Functional recovery following vitreoretinal surgery

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CHAPTER 1

Introduction

INTRODUCTION

The retina is a thin transparent neural layer of photosensitive tissue covering the inner surface of the eye. Its main functions are to convert light into electric signals and to transmit these signals, through the optic nerve, to the brain for visual recognition. Retinal diseases affecting this signal transduction can cause visual impairment.

The aim of this thesis is to evaluate functional recovery following vitreoretinal surgery. More specifically, we investigate two topics: idiopathic epiretinal membrane (iERM) and rhegmatogenous retinal detachment. We focus on the prediction of visual outcome of surgery in patients with an iERM, and on a serious complication of RRD surgery. This chapter provides background information on retinal anatomy and the two retinal disorders iERM and RRD, that are the object of this thesis. In addition, a few relevant ophthalmological examinations to visualize retinal anatomy in vivo and to assess retinal function will be discussed. This is followed by a description of the scope of the thesis.

Retinal anatomy

The human retina consists of 10 distinct layers and any disorder affecting one of these layers may affect retinal functioning and visual function. The layers are, from the inner to the outer retinal surface:

- 1. Internal limiting membrane
- 2. Nerve fiber layer
- 3. Ganglion cell layer
- 4. Inner plexiform layer
- 5. Inner nuclear layer
- 6. Outer plexiform layer
- 7. Outer nuclear layer
- 8. External limiting membrane
- 9. Photoreceptor layer containing cones and rods
- 10. Retinal pigment epithelium

The macula lutea or the yellow spot

is a pigmented area within the temporal vascular arcades (Figure 1). It has a diameter of 5 to 6 millimetres and serves the central 15-20° of the visual field. The fovea is a depression in the central part of the macula and contains the largest concentration of cones. These structures are fundamental for the central high-acuity vision. Macular disorders can also affect other aspects of

visual functioning, such as contrast sensitivity, reading ability and distortion of vision.



Idiopathic epiretinal membrane

An epiretinal membrane is a fibrocellular proliferation on the inner surface of the retina (Figure 2B).^{1,2} These membranes can develop secondary to an ophthalmological trauma or disease, such as uveitis, proliferative diabetic retinopathy or proliferative vitreoretinopathy in retinal detachment.³⁻⁵ However, most commonly there is no apparent cause and such a membrane is termed an idiopathic epiretinal membrane (iERM).^{3–5} An iERM can lead to retinal thickening and, when the membrane becomes contractile, to retinal wrinkling. Patients can be asymptomatic but they also can present with loss of visual acuity, visual distortion (metamorphopsia), diplopia, or binocular complaints.^{6,7} The prevalence of an iERM ranges among published series from 1.0% to 34.6% and increases with age. Surgery is required in 0.4% to 3.9% of the cases.^{1,3} An iERM in both eyes is seen in 19.5-31% of the patients.³⁻⁵ If left untreated, 28.6% of the iERMs will show progression within 5 years.⁴ The standard treatment is pars plana vitrectomy with removal of the iERM. This is often accompanied by removal of the ILM because this 0.01-0.10 µm thin layer is considered to serve as a scaffold for new epiretinal membranes.⁸⁻¹⁰ Removing this membrane secures complete removal of the ERM and reduces the risk of recurrent membrane formation.⁹⁻¹¹ Surgery for iERM is an elective procedure that is indicated in patients with deterioration of their symptoms. Recently, early surgical intervention has been advocated to preserve good visual acuity.¹²⁻¹⁴ However, surgery can be complicated by cataract formation, a retinal detachment, and cystic macular oedema.¹⁵⁻¹⁷ In that case, additional treatment is required and these complications can have a negative effect on visual acuity.^{15–17} Furthermore, substantial visual improvement is reported in eyes with low visual acuity.^{18,19} But postoperative visual outcome in an absolute sense is lower compared to eyes with good preoperative visual acuity.¹⁸⁻²¹ An iERM may eventually induce irreversible damage to the retina and surgery will not be beneficial in those eyes. Individual visual outcome is still hard to predict. Our aim is to provide an overview of predictors for visual outcome and to develop a prediction model. This could be helpful for balancing the risks and benefits of surgery and improve patient counselling.

