Chapter 1

General introduction
INTRODUCTION

Rhegmatogeneous retinal detachment (RRD) refers to a detachment between the neuroretina and the underlying retinal pigment epithelium (RPE) due to one or more breaks / tears in the neuroretina (rhegma means break in Greek).\textsuperscript{[1]} The outer neuroretina, consisting of rods and cones, is the light sensitive layer of the eye.\textsuperscript{[2]} The RPE is responsible for outer neuroretinal metabolism.\textsuperscript{[2]} In addition, the RPE is responsible for keeping the neuroretina in its attached position, by the outward movement of fluid across the RPE and towards the choroid.\textsuperscript{[2]} For an RRD to develop, a cascade of events has to take place.

PATHOPHYSIOLOGY OF RHEGMATOGENOUS RETINAL DETACHMENT

The first event in this cascade is posterior vitreous detachment (PVD).\textsuperscript{[1-3]} The vitreous body is a gel-like structure and fills the eye. The greatest part of vitreous consists of water (98-99%).\textsuperscript{[4]} The remaining part consist of inorganic salts and organic lipids of low molecular weight (1%).\textsuperscript{[4-5]} A small percentage of vitreous consist of macromolecules (0.1%) (i.e glycosaminoglycans (i.e. hyaluronan),\textsuperscript{[4-6]} proteoglycans,\textsuperscript{[4-5]} glycoproteins,\textsuperscript{[7-9]} collagens (responsible for maintaining stabilisation of the vitreous gel)\textsuperscript{[10-16]} and noncollagenous structural proteins).\textsuperscript{[8,17-18]} With advancing age, morphological changes in the vitreous take place.\textsuperscript{[3,19-20]} There is a progressive increase in the volume of liquefied spaces (synchisis),\textsuperscript{[3,19-20]} and an increase in optically dense areas (syneresis).\textsuperscript{[1,3,21]} Synchisis is characterized by the replacement of vitreous gel by liquefied vitreous (free of collagen fibrils) which is surrounded by optically dense structures and condensations.\textsuperscript{[3,19-20]} As these alterations progress with age, they may interfere with the passage of light and cause symptoms referred to as “mouches volantes” or floaters.\textsuperscript{[10]} During aging, posterior vitreoretinal attachments weaken, and anterior vitreoretinal adhesions increase.\textsuperscript{[22-24]} Finally, these processes may lead to a PVD, a separation between the vitreous cortex and the retina.\textsuperscript{[1,3]} Because of traction of the vitreous at the retina, patients may experience flashes of light, and a tear may occur in the retina.\textsuperscript{[1]} The formation of a retinal tear is the second step in the cascade.\textsuperscript{[25-26]} Retinal tears occur in about 15% of patients with acute PVD.\textsuperscript{[26]} These tears most likely occur at the peripheral (equatorial and anterior) retina were the vitreous is most firmly attached to the retina.\textsuperscript{[27]} Finally, as a result of the tear(s) in the retina, fluid from the vitreous cavity can penetrate through the tear in the neuroretina, in the potential subretinal space between the neuroretina and the RPE.\textsuperscript{[1]} As long as the rupture is open, and the RPE pump remains overwhelmed (depending on the distance between RPE and neuroretina), an RRD tends to extend itself due to gravity, as the subretinal fluid is heavier than the vitreous. This will eventually result in a total detachment of the retina.\textsuperscript{[1]}
Approximately 126 million sensory cells are present in the neuroretina.\cite{2} Histologically, viewed from vitreous to RPE – the neuroretina consists of the internal limiting membrane (ILM), nerve fiber layer (NFL i.e. the axons of the ganglion cell layer), ganglion cell layer, inner plexiform layer, inner nuclear layer, outer plexiform layer, outer nuclear layer (i.e. the nuclei of the photoreceptors), external limiting membrane (ELM), and the rod and cone inner and outer segments.\cite{2} The photoreceptor cells can be divided into rods (sensitive to dark and light changes) and cones (color differences).\cite{2} Central visual function (visual acuity, contrast acuity, and color vision) occurs particularly with the macula, which primarily consists of cones.\cite{2} In darker conditions, vision depends on the periphery of the retina containing predominantly rods and fewer cones.\cite{2} The metabolic needs of the inner layers of the neuroretina are met by the central retinal artery and its branches.\cite{2} The metabolism of the outer layers of the neuroretina is largely dependent on their attachment to a well-functioning RPE.\cite{2} During an RRD, the outer layers of the neuroretina get deprived of their immediate source of nourishment through the RPE and choroid.\cite{28} As a result of an RRD, the neuroretina gets dependent on the subretinal fluid for nourishment.\cite{28} Depending on the duration of the detachment and the distance between the neuroretina and the RPE, irreversible retinal damage may occur.\cite{28-39}

