enucleated after trauma in childhood. One month after surgery residual hemorrhage nasally from transplant. Good centration of transplant but surrounding rim of atrophic area (*black arrows*)

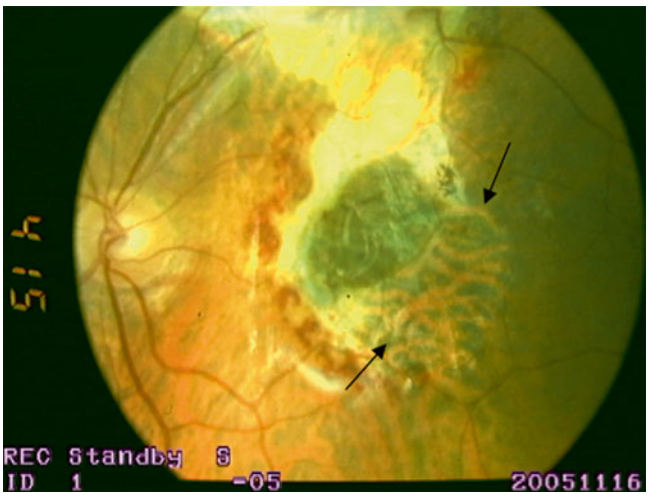


**Figure V.A.1-9** Six months postop. VA = 0.04 (20/400). Bridging between healthy pigment epithelium and transplant visible (*black arrows*)

The natural history of thick submacular hemorrhage in exudative macular degeneration is especially poor when compared to other etiologies without choroidal neovascular membranes such as choroidal rupture [91–93], At 36 months 44 % of eyes with subfoveal blood had lost six or more lines of vision, and size and height of the subretinal blood were important factors [94]. Preexisting abnormalities of the photoreceptor and retinal pigment epithelium in age-related macular degeneration may lower the threshold to damage from subretinal blood. The results of anti-VEGF monotherapy for submacular hemorrhage due to AMD may be better than the natural history, but good visual acuity is rarely attained [95–97].

## B. Surgery for Submacular Hematoma

### 1. History

In 1987 Hanscom and Diddie in California first reported the evacuation of subretinal hemorrhage of 1 week's duration from two patients (one with AMD and one with ruptured macroaneurysm) [98]. In 1988 de Juan and Machemer reported improvement in visual acuity after pars plana vitrectomy and removal of the subretinal clots in three of four patients with large submacular hemorrhage and AMD. Subsequent reports followed [93, 99, 100]. The surgeon waited for the submacular hemorrhage to hemolyze before performing pars plana vitrectomy. After pars plana

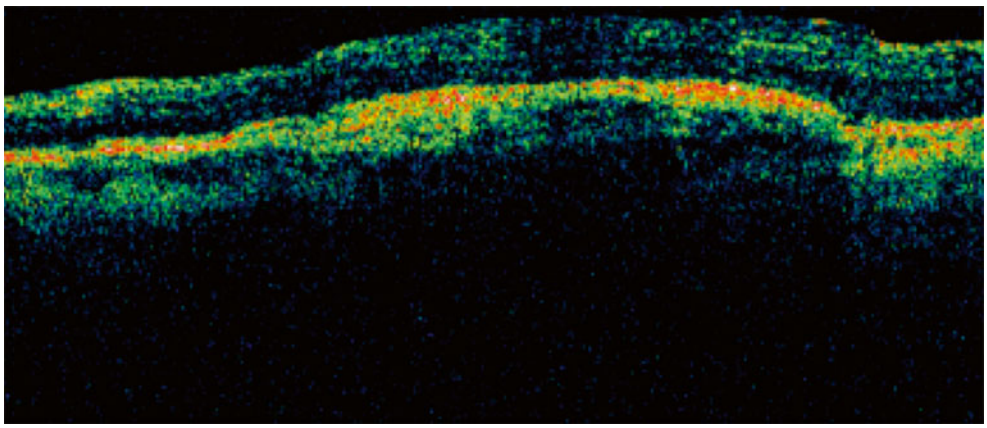

**Figure V.A.1-10** Six months postoperatively. OCT shows nice integration of patch as well as a connection with healthy RPE

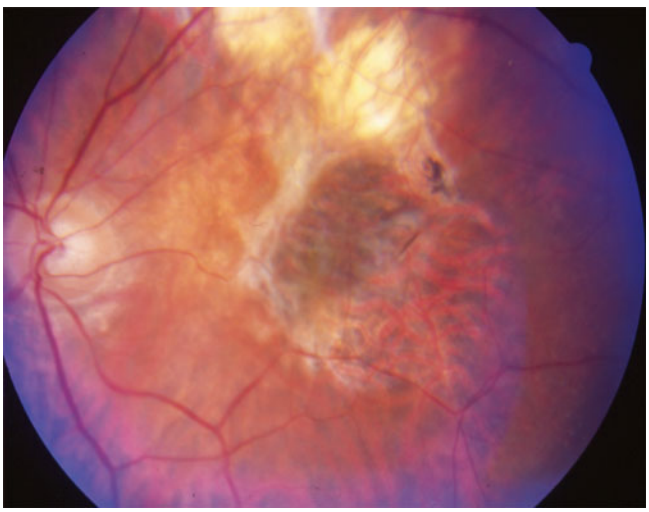

**Figure V.A.1-11** Twenty-eight months postoperatively. Same clinical situation. VA improved to 0.1 (20/200) Jaeger 7

vitrectomy, a retinotomy was made through which intraocular forceps were introduced to grasp the clot and extract it or liquefied blood was lavaged. There was significant discussion about the timing of the intervention. Intervention too early could physically shear and damage the photoreceptors. A delay in intervention could result in an irreversibly damaged sensory retina.

## 2. Tissue Plasminogen Activator

Tissue plasminogen activator (tPA) is a serine protease found on endothelial cells. It is an enzyme that catalyzes the conversion of plasminogen to plasmin, the major enzyme responsible for hemolysis [101]. It has advantages over other thrombolytic agents such as streptokinase and urokinase because its activity is enhanced in the presence of a fibrin clot, and a complex of fibrin, tissue plasminogen activator, and plasminogen is formed. These qualities make it fibrin specific and clot selective [102]. tPA available for clinical use is manufactured using recombinant biotechnology and includes alteplase, reteplase, and tenecteplase. Alteplase is FDA approved for treatment of myocardial infarction with ST elevation, acute ischemic stroke, acute massive pulmonary embolism, and central venous access devices. Reteplase is FDA approved for acute myocardial infarction. Tenecteplase is indicated for acute myocardial infarction.