Rhegmatogenous retinal detachment

Rhegmatogenous retinal detachment (RRD) refers to a separation of the neuroretina and the underlying retinal pigment epithelium as a result of a defect in the retina (Figure 2C). Liquefied vitreous flows through this retinal defect into the subretinal space, causing a progressive detachment. In the Netherlands, RRD has an annual incidence of 18.2 per 100,000 people, with a peak incidence of 52.5 per 100,000 between 55 and 59 years of age.²² Visual symptoms and prognosis depend on whether the macula is involved in the detachment.²³⁻²⁵ Patients with a RRD without macular involvement, a macula-on RRD, present with gradual loss of peripheral sight, the sudden appearance of floaters or light flashes. A RRD involving the macula, a macula-off RRD, not only causes visual field loss but also loss of visual acuity. In the Netherlands, 54.5% of the patients present with a detached macula.²² Visual prognosis is favourable in eyes in which the macula remains attached.²³ Treatment of RRD consists of closing the retinal break and relieving retinal traction. A successful fulfilment of these two conditions will achieve a retinal reattachment. An extraocular approach to relieve retinal traction is scleral buckling surgery, which can be considered in eyes without complicating factors or in younger patients with clear lenses.^{24,25} Usually however, RRD is treated by pars plana vitrectomy in combination with laser retinopexy and intraocular tamponade with air, gas or silicone oil (SO). SO is used in vitreoretinal surgery for complex retinal detachments associated with proliferative vitreoretinopathy (PVR) or an increased risk of PVR formation. Compared to gas, which dissolves spontaneously, SO provides a prolonged tamponade.²⁶⁻²⁸ Its optical clarity facilitates good postoperative assessment and laser photocoagulation. SO is usually removed once reattachment is accomplished, because of the risk of oil emulsification, cataract, glaucoma and keratopathy in case of long-lasting SO tamponade.^{27,29,30} Although considered to be safe, well tolerated, and not affecting retinal physiology, case series reported on an unexplained visual loss in patients treated by SO tamponade for RRD without macular involvement.³¹⁻³⁸ This irreversible and profound visual loss can occur during SO tamponade or immediate after SO removal and cannot be explained by complications such as cystoid macular edema, ocular hyper- or hypotony, or epiretinal membranes.²⁷⁻³⁷ Visual field examination in these eyes reveals a central scotoma.³¹⁻³⁸ Our goal was to investigate whether this profound visual loss was indeed related to the use of intraocular SO, to report its incidence and to identify risk factors. Currently, the pathophysiology of this intriguing and serious adverse event is unknown.³¹⁻³⁸ Several hypotheses on the underlying mechanism are proposed in literature but studies investigating them are lacking.^{31–38} Our aim was to test one of these hypotheses and to study the clinical and functional characteristics of this profound visual loss. We performed microperimetry and a combination of electrophysiological examinations assessing different aspects of macular functioning to better understand the origin of the visual loss. This knowledge could help in elucidating its underlying pathophysiology.

Macular imaging and functioning

Optical coherence tomography

Retinal anatomy can be visualized in vivo by means of optical coherence tomography (OCT). This technique provides non-invasive cross-sectional imaging of, amongst others, the retina.³⁹ The OCT technique is equivalent to echography but using light instead of ultrasound waves.⁴⁰ In short: light emitted by a low coherence light source is split into two beams, by a beam splitter; one part is directed to the tissue to be imaged and the other to a reference mirror. Returning light beams from the tissue and the mirror are combined and processed into images.^{40–42} Contrast in OCT images results from differences in refractive indices of tissue particles.^{40–42} Since its introduction in 1991, new developments in OCT imaging have improved acquisition time and image quality offering visualization of the separate retinal layers.^{39,42} An example of a normal OCT-scan of the retina is shown in Figure 2A. OCT imaging is very useful in diagnosing retinal disorders. Figure 2B shows a scan of an iERM. The membrane is visible as a hyperreflective layer on the inner surface of the retina accompanied by retinal thickening and wrinkling. The separation of the neuroretina and the underlying retinal pigment epithelium that characterizes RRD is depicted in Figure 2C.