**RISK FACTORS OF RHEGMATOGENOUS RETINAL DETACHMENT**

Patients at risk for developing RRD are those of 55-65 years of age, and of male gender.\cite{40-48} Particular at risk are eyes of patients who have had previous cataract extraction (CE), ocular trauma, or who are myopic.\cite{40-53}

**Age & posterior vitreous detachment**

There is a strong association between increasing age and RRD.\cite{40-53} The high incidence rates of RRD at 55-65 years of age, may well be explained by the occurrence of a PVD around this age.\cite{3,25} PVD is generally assumed to be the main cause of RRD,\cite{3,25} PVD is a rarity in individuals younger than 50 years of age; on average, its onset is at 60 years, with increasing prevalence thereafter.\cite{3,25}

**Male gender**

Many studies observed a preponderance for RRD in males.\cite{44-47,53-55} A possible explanation for this may be differences in the prevalence of the other risk factors in males in contrast to females. For instance, symptomatic PVD even though more common in females than males,\cite{3,56-58} is more often complicated by a retinal tear in males, possibly resulting in a higher attributable RRD risk in males.\cite{121} In addition, some suggested that the attributable risk of RRD from ocular trauma may be higher in males than in females,\cite{54} which will consequently lead to a higher RRD incidence in males.\cite{54} Finally, a history of cataract surgery or myopia may be more prevalent in males.
Cataract surgery

The cumulative risk of RRD is increased in eyes with a history of CE. The RRD risk in eyes with a history of CE depends on the surgical technique used. Intracapsular cataract extraction (ICCE) holds the highest and extracapsular cataract extraction (ECCE), yields the second highest risk of RRD. Both techniques have been replaced by the safer procedure of phacoemulsification, which holds the lowest risk of the three surgical techniques. Several theories concerning the pathophysiological mechanisms on phakic versus post-CE RRD have been advocated. First, a newly induced PVD in non-PVD eyes can occur, because CE causes mechanical and biochemical changes in the vitreous. Also, a second mechanism could be at play, namely, the altered mechanical forces at the anterior vitreous base area because of the loss of lens volume.

Ocular trauma

Direct and indirect injuries may give rise to RRD. Direct injuries, such as penetrating and perforating trauma, may give rise to two types of RRD. The first type is an RRD at the time of trauma, owing to the trauma. The second is an RRD at a later stage, due to cicatrisation and traction of scar tissue. Indirect injuries act not as the primary cause of RRD but merely as the precipitating agent in an eye already prone to retinal tearing. The sudden strain may luxate the formation of a tear in a predisposed area of the retina (i.e. degenerative changes or region of weakness).

Myopia

It has consistently been found that high myopia is associated with RRD. Myopia as a risk factor of RRD may be due to the more common presence of degenerative changes in the peripheral retina, as well as the development of early degeneration of the vitreous in myopic eyes. It has been estimated that about two-thirds of RRD cases occur in myopes, whereas in more than half of these no other obvious cause was noted. Moreover, they tend to develop RRD at an earlier age than hypermetropes and emmetropes. The peak incidence of RRD in myopes is at ages 36 to 40 years as compared to a peak incidence of 55 to 65 years in the entire population.

RRD-incidence in relation to the prevalence of risk factors

The annual incidence of primary RRD is reported to be between 8 and 14 per 100,000 persons, with a peak incidence in the 7th decade of life. Population ageing is a shift in the distribution of a country’s population towards older ages. This is usually reflected in an increase in the population’s mean or median ages, a decline in the proportion of the population composed of children, and a rise in the proportion of the population that is elderly. Population ageing is widespread across the world. It is most advanced in the most highly developed countries. The incidence of PVD increases in the elderly population, and is a significant risk factor for acquiring...
In addition, the prevalence of cataract and hence cataract extractions, another significant risk factor of RRD, increases in the elderly population. Population aging may therefore lead to a higher incidence of RRD in aging populations.