The introduction of subretinal injection of tPA allowed immediate surgical intervention of submacular hemorrhage. A number of animal studies established the retina toxicity profiles for intravitreal injection of tPA injected in the rabbit [103, 104], and cat [105–107]. In the rabbit eye, toxicity was not seen in doses up to 50 microgram/0.1 cc. Above 50 µg/0.1 cc, large necrotic retinal holes, bullous retinal detachment, and marked retinal vessel attenuation were seen. In the human, four patients developed exudative retinal detachment followed by hyperpigmentation after intravitreal injection of 100 µg of tPA [108]. The retinal toxicity of tPA has been attributed to l-arginine in the vehicle which prevents the self-degradation of tPA [106]. Hemolytic effects have been seen clinically with doses as low as 6 µg (delivered in 0.1 cc volume) injected into the vitreous [109] and 6 µg/0.1 cc injected into the subretinal space [110]. Clinically doses between 5 and 50 µg per 0.1 cc are used.

Early worries that tPA could not enter the subretinal space because of its large size (molecular weight of over 70 kD) were seemingly confirmed when labeled tPA injected into the vitreous could not be detected in the subretinal space of rabbits [111]. Yet intravitreally injected albumin at 69 kD diffused through the retina within 1 h in rabbit eyes [112], and subretinal clots were hemolyzed by intravitreal tPA compared to saline injections in rabbits [113] and pigs [114]. These worries were quickly dispelled by its clinical effectiveness. Kimura et al. found hemolyzed blood at time of vitrectomy 12–36 h after intravitreal injection of tPA [109]. More recently this discrepancy between failure of tPA to penetrate the rabbit retina and its clinical utility has been

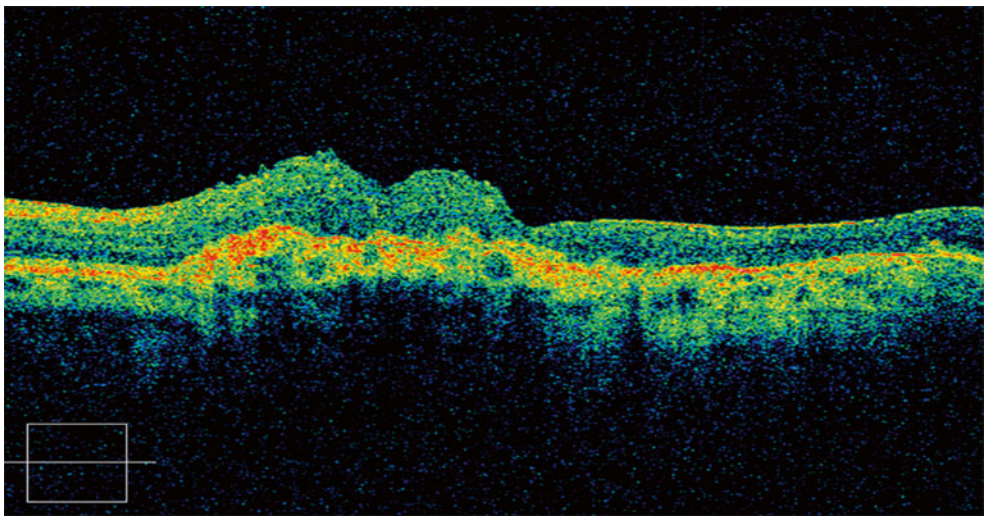

**Figure V.A.1-12** Twenty-eight months postoperatively. OCT shows well-integrated patch and development of foveal contour

attributed to species differences. A third-generation thrombolytic agent, a variation of native tPA produced by recombinant DNA technology with multiple point mutations, was shown to penetrate all layers of the pig eye after intravitreal injection [115]. Subretinal injection of tPA in experimental animal models enhanced the clearance of subretinal hemorrhage [104, 107], or facilitated surgical removal [116] and protected the outer retina.

## 3. Surgery

The use of subretinal tPA allowed earlier surgical intervention and the prospect of better visual outcome [110, 117–119]. Small gauge subretinal cannulas which had been developed to infuse fluid underneath the retina for excision of subfoveal choroidal neovascular membrane and macular translocation were adapted for injection of tPA (see Video V.A.1-2). Preoperative intravitreal injection of tPA also seemed to facilitate the removal of subretinal hemorrhage during pars plana vitrectomy a day later [109]. Perfluorocarbon liquids could be used to squeeze the liquefied blood into the vitreous cavity [110, 120]. To date published reports of surgical interventions for submacular hemorrhage have been retrospective, studying relatively few patients with variable follow-up and hemorrhage size. The SST Group B trial randomized 336 patients with relatively large hemorrhages (subfoveal choroidal neovascular lesions greater than 3.5 disc areas and composed of at least 50 % blood), but could not demonstrate any benefit to submacular surgery [121]. However, tPA was used in only 38 % of eyes, blood remained underneath the fovea in 62 % of eyes with greater than 4 disc areas of blood, and the duration of hemorrhage before intervention was not reported.

At the 1996 Vail Vitrectomy Meeting Heriot presented his success in displacing submacular hemorrhage from the fovea with intravitreal tPA, intravitreal gas injection, and facedown positioning [122]. Other reports followed [108, 123–125]. One hundred micrograms of tPA was injected through the pars plana in a volume of 0.1 cc. A day later gas was injected into the eye. The patient was positioned in a prone position to localize the gas bubble to the macula to displace the hemolyzed blood. This captured the imagination of retinal surgeons around the world. There was discussion about how long to wait after tPA injection before gas should be injected. Submacular hemorrhage could be displaced even without tPA [126]. Surgeons soon adapted Heriot's idea of displacing submacular hemorrhage to the surgical management of this problem [127]. Eighty-seven percent of eyes had no subfoveal blood after this technique with 2 line visual acuity improvement in 59 % of eyes [128]. The risk of retinotomy-related complications was avoided. Direct injection of tPA into the subretinal space appeared to be more efficacious and predictable than intravitreal tPA.