In clinical practice, OCT is indicated in patients suspected of having macular abnormalities. For example, to establish the presence of an iERM or to evaluate the cause of a low visual acuity after a RRD. Macular pathology can have a negative effect on fixation. It can be challenging to obtain images of sufficient quality in eyes with fixation difficulties. In this thesis, an OCT system is used with a simultaneously running scanning laser ophthalmoscope (SLO) (Optos OCT/SLO; Optos Plc., Dunfermline, UK). SLO is merged with OCT for tracking of the eye

movements and for correction of fixation instability which improves the quality of the OCT-scans.42 We used the combination of SLO and OCT to study a broad range of OCT characteristics and their potential to predict visual outcome after iERM surgery. In eyes with visual loss following RRD, OCT imaging is useful to establish or to exclude structural abnormalities. The built-in SLO is particularly useful in eyes with fixation problems due to profound visual loss after SO tamponade.



Figure 2 - Optical coherence tomography
A. Normal retinal anatomy
B. An idiopathic epiretinal membrane with retinal thickening and wrinkling
C. Separation of the retina and the retinal pigment epithelium characteristic for a rhegmatogenous retinal detachment

Fundus autofluorescence

Lipofuscin in the retinal pigment epithelium (RPE) is capable of autofluorescence when excited with short wavelength light. Under normal physiological conditions, the amount and distribution of lipofuscin is reflected by the intensity of autofluorescence.^{43,44} Autofluorescence is increased with excessive accumulation of lipofuscin, which is mainly derived from incompletely digested photoreceptors.^{43,44} Decreased autofluorescence results from RPE or photoreceptor loss or from the presence of absorbing material anterior to the RPE.^{43,44} Fundus autofluorescence (FAF) imaging is obtained by the use of short wavelength light generated by a laser and a barrier filter to block the reflected light and to allow the emitted autofluorescent light to pass.^{43,44} FAF imaging is considered a valuable tool to detect and to monitor metabolic changes within the RPE.^{43–47} FAF is included in this thesis to evaluate whether it could indicate irreversible damage due to an iERM and predict functional recovery following surgery. An example of a fundus image with a normal autofluorescence pattern is shown in Figure 3A and an example of increased autofluorescence in de macula in Figure 3B.



Microperimetry

By means of microperimetry, macular sensitivity can be assessed as a measure for macular function. It is based on the ability to discriminate signals of low contrast.⁴⁸ Microperimetry provides additional information on the damage induced by retinal diseases and on the recovery of macular function following treatment. Reliable assessment may be hindered by fixation difficulties, which can occur in patients with decreased macular function.^{48–50} The introduction of an OCT/SLO technique together with microperimetry (Optos OCT/SLO; Optos Plc., Dunfermline, UK) makes it possible to combine assessment of retinal anatomy and function and to correlate structural and functional abnormalities.^{51–53} Also, it enables the operator to observe and evaluate the fundus during the examination, which improves the accuracy of functional testing.^{51–53} Macular function was assessed in patients with an iERM because we hypothesized that it may

better predict visual outcome following surgery than OCT characteristics. In eyes with a profound visual loss after SO use, the function of the macula can be accurately assessed by microperimetry with SLO (Figure 4). Furthermore, microperimetry can detect subtle abnormalities, such as microscotomas, that interfere with visual function but that are not detected by assessment of visual acuity. The SLO also secures reliable reassessment of a previously tested area for clinical follow-up.⁴² This enables the evaluation of functional recovery over time after iERM surgery. Additionally, the combination of microperimetry with SLO makes it possible to monitor macular function during SO tamponade and to detect subtle macular damage that might precede the occurrence of profound visual loss.