TREATMENT OF RHEGMATOGENOUS RETINAL DETACHMENT

Historical perspective
Because of Gonin, a surgical therapy for RRD patients became available almost 100 years ago. Before this, acquiring an RRD would eventually in almost all cases implicate blindness. Gonin recognized that - although all patients had a variable presentation - the aim of the treatment had to be to close or effectively isolate the perforation in the retina, resulting in reattachment of the detached retina. To do so, a watertight adhesion between the neuroretina and choroid surrounding the retinal tear had to be made, followed by drainage of subretinal fluid. Although the basic principle as proposed by Gonin, remained the cornerstone of the treatment of RRD, the methods to do so evolved. Gonin used thermocautery to close the retinal hole. Thermocautery was replaced by diathermy. To reduce further chorioretinal reaction, cryoapplication was introduced. Silicone was introduced as buckling or encircling material to close the retinal hole. Others realised that drainage of subretinal fluid was not essential for reattachment of the retina. The surgical success rate kept increasing by the introduction of these new techniques.

However, in some cases surgical attempts to reattach the retina fail. This is mainly due to proliferative vitreoretinopathy (PVR). PVR is the development of contractile membranes around the retina, detaching or preventing attachment of the neuroretina to the RPE, which occurs in 5-10% of cases. Further, some retinal detachments were inoperable due to PVR. The development and introduction of the trans pars plana vitrectomy (TPPV) by Machemer became the solution for these challenging cases. Further developments were the introduction of intraocular tamponading gases, silicone oils, and smaller vitrectomes. Today, the following surgical methods are used: pneumatic retinopexy, scleral buckling, and trans pars plana vitrectomy (TPPV). With these methods, surgical reattachment of the detached retina is successful in > 95% of cases after one or more surgical procedures. Surgical failure is primarily caused by severe PVR. Other causes are new- or missed breaks.

Pneumatic retinopexy
In pneumatic retinopexy, a bubble of expandable gas (e.g. hexafluoride (SF6)) is injected into the eye. When the detached neuroretina becomes reattached to the RPE, cryocoagulation or lasercoagulation is performed at the location of the tear. This technique can be successfully
used in case of one tear or multiple tears within 1 clock hour if the tear is localized within the superior 8 clock hours (8 to 4 o’clock), and there are no abnormalities such as PVR.[68]

Scleral buckling surgery
In scleral buckling, an encircling band may be sutured around the circumference of the sclera, under the ocular muscles.[67-68] A grooved (radial, circumferential, or other) buckle (solid silicone rubber or silicone sponge) is placed either directly at the sclera at the level of the tear or placed under an encircling band at the level of the tear.[67-68] Using this method, an indentation in the eye wall is created causing the underlying choroid and sclera to press against the retinal tear and close it.[67-68] To reduce the volume of subretinal fluid, transscleral puncture can be performed.[67-68] Thereafter, applying cryocoagulation around the tear can achieve adhesion of the retina.[67-68] In addition, a bubble of expandable gas (e.g. hexafluoride (SF6)) may be injected into the eye to achieve adhesion between the neuroretina and the underlying choroid.[67-68] This technique is most commonly performed in case of one or more tears (i.e. horseshoe shaped tear, round holes, ora dialysis), and a retinal detachment extending over one or two quadrants.[62]

Trans Pars Plana Vitrectomy
TPPV is the surgical removal of vitreous through sclerotomies, (small incisions in the pars plana).[68,74-76] Sclerotomies are made at 3-5 mm from the corneal limbus.[68,74-76] The sclerotomies can be of various sizes, they can be self-sealing or non-self sealing, and the vitreous cavity can be accessed through the sclerotomies with or without the use of trocars. One of the sclerotomies is used for fluid infusion to maintain intraocular pressure. The other two sclerotomies enable the surgeon to work bimanually. A high intensity fibre optic light source (inserted through one of the sclerotomies) is used to illuminate the inside of the eye during surgery. After removing the vitreous, drainage of subretinal fluid through a retinal tear is performed. Thereafter, endolasercoagulation or exocryocoagulation around the tear can achieve adhesion of the retina. To maintain some degree of postoperative pressure on the retina and to achieve stronger adhesion, a gas bubble or oil can be injected. This technique is indicated in the more challenging cases of RRD (i.e. severe proliferative vitreoretinopathy (PVR), giant retinal tears and those presenting with vitreous haemorrhage).[68,74-76]

Choosing a surgical technique
Primary cases of RRD vary from relatively local detachment with one tear to total detachments, with numerous tears, and severe PVR. Therefore it is impossible to dogmatize the choice of technique for particular cases. The common sense is to use the simplest method applicable to a particular case of RRD (i.e. pneumatic retinopexy or scleral buckling in relatively straightforward cases, and TPPV in more challenging cases). In between this spectrum of relatively straightforward cases and more challenging ones, there is a grey zone. The selection of one particular surgical
procedure in these cases is still a matter of ongoing debate, although, a shift towards TPPV in these cases has been observed in several countries including the Netherlands.[83-88]