### a. Technique

The author (LPC) uses the following technique:

- Tissue plasminogen activator at a concentration of 25 µg/0.1 cc is prepared in the pharmacy and delivered to the operating room. The tPA is transferred to a 3 cc Luer-Lock syringe on the surgical field.
- A 39 or 41 gauge subretinal cannula is connected to the 3 cc syringe with a small length of intravenous tubing. This isolates movement at the syringe from inadvertently displacing the tip of the subretinal cannula at the time of tPA injection. All air in the tubing and cannula is carefully removed.
- After pars plana vitrectomy, the subretinal cannula is advanced to the surface of the retina until the choroid focally whitens. The view of a 68 diopter macula panoramic contact lens (Advanced Visual Instruments, Inc., New York, New York) provides both magnified detail as well as an arcade to arcade view of the macula.

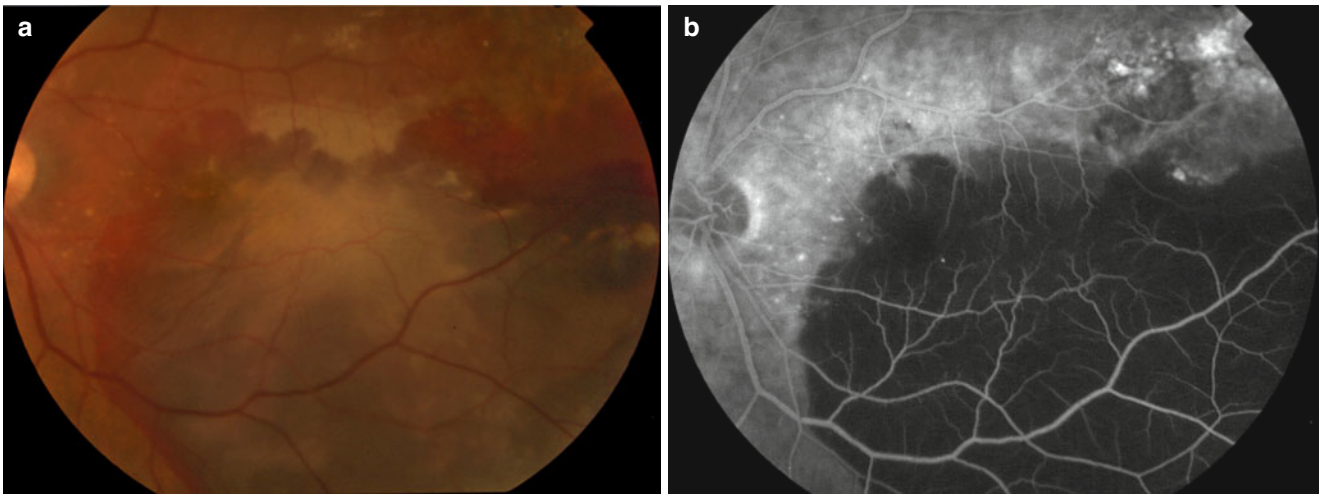


**Figure V.A.1-13** (**a**) Preoperative photograph of the left eye in a 77-year-old man with exudative age-related macular degeneration and submacular hemorrhage lowering visual acuity to count fingers (Courtesy of J. Sebag, MD; VMR Institute for Vitreous Macula Retina). (**b**) Preoperative fluorescein angiography of the same eye as in figure (a) demonstrating profound blocked fluorescence by the submacular hemorrhage (Courtesy of J. Sebag, MD; VMR Institute for Vitreous Macula Retina)

- The surgical assistant depresses the plunger on the syringe to inject the tPA into the subretinal space. These injections are made at the borders of the submacular hemorrhage and not over the clot itself. Injections made directly over the clot may result in failure at the retinotomy site from clot contraction or proliferation stimulated by the clot.
- Multiple injections are usually necessary to bathe the blood clot. The optic nerve limits the subretinal tPA from migrating to the nasal side.
- The induced detachment of the retina should be limited to the posterior pole just outside the temporal vascular arcades. Induction of retinal detachment beyond the equator increases the risk of postoperative rhegmatogenous retinal detachment.
- After subretinal tPA injection a small air bubble is injected into the subretinal space. This augments the displacement of the subfoveal blood to the periphery [129].
- In the recovery room, the patient is positioned supine for 1 h before positioning the head erect for 24 h.

Intraocular gas is not necessary to displace the blood or to tamponade the small retinotomies made by the 39 or 41 gauge subretinal cannulas. Therefore, I do not put any gas into the eye. Should gas be injected, then the head is conventionally positioned face down. Stopa et al. concluded that the head erect positioning is preferential to prone positioning because this maximizes the force of gravity force parallel to the subretinal space [130]. Foster and Chou demonstrated that a partial gas bubble has no buoyant force at the top in a vessel with gas in the upper portion and liquid in the lower portion [131]. This also favors head erect positioning without an intraocular gas bubble in the immediate postoperative period. The retina is usually completely attached after 24 h. This means that submacular hemorrhage is again locked into place after 24 h, and further head erect positioning beyond this time is not useful. The submacular hemorrhage is most often displaced to just beyond the inferotemporal arcade and is a function of the volume of tPA injected into the subretinal space (Figures V.A.1-13 and V.A.1-14).

### b. Complications

Complications include spontaneous rupture at the fovea with release of subretinal hemorrhage through the fovea during tPA injection, postoperative rhegmatogenous retinal detachment, inadequate displacement of hemorrhage, and breakthrough of submacular hemorrhage into the vitreous cavity. The fovea is the thinnest point of the sensory retina and therefore prone to spontaneous rupture. Despite this occurrence, the visual outcome remains good similar to successful macular hole repair. As mentioned, creation of retinal detachment beyond the equator increases the risk of rhegmatogenous retinal detachment. The subretinal blood can stimulate the development of proliferative vitreo-retinopathy. Inadequate displacement of hemorrhage may necessitate a repeat procedure to displace the remaining hemorrhage. Recurrent submacular hemorrhage is rarely seen after successful displacement of submacular hemorrhage secondary to exudative age-related macular degeneration. A definitive choroidal neovascular membrane is often not identifiable by fluorescein angiography.

Massive submacular hemorrhages for which displacement is ineffective are best managed with subretinal tPA and 360 retinotomy techniques. These techniques were described in the seminal report by Machemer and Steinhorst describing this approach in three eyes with severe and recent massive submacular hemorrhage [23] [see section II. Macular translocation in AMD].