Electrophysiology

The function of the visual pathway from the retinal photoreceptors to the visual cortex in the brain can be assessed by electrophysiological examinations. Electrophysiological testing is useful for diagnosing a variety of ophthalmological conditions, such as (inherited) diseases of the retina or the optic nerve or drug-induced toxicity. Information obtained by electrophysiology may help to indicate the functional origin of unexplained visual loss following SO tamponade. Accordingly, this could help to understand the potential underlying mechanism. Electrical responses are evoked by visual stimuli and are recorded by corneal or skin electrodes, from the eye and the brain respectively. Visual electrophysiology includes several tests and only those included in this thesis will be discussed.

The responses evoked by pattern electroretinogram (pERG) have been suggested to arise in the retinal ganglion cells, driven by the photoreceptors and corresponding retinal cells.⁵⁴ A contrast-reversing pattern, usually a black and white checkerboard, is used to generate a response (Figure 5).⁵⁴ The single checks within the checkerboard stimulus reverse abruptly and repeatedly from black to white and from white to black.⁵⁴ Averaged electrical responses typically exist of a negative (N35), positive (P50) and negative (N95) deflection. Since the pattern stimulus is limited to a central macular region, with a typical field width of 15 degrees, the pERG it is claimed to monitor central function specifically. The amplitude of the P50 is considered to reflect macular function and the amplitude of the N95 the ganglion cell function (Figure 5B).⁵⁴



The advantage of the multifocal electroretinogram (mfERG) over the pERG is that it is able to detect local electrical responses from different locations of the cone-driven macula, instead of a single response. Thus, mfERG is useful for the assessment of macular function and local, up to 25 degrees eccentricity, retinal functional defects.⁵⁵ Responses are evoked by an array of 61 hexagons, which are illuminated in a pseudo-random sequence. Every time the frame changes, each hexagon has a 50% change of being illuminated (Figure 6). Hexagon sizes are adapted to the boundary condition that each hexagon would evoke equal responses in a normal subject. This is necessary to ensure that within one recording sequence the responses for all hexagons have about equal signal to noise ratio. The derived responses represent the local macular function (Figure 6).



Visual evoked potentials (VEP) provide information on the functional integrity of the postretinal visual pathway, including the optic nerve, optic radiations, and occipital cortex, in case of normal retinal functioning.⁵⁶ Several VEP protocols are available to assess different aspects of this visual pathway.⁵⁶ In clinical practice, the pattern-reversal VEP is the most commonly used because the derived responses are less variable compared to responses elicited by other stimuli.⁵⁶ Pattern-reversal VEP is predominantly used in patients suspected of an optic neuropathy. Like pERG, responses of the pattern-reversal VEP are provoked by a black and white contrast-reversing checkerboard.⁵⁶ The pattern-reversal VEP reflects the function of the postretinal visual pathway. However, factors that affect the luminance of the stimuli or impaired retinal function could also influence the response. The combination of electroretinography (pERG and mfERG) and pattern-reversal VEP has the potential of discriminating abnormal VEP recordings secondary to a retinal disorder from dysfunction of the postretinal visual pathway.

A central scotoma as is observed in patients with severe visual loss following SO tamponade could result from a maculopathy, an optic neuropathy or damage to the retinal ganglion cells in the papillomacular bundle. The combination of pERG, mfERG and pattern-reversal VEP may contribute to the localisation of the functional defect in those eyes, and provide knowledge on the pathophysiology.

SCOPE OF THE THESIS

The general aim of this thesis is to evaluate functional outcome following vitreoretinal surgery. In particular, two specific issues concerning idiopathic epiretinal membranes (iERM) and rhegmatogenous retinal detachment (RRD) are investigated.