POSTOPERATIVE RECOVERY OF VISUAL FUNCTION

Postoperative recovery of visual function in rhegmatogenous retinal detachment

The postoperative recovery of visual function may be disappointing in RRD patients. This is particularly true in macula-off RRD. For example, only 42% of macula-on detachment eyes achieve 20/40 visual acuity or better, whereas only 37% of macula-off detachment eyes achieve 20/50 visual acuity or better.[77-78] Postoperative contrast acuity scores after macula-off RRD are lower when compared to a control group of similar age[89] and to fellow eyes.[32] Postoperative color vision disturbances are significantly more present in macula-off RRD eyes, when compared to their healthy fellow eyes.[32,36] In addition, in macula-off RRD postoperative metamorphopsia is a highly prevalent problem that occurs in around two-thirds of patients. Postoperative vision related quality of life is worse in macula-off RRD patients compared to macula-on RRD patients.[90-91] Vision related quality of life is strongly related to postoperative visual function (i.e. best corrected visual acuity (BCVA), contrast acuity, and color vision disturbances) in macula-off RRD patients.[92-94]

Postoperative recovery of visual function in macula-off detachments

The most important factors that may negatively influence functional recovery after macula-off RRD are a longer duration of macular detachment,[29-30,36,42,77,95-97] and a larger height of macular detachment at presentation.[28,36-39,77] In contrast to the above mentioned, a shorter or longer duration of macular detachment within the first week (24 hours – 1 week) does not affect final visual outcome.[29-30,31] It is therefore common clinical practice to consider macula-off RRD eyes with macular detachment of one week a surgical urgency, but not an emergency. Within the first week of macular detachment, a lower height of macular detachment is associated with better postoperative visual acuity.[37]

HYPOTHESIS ADRESSED

We had several main goals while conducting this study. Our first goal was to identify disease incidence and risk factors for acquiring RRD in our population (both in our own adherent population in the North of the Netherlands, as well as in the entire Dutch population). Our second goal was to identify various factors that influence postoperative recovery of visual function in macula-off RRD (prior to this we validated a measuring method to obtain reliable results).
Our third goal was to determine postoperative vision related quality of life in macula-off RRD, and to determine which factors (postoperative visual function, surgery or patient related factors) have an effect on the vision related quality of life. Our final goal was to determine postoperative metamorphopsia prevalence, and its relation to postoperative optical coherence tomography (OCT) disturbances. In addition, we were interested if these disturbances affect visual function, and hence vision related quality of life.

To achieve these various goals, we first determined RRD incidence in the North of the Netherlands, and in the Netherlands. In chapter 2 we describe both the incidence of RRD surgery, and risk factors in 2008 and 2009 in the North of the Netherlands. Additional analyses are performed to demonstrate that RRD surgery incidence in this area remains steady over a two-year period. We state that in case of RRD surgery, the subpopulation in the North of the Netherlands can be considered as representative for the entire Dutch population. Chapter 3 describes the incidence of RRD and macula-off RRD in the Netherlands in 2009. In addition, we give descriptive information on risk factors, such as the percentage of patients with previous cataract extraction, and the distribution of age and gender in our RRD population in relation to demographic characteristics of our population. We also comment on a possible increase in RRD incidence in our population due to population aging. Chapter 4 describes a measuring method to determine the position of the fovea by ultrasonography (USG), using fundus photographs. This method was designed to be able to determine macular height in our prospective study on the recovery of visual function after surgery for macula-off RRD. In that way, we could evaluate the effect of macular height on the postoperative recovery of visual function in macula-off RRD. In Chapter 5 the effect of various pre-operative factors (age, preoperative refractive error, duration, and height of macular detachment) on the postoperative recovery of visual function in macula-off RRD patients is described. Chapter 6 comments on postoperative vision related quality of life in macula-off RRD patients. In addition, correlations with postoperative visual function are addressed as well as various patient related factors. In Chapter 7, the prevalence of postoperative metamorphopsia is addressed and its relation with OCT disturbances is evaluated as well as the effect of both aspects on vision related quality of life. In Chapters 8 & 9 an English summary and a Dutch summary are provided.
REFERENCES


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PART I
EPIDEMIOLOGY