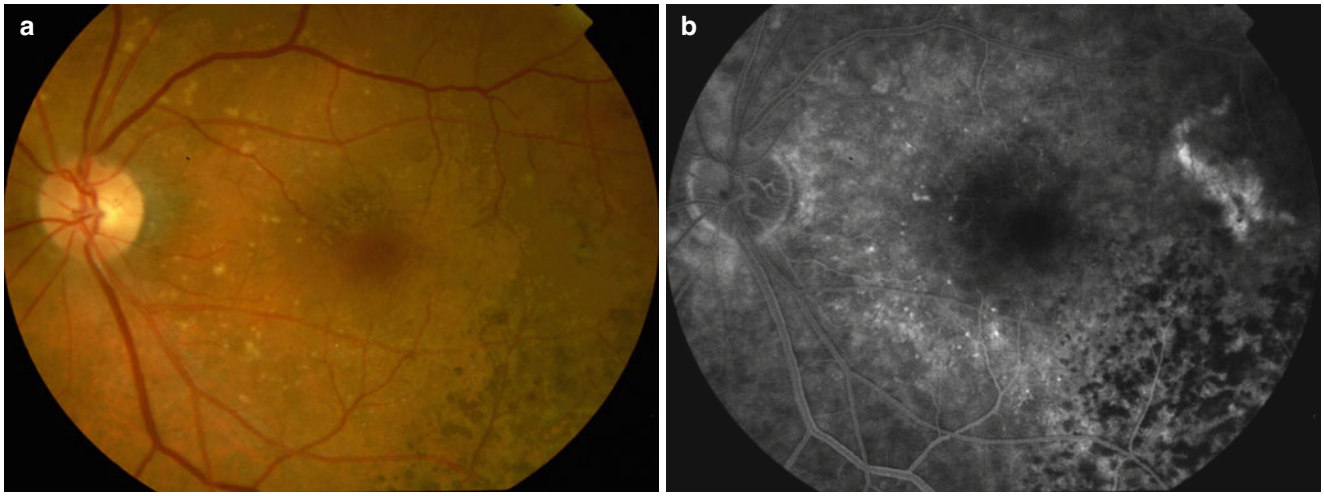


**Figure V.A.1-14** (**a**) Postoperative photograph of the same eye as in Figure V.A.1-13 with successfully displaced submacular hemorrhage by vitrectomy with submacular tPA injection and perfluoropropane vitreous substitute. Drusen is noted nasally and RPE changes are seen inferotemporally. Visual acuity improved to 20/30 (0.67) [Courtesy of J. Sebag, MD; VMR Institute for Vitreous Macula Retina]. (**b**) Postoperative fluorescein angiogram of the same eye as in figure (a) demonstrating that the source of the submacular hemorrhage was choroidal neovascularization in the distal temporal macula (Courtesy of J. Sebag, MD; VMR Institute for Vitreous Macula Retina)

**Abbreviations**

| | |
|---|---|
| AMD | Age-related macular degeneration |
| bFGF | Basic fibroblast growth factor |
| CC | Cubic centimeter |
| CNV | Choroidal neovascularization |
| DNA | Deoxyribonucleic acid |
| ERG | Electroretinography |
| FDA | Food and Drug Administration |
| IPE | Iris pigment epithelium |
| kD | Kilodalton |
| MTS 360 | Full macular translocation |
| NLP | No light perception |
| PDT | Photodynamic therapy |
| PFCL | Perfluorocarbon liquids |
| PVR | Proliferative vitreo-retinopathy |
| RCS | Royal College of Surgeons |
| RPE | Retinal pigment epithelium |
| SST | Submacular Surgery Trial |
| t-PA | Tissue plasminogen activator |
| VEGF | Vascular endothelial growth factor |

## References


1. Machemer R. Surgical approaches to subretinal strands. Am J Ophthalmol. 1980;90:81–5.
2. Lewis H, Aarberg TM, Abrams GW. Subretinal membranes in proliferative vitreoretinopathy. Ophthalmology. 1989;96:1403–14.
3. Zivonovic R. Silicone oil in vitreoretinal surgery. Dordrecht, 1987, Martinus/Nijhoff/DW Junk.
4. Chang S, Lincoff G, Zimmerman NJ. Giant retinal tears: surgical technique and results using perfluorocarbon liquids. Arch Ophthalmol. 1989;107:761–6.
5. de Juan Jr E, Machemer R. Vitreous surgery for haemorrhagic and fibrous complications of age-related macular degeneration. Am J Ophthalmol. 1988;105:25–9.
6. Thomas MA, Kaplan HJ. Surgical removal of subfoveal neovascularisation in the presumed ocular histoplasmosis syndrome. Am J Ophthalmol. 1991;111:1–7.
7. Thomas MA, Grand MG, Williams DF. Surgical management of subfoveal choroidal neovascularisation. Ophthalmology. 1992;99:952–68.
8. Binder S. Surgical treatment of peripapillary choroidal neovascularisation. Br J Ophthalmol. 2007;91:990–1. Editorial.
9. Krebs I, Brannath W, Glittenberg C, Zeiler F, Sebag J, Binder S. Posterior vitreomacular adhesion: a potential risk factor for exudative age-related macular degeneration? Am J Ophthalmol. 2007;144(5):741–6.
10. Bressler NM, Bressler SB, Childs AL, et al. Surgery for hemorrhagic choroidal neovascular lesion of age-related macular degeneration: ophthalmic findings: sst report No 13. Ophthalmology. 2004;111(11):1993–2006.
11. Gass JDM. Biomicroscopic and histopathologic considerations regarding the feasibility of surgical excision of subretinal neovascular membranes. Am J Ophthalmol. 1994;118:285–98.
12. Lambert HM, Capone Jr A, Aaberg T. Surgical excision of subfoveal neovascular membranes in age-related macular degeneration. Am J Ophthalmol. 1992;113:257–62.
13. Berger AS, Kaplan HJ. Clinical experience with the surgical removal of subfoveal neovascular membranes: short term postoperative results. Ophthalmology. 1992;99:969–76.
14. Thomas MA, Dickinson JD, Melberg NS, et al. Visual results after surgical removal of subfoveal neovascular membranes. Ophthalmology. 1994;101:1384–96.
15. Scheider A, Gündisch O, Kampik A. Surgical extraction of subfoveal new vessels and submacular haemorrhage in AMD. Results of a prospective study. Graefes Arch Clin Exp Ophthalmol. 1998;237:10–5.
16. Nasir MA, Sugino I, Zarbin MA. Decreased choriocapillaris perfusion following surgical excision of choroidal neovascular membranes in age-related macular degeneration. Br J Ophthalmol. 1997;81:481–9.
17. Rabenlehner D, Stanzel BV, Krebs I, Binder S, Goll A. Reduction of iatrogenic RPE lesions in AMD patients: evidence for wound healing? Graefes Arch Clin Exp Ophthalmol. 2008;246(3):345–5.

18. Falkner CI, Leitich H, Frommelt F, Bauer P. Binder S The end of submacular surgery for age-related macular degeneration? A meta-analysis. Graefes Arch Clin Exp Ophthalmol. 2007;245(4): 490–501.
19. Bressler NM, et al. Submacular Surgery Trials Pilot Study Investigators. Submacular surgery trials randomized pilot trial of laser photocoagulation versus surgery for recurrent choroidal neovascularisation secondary to age-related macular degeneration: I. Ophthalmic outcomes. Submacular surgery trials pilot study report NR 1. Am J Ophthalmol. 2000;130:387–409.
20. Schachat AP. Should we recommend vitreous surgery for patients with choroidal neovascularisation? Arch Ophthalmol. 1994;112: 459–61.
21. Lindey P, Finkelstein D, D'anna S. Experimental retinal translocation. Invest Ophthalmol Vis Sci. 1983;24:5242.
22. Tiedeman JS, de Juan JE, Machemer R, et al. Surgical rotation of the macula. Invest Ophthalmol Vis Sci. 1985;26:559.
23. Machemer R, Steinhorst UH. Retinal separation, retinotomy and macular relocation.II A surgical approach for age-related macular degeneration. Graefes Arch Clin Exp Ophthalmol. 1993;231:635–41.
24. Eckardt C, Eckardt U, Conrad HG. Macular rotation with and without counterrotation of the globe in patients with age-related macular degeneration. Graefes Arch Clin Exp Ophthalmol. 1999; 237:313–25.
25. Toths CA, Freedman SF. Macular translocation with 360 degree peripheral retinectomy impact of technique and surgical experience on visual outcomes. Retina. 2001;21:293–303.
26. Tano Y. Pathologic myopia. Where are we now? Am J Ophthalmol. 2002;134:645–60.
27. Ninimya Y, Lewis JM, Hasegawa T, et al. Retinotomy and foveal translocation for surgical management of subfoveal choroidal neovascular membranes. Am J Ophthalmol. 1996;122:613–21.
28. De Juan Jr E, Loewenstein A, Bressler NM, et al. Translocation of the retina for management of subfoveal choroidal neovascularisation. II: a preliminary report in humans. Am J Ophthalmol. 1998;128:635–46.
29. Lewis H. Macular translocation with chorioscleral outfolding: a pilot clinical study. Am J Ophthalmol. 2001;132:156–63.
30. Kamei M, Tano Y. Limited macular translocation. In: Alfaro V, Ligett P, Mieler WF, Qirioz Mercado H, Jager RD, Tano Y, editors. Age-related macular degeneration. A comprehensive textbook. Philadelphia: Lippincott Williams + Wilkins; 2006.
31. Fujii GY, Pieramici DJ, Humajun MS, et al. Complications associated with limited macular translocation. Am J Ophthalmol. 2000; 130:751–62.
32. Fujii GY, de Juan Jr E, Pieramici DJ. Inferior limited macular translocation for subfoveal choroidal neovascularisation secondary to age-related macular degeneration: 1 year visual outcome and recurrence report. Am J Ophthalmol. 2002;34:69–74.
33. Mruthyunjaja P, Stinnet SS, Toth CA. Change in visual function after macular translocation surgery with 360 degree peripheral retinectomy for neovascular age-related macular degeneration. Ophthalmology. 2004;111(9):1715–24.
34. Ohji M, Fujicado T, Kusaka S, et al. Comparison of three techniques of foveal translocation in patients with subfoveal choroidal neovascularisation resulting from age-related macular degeneration. Am J Ophthalmol. 2001;132:88–96.
35. Aisenbrey S, Lafout BA, Szurman P, et al. Macular translocation with 360 degree retinotomy for exudative age-related macular degeneration. Arch Ophthalmol. 2002;120:451–9.
36. Ehlers JP, Toth CA. Macular translocation. In: Retina. 5th ed. Ryan SJ. Wilkinson CP, Wiedemann P, editors. Surgical retina, vol. 3. 1996–2009.
37. Fricke J, Neugebauer A, Nobis H, et al. Counterrotation of the globe in macular translocation. Graefes Arch Clin Exp Ophthalmol. 2000;238:664–8.
38. Pertile G, Claes C. Macular translocation with 360 degree retinectomy for management of age-related macular degeneration. Am J Ophthalmol. 2002;134:560–5.
39. Lai JC, Lapolice DJ, Stinnett SS. Visual outcome following macular translocation with 360-degree peripheral retinectomy. Arch Ophthalmol. 2002;120:1317–24.
40. Luke M, Ziemsen F, Völker M, et al. Full macular translocation (FMT) versus photodynamic therapy (PDT) with verteporfin in the treatment of neovascular age-related macular degeneration: 2 year results of a prospective, controlled randomized pilot trial (FMT-PDT). Graefes Arch Clin Exp Ophthalmol. 2009;247: 745–54.
41. Björklund A, Stenevi U. Growth of central catecholamine neurons into smooth muscle grafts in the rat mesencephalon. Brain Res. 1971;31(1):1–20.
42. Widner H, Rhencrona S. Transplantation and surgical treatment of parkinsonian syndromes. Curr Opin Neurol Neurosurg. 1993;6: 344–9.
43. Tansley K. The development of the rat eye in graft. J Exp Biol. 1946;22:221–3.
44. Royo PE, Quay WB. Retinal transplantation from fetal to maternal mammalian eye. Growth. 1959;23:313–36.
45. Flood MT, Gouras P, Kjeldbye H. Growth characteristics and ultrastructure of human retinal pigment epithelium in vitro. Invest Ophthalmol Vis Sci. 1980;19(11):1309–20.
46. Gouras P, Flood MT, Kjeldbye H, et al. Transplantation of cultured human retinal pigment epithelium to Bruch's membrane of the owl monkeys eye. Curr Eye Res. 1985;4:253–65.
47. Lopez R, Gouras P, Brittis M, et al. Transplantation of cultured rabbit retinal epithelium to rabbit retina using a closed eye method. Invest Ophthalmol Vis Sci. 1987;28:1131–7.
48. Li LX, Turner JE. Inherited retinal dystrophy in the RSC rat prevention of photoreceptor degeneration by pigment epithelial cell transplantation. Exp Eye Res. 1988;47:911–7.
49. Gouras P. Transplantation of retinal pigment epithelium. In: Marmor M, Wolfensberger TH, editor. The retinal pigment epithelium, vol. 25. Oxford University Press, Oxford, England; 1998. p. 492–507.
50. Das SR, Bhardwaj N, Gouras P. Synthesis of retinoids by human retinal epithelium and transfer to rod outer segments. Biochem J. 1990;268:201–6.
51. Gouras P, Lopez R, Brittis M, et al. Transplantation of cultured retinal epithelium. In: Agarth E, Ehinger B, editors. Retinal signals system, degenerations and transplants. Amsterdam: Elsevier; 1986. p. 271–86.
52. Repucci V, Goluboff E, Wapner F, et al. Retinal pigment epithelium transplantation in the RCS rat. Invest Opthalmol Vis Sci. 1988;29 (ARVO) suppl 144.
53. Bourne M, Campell D, Tansley K. Hereditary degeneration of the rat retina. Br J Ophthalmol. 1938;22:613–23.
54. Mullen RJ, La Vail MM. Inherited retinal dystrophy: primary defect in retinal pigment epithelium determined with chimeric rats. Science. 1976;192:799–801.
55. Heron WL, et al. Retinal dystrophy in the rat. A pigment epithelial disease. Invest Ophthalmol Vis Sci. 1969;8:595–604.
56. Whiteley SJ, Lichfield TM, Tyers P, et al. Retinal pigment epithelium transplanted to the subretinal space improves the papillary light reflex in RCS rats. Invest Ophthalmol Vis Sci. 1995;36(4):212–9.
57. Factorovich EG, Steinberg RH, Tasumura D, et al. Photoreceptor degeneration in inherited retinal dystrophy delayed by basic fibroblast growth factor. Nature. 1990;347:83–6.
58. Perry J, Du J, Kieldbye H, et al. The effects of bFGF on RSC rat eyes. Curr Eye Res. 1995;14:585–92.
59. Peyman GA, Blinder KJ, Paris KJ, et al. A technique for retinal pigment epithelial transplantation for age related macular degeneration secondary to extensive subfoveal scarring. Ophthalmic Surg. 1991;22:102–8.

60. del Cerro M, Das T, Reddy VI, et al. Human fetal neural cell transplantation in retinitis pigmentosa. Vision Research. 1995;35, suppl 140 (abstract).
61. Das T, del Cerro M, Jalali S, et al. The transplantation of human fetal neuroretinal cells in advanced retinitis pigmentosa: results od a long term safety study. Exp Neurol. 1999;157:58–68.
62. Kaplan HJ, Tezel TH, Berger AS, et al. Human photoreceptor transplantation in retinitis pigmentosa; a safety study. Arch Opthalmol. 1997;115:1168–72.
63. Algvere PV, Berglin L, Gouras P, et al. Transplantation of fetal retinal pigment epithelium in age-related macular degeneration with subfoveal neovascularisation. Graefes Arch Clin Exp Ophthalmol. 1994;232:707–16.
64. Rezai KA, Kohen L, Wiedemann P, et al. Iris pigment epithelium transplantation. Graefes Arch Clin Exp Ophthalmol. 1997;235(9): 558–62.
65. Gelance M, Meneses P, Rosenfeld MR, et al. Long-term results of autologous transplantation of iris pigmented epithelial cells into the subretinal space. Invest Ophthalmol Vis Sci. 1997;38(4):334–42.
66. Tamai M, Abe T, Tomita H, et al. Autologous iris pigment transplantation in age related macular degeneration. In: Das T, editor. Retina. Current practice and future trends. Hyderabad: PARAS Publishing; 1999. p. 151–61.
67. Thumann G, Aisenbrey S, Schraemeyer U. Transplantation of autologous iris pigment epithelium after removal of choroidal neovascular membranes. Arch Ophthalmol. 2000;118(10):1350–5.
68. Thuman G, Heimann K, Schraemeyer U. Quantitative phagocytosis of rod outer segments by human and porcine iris pigment epithelial cells in vitro. Invest Ophthalmol Vis Sci. 1997;38(4):330.
69. Bisantis F, Fregona I, Mancini A. Is phagocytosis in iris pigmented (IPE) cultures by human iridectomies a self limited and dose dependant mechanism ? Invest Ophthalmol Vis Sci. 1997;38(4):5330.
70. Dintelman T, Heimann K, Kayatz P. Comparative study of ROS degradation by IPE and RPE cells in vitro. Graefes Arch Clin Exp Ophthalmol. 1999;237:830–9.
71. Binder S, Stolba U, Krebs I, et al. Zur Transplantation autologer Pigmentepithelzellen. Spektrum Augenheilk. 2000;14/5:249–53.
72. Assadolina A, Binder S, Stanzel B, et al. Harvesting efficacy and viability of retinal pigment epithelial cells in aspirates from posterior retinal areas – a study in human eyes. Spectrum Augenheilk. 2003;17/1:8–10.
73. Binder S, Stolba U, Krebs I, et al. Transplantation of autologous retinal pigment epithelium in eyes with foveal neovascularisation resulting from age-related macular degeneration: a pilot study. Am J Ophthalmol. 2002;133(2):215–25.
74. Binder S, Krebs I, Hilgrers HD, et al. Outcome after transplantation of autologous RPE in age related macular degeneration – a prospective trial. Invest Ophthalmol Vis Sci. 2004;45: 4151–60.
75. Awylard GW, Kyrchenthal A, Stanga PE, et al. RPE-transplantation. A new surgical technique for treatment of choroidal NV in AMD. 12th annual meeting of the Retinal Society, Regensburg; 1999.
76. Stanga PE, Kychenhal A, Fitzke F. Retinal pigment epithelium translocation after choroidal neovascular membrane removal in age-related macular degeneration. Ophthalmology. 2002;109: 1492–8.
77. Joussen AM, Heussen FM, Joeres S, et al. Autologous translocation of the choroid and retinal pigment epithelium in age-related macular degeneration. Am J Ophthalmol. 2006;142:17–30.
78. Mac Laren RE, Uppal GS, Balaggan KS, et al. Autologous transplantation of the retinal pigment epithelium and choroid in the treatment of neovascular age-related macular degeneration. Ophthalmology. 2007;114:561–70.
79. Falkner-Radler CI, Krebs I, Glittenberg C, Binder S. Human retinal pigment epithelium (RPE) transplantation: outcome after autologous RPE-choroid sheet and RPE cell suspension in a randomized clinical study. Br J Ophthalmol. 2011;95:370–5.
80. Mac Laren RE, Bird AC, Sathia PJ, et al. Long term results of submacular surgery combined with macular translocation of the retinal pigment epithelium in neovascular age-related macular degeneration. Ophthalmology. 2005;112:2081–7.
81. Cereda MG, Parolini B, Bellesini E, Pertile G. Surgery for CNV and autologous choroidal RPE patch transplantation: exposing the submacular space. Graefes Arch Clin Exp Ophthalmol. 2009;248:37–47.
82. van Zeeburg EJ, Cereda MG, van der Schoot J, Pertile G, van Meurs JC. Early perfusion of a free RPE-choroid graft in patients with exudative macular degeneration can be imaged with spectral domain OCT. Invest Ophthalmol Vis Sci. 2011;52(8):5881–6.
83. Van Meurs JC, Van Den Biesen PR. Autologous retinal pigment epithelium and choroid translocation in patients with exudative age-related macular degeneration: short term follow-up. Am J Ophthalmol. 2003;136:688–95.
84. El Baba F, Jarrett 2nd WH, Harbin Jr TS, Fine SL, Michels RG, Schachat AP, Green HR. Massive hemorrhage complicating age-related macular degeneration: clinicopathologic correlation and role of anticoagulants. Ophthalmology. 1986;93:1591–2.
85. Tilanus MA, Vaandrager W, Cuypers MH, Verbeek AM, Hoyng CB. Relationship between anticoagulant medication and massive intraocular hemorrhage in age-related macular degeneration. Graefes Arch Clin Exp Ophthalmol. 2000;238:482–5.
86. Kulli-Hattenbach C, Fischer IB, Schalnus R, Hattenbach LO. Subretinal hemorrhages associated with age-related macular degeneration in patients receiving anticoagulation or antiplatelet therapy. Am J Ophthalmol. 2010;149:316–21.
87. Yannuzzi LA, Wong DWK, Sforzolini BS, Goldbaum M, Tang KC, Spaide RF, Freund KB, Slakter JS, Guyer DR, Sorenson JA, Fisher Y, Maberley D, Orlock DA. Polypoidal choroidal vasculopathy and neovascularized age-related macular degeneration. Arch Ophthalmol. 1999;117:1503–10.
88. Uyama M, Matsubara T, Fukushima I, Matsunaga H, Iwashita K, Nagai Y, Takahashi K. Idiopathic polypoidal choroidal vasculopathy in Japanese patients. Arch Ophthalmol. 1999;117:1035–42.
89. Glatt H, Machemer R. Experimental subretinal hemorrhage in rabbits. Am J Ophthalmol. 1982;94:762–73.
90. Toth CA, Morse LS, Hjelmeland LM, Landers 3rd MB. Fibrin directs early retinal damage after experimental subretinal hemorrhage. Arch Ophthalmol. 1991;109:723–9.
91. Bennett SR, Folk JC, Blodi CF, Klugman M. Factors prognostic of visual outcome in patients with subretinal hemorrhage. Am J Ophthalmol. 1990;109:33–7.
92. Berrocal MH, Lewis ML, Flynn Jr HW. Variations in the clinical course of submacular hemorrhage. Am J Ophthalmol. 1996;122: 486–93 (published erratum appears in Am J Ophthalmol 1996;122:920).
93. Wade EC, Flynn Jr HW, Olsen KR, Blumenkrantz MS, Nicholson DH. Sub-retinal hemorrhage management by pars plana vitrectomy and internal drainage. Arch Ophthalmol. 1990;108:973–8.
94. Avery RL, Fekrat S, Hawkins BS, Bressler NM. Natural history of subfoveal subretinal hemorrhage in age-related macular degeneration. Retina. 1996;16:183–9.
95. Stifter E, Michels S, Prager F, Georgopoulos M, Polak K, Hirn C, Schmidt-Erfurth U. Intravitreal bevacizumab therapy for neovascular age-related macular degeneration with large submacular hemorrhage. Am J Ophthalmol. 2007;144:886–92.
96. Shienbaum G, Garcia Filho AA, Flynn HW, Nunes RP, Smiddy WE, Rosenfeld PJ. Management of submacular hemorrhage secondary to neovascular age-related macular degeneration with anti-vascular endothelial growth factor monotherapy. Am J Ophthalmol. 2013;155:1009–13.

97. Chang MA, Do DV, Bressler SB, Cassard SD, Gower EW, Bressler NM. Prospective one-year study of ranibizumab for predominantly hemorrhagic choroidal neovascular lesions in age-related macular degeneration. Retina. 2010;30:1171–6.
98. Hanscom TA, Diddie DR. Early surgical drainage of macular subretinal hemorrhage. Arch Ophthalmol. 1987;105:1722–3.
99. Vander JF, Federman JL, Greven C, Slusher MM, Gabel VP. Surgical removal of massive subretinal hemorrhage associated with age-related macular degeneration. Ophthalmology. 1991; 98:23–7.
100. Mandelcorn MS, Menezes AV. Surgical removal of subretinal hemorrhage and choroidal neovascular membranes in acute hemorrhagic age-related macular degeneration. Can J Ophthalmol. 1993;28:19–23.
101. Collen D, Lijnen HR. Tissue-type plasminogen activator: mechanisms of action and thrombolytic properties. Haemostasis. 1986;16 suppl 3:25–32.
102. Holyaerts M, Rijken OC, Lijnen HR, Collen D. Kinetics of the activation of plasminogen by human tissue plasminogen activator. Role of fibrin. J Biol Chem. 1982;257:2912.
103. Irvine WD, Johnson MW, Hernandez E, Olsen KR. Retinal toxicity of human tissue plasminogen activator in vitrectomized rabbit eyes. Arch Ophthalmol. 1991;109:718–22.
104. Lewis H, Resnick SC, Flannery JG, Straatsma BR. Tissue plasminogen activator treatment of experimental subretinal hemorrhage. Am J Ophthalmol. 1991;111:197–204.
105. Benner JD, Morse LS, Toth CA, Landers MDIII, Hjelmeland LM. Evaluation of a commercial recombinant tissue-type plasminogen activator preparation in the subretinal space of the cat. Arch Ophthalmol. 1991;109:1731–6.
106. Hrach CJ, Johnson MW, Hassan AS, Lei B, Sieving PA, Elner VM. Retinal toxicity of commercial intravitreal tissue plasminogen activator solution in cat eyes. Arch Ophthalmol. 2000;128: 650–63.
107. Johnson MW, Olsen DR, Hernandez E. Tissue plasminogen activator treatment of experimental subretinal hemorrhage. Retina. 1991;11:250–8.
108. Hesse L, Schmidt J, Kroll P. Management of acute submacular hemorrhage using recombinant tissue plasminogen activator and gas. Graefes Arch Clin Exp Ophthalmol. 1999;237:273–7.
109. Kimura AE, Reddy CV, Folk JC, Farmer SG. Removal of subretinal hemorrhage facilitated by preoperative intravitreal tissue plasminogen activator. Retina. 1994;14:83–4.
110. Lim JI, Drews-Botsch C, Sternberg Jr P, Capone Jr A, Aaberg Sr TM. Submacular hemorrhage removal. Ophthalmology. 1995;102: 1393–9.
111. Kamei M, Misono K, Lewis H. A study of the ability of tissue plasminogen activator to diffuse into the subretinal space after intravitreal injection in rabbits. Am J Ophthalmol. 1999;128: 739–46.
112. Takeuchi A, Kricorian G, Yao XY, Kenny JW, Marmor MF. The rate and source of albumin entry into saline-filled experimental retinal detachments. Invest Ophthalmol Vis Sci. 1994;35:3792–8.
113. Coll GE, Sparrow JR, Marinovic A, Chang S. Effect of intravitreal tissue plasminogen activator on experimental subretinal hemorrhage. Retina. 1995;15:319–26.
114. Boone DE, Boldt HC, Ross RD, Folk JC, Kimura AE. The use of intravitreal tissue plasminogen activator in the treatment of experimental subretinal hemorrhage in the pig model. Retina. 1996;16:518–24.
115. Kwan ASL, Vijaysekaran S, McAllister IL, Yu PK, Yu D. A study of retinal penetration of intravitreal tenecteplase in pigs. Invest Ophthalmol Vis Sci. 2006;47:2662–7.
116. Johnson MW, Olsen DR, Hernandez E. Tissue plasminogen activator thrombolysis during surgical evacuation of experimental subretinal hemorrhage. Ophthalmology. 1992;99:515–21.
117. Peyman GA, Nelson Jr NC, Alturki W, Blinder KJ, Paris CL, Desai UR, Harper 3rd CA. Tissue plasminogen activating factor assisted removal of subretinal hemorrhage. Ophthalmic Surg. 1991;22:575–82.
118. Lewis H. Intraoperative fibrinolysis for submacular hemorrhage with tissue plasminogen activator and surgical drainage. Am J Ophthalmol. 1994;118:559–68.
119. Ibanez HE, Williams DF, Thomas MA, Ruby AJ, Meredith TA, Boniuk I, Grand MG. Surgical management of submacular hemorrhage: a series of 47 consecutive cases. Arch Ophthalmol. 1995; 113:62–9.
120. Kamei M, Tano Y, Maeno T, Ikuno Y, Mitsuda H, Yuasa T. Surgical removal of submacular hemorrhage using tissue plasminogen activator and perfluorocarbon liquid. Am J Ophthalmol. 1996;121: 267–75.
121. Bressler NM, et al.; Submacular Surgery Trials (SST) Research Group. Surgery for hemorrhagic choroidal neovascular lesions of age-related macular degeneration: ophthalmic findings. SST report no. 13. Ophthalmology. 2004;111:1993–2006.
122. Heriot WJ. Intravitreal gas and TPA: an outpatient procedure for sub-retinal hemorrhage. Presented at Vail Vitrectomy meeting, Vail; Mar 1996.
123. Hassan AS, Johnson MW, Schneiderman TE, et al. Management of submacular hemorrhage with intravitreous tissue plasminogen activator injection and pneumatic displacement. Ophthalmology. 1999;106:1900–7.
124. Meier P, Zeumer C, Jochmann C, Wiedemann P. Management of submacular hemorrhage by tissue plasminogen activator and SF(6) gas injection. Ophthalmologe. 1999;96:643–7.
125. Karlsson E, Carlsson J, Crafoord S, Jemt M, Martensson PA, Stenkula S. Tissue plasminogen activator and expanding gas intravitreally in treatment of submacular hemorrhage. Acta Ophthalmol Scand. 1999;77:119.
126. Ohji M, Saito Y, Hayashi A, Lewis JM, Tano Y. Pneumatic displacement of subretinal hemorrhage without tissue plasminogen activator. Arch Ophthalmol. 1998;116:1326–32.
127. Haupert CL, McCuen 2nd BW, Jaffe GJ, Steuer ER, Cox TA, Toth CA, Fekrat S, Postel EA. Pars plana vitrectomy, subretinal injection of tissue plasminogen activator, and fluid-gas exchange for displacement of thick submacular hemorrhage in age-related macular degeneration. Am J Ophthalmol. 2001;131:208–15.
128. Olivier S, Chow DR, Packo KH, MacCumber MW, Awh CC. Sub-retinal recombinant tissue plasminogen activator injection and pneumatic displacement of thick submacular hemorrhage in age-related macular degeneration. Ophthalmology. 2004; 111:1201–8.
129. Martel JN, Mahmoud TH. Subretinal pneumatic displacement of subretinal hemorrhage. JAMA Ophthal. 2013;131:5464.
130. Stopa M, Lincoff A, Lincoff H. Analysis of forces acting upon submacular hemorrhage in pneumatic displacement. Retina. 2007;27:370–4.
131. Foster WJ, Chou T. Physical mechanisms of gas and perfluoron retinopexy and sub-retinal fluid displacement. Phys Med Biol. 2004;49:2989–97.