Chapter 2 - Idiopathic epiretinal membrane

In chapter 2, we evaluate the prediction of visual outcome following surgery for iERM. Pars plana vitrectomy with removal of the ERM is considered to be the standard treatment, but the indication and timing of surgery has not been standardized and clinical outcome varies.^{9,16,57–59} Careful selection of patients is important since it concerns an elective procedure in which the benefits should exceed the risks and side effects. However, individual outcome is hard to predict. A prognostic model for visual outcome following iERM surgery could improve patient counselling and the indication criteria for surgical intervention.

Chapter 2.1 provides a systematic review of the literature on potentially predictive factors for postoperative visual acuity in iERM. The predictive values of these factors were subsequently evaluated in both a retrospective and a prospective cohort of patients referred to the University Medical Center Utrecht (chapter 2.2 and 2.3). A prognostic model that can predict individual change in visual acuity after iERM surgery is described in chapter 2.3.

Chapter 3 - Rhegmatogenous retinal detachment

In chapter 3, address the clinical and functional findings, and the pathophysiology of unexplained visual loss following silicone oil (SO) tamponade. In general, the visual prognosis after surgery for RRD with an attached macula is very good.^{23,60} In certain types of RRD, intraocular SO is indicated as an intraocular tamponade. In the past 10 years, a number of case series were published on a profound and unexplained visual loss that occurred during SO tamponade or following SO removal.^{31–38} Hitherto, the underlying pathophysiology is unknown. ^{31–38} A few patients diagnosed with this complication in our clinic triggered the investigations that are described in this chapter.

Chapter 3.1 reports on the incidence, risk factors and clinical characteristics of SORVL in a retrospective cohort of patients. Chapter 3.2 demonstrates the functional and structural changes in the retina following gas and SO tamponade in a prospective cohort of patients with maculaon as well as macula-off RRD. Subsequently, we studied the electrophysiology of the macula in order to localize the functional defect in SORVL and to discriminate between a maculopathy and an optic neuropathy (chapter 3.3). To better understand the underlying mechanisms of SORVL, we investigated one particular hypothesis that is proposed in literature (chapter 3.4).

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CHAPTER 2

Idiopathic epiretinal membrane

CHAPTER 2.1

Predictive factors for postoperative visual acuity in idiopathic epiretinal membrane: a systematic review

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Abstract

The aim of this study was to review the literature on predictive factors for postoperative visual acuity (VA) in surgery for idiopathic epiretinal membrane (ERM). A systematic review of the literature in the databases of PubMed and Embase was performed. The risk of bias was assessed based on predefined criteria and the results were summarized. In total, 1927 studies were retrieved of which 35 were potentially eligible. Nineteen studies were of adequate quality in terms of bias. Preoperative VA, central foveal thickness (CFT) and inner segment/outer segment (IS/OS) integrity on optical coherence tomography (OCT) were most extensively studied. Other preoperative factors studied were severity of metamorphopsia, several OCT parameters, fundus autofluorescence and multifocal electroretinogram. In the current literature, preoperative VA is the only variable consistently associated with postoperative VA. IS/OS integrity on OCT is probably associated, and the severity of metamorphopsia, cone outer segment tips integrity and fundus autofluorescence are possibly associated with postoperative VA. CFT is not associated with postoperative VA. Further studies with adequate methodological quality are needed to confirm these findings. Therefore, an overall prediction model, including different parameters, is still awaited.

Introduction

An idiopathic epiretinal membrane (ERM) is a common condition that can affect visual function. It may cause metamorphopsia and a slow decrease in visual acuity (VA). However, the severity of these symptoms varies, as well as the rate of progression. Pars plana vitrectomy with removal of the ERM is considered to be the standard treatment. The indication for this surgical procedure has not been standardized and clinical outcome varies.^{1–5} Careful selection of patients requiring treatment as well as timing of surgery is important in this elective procedure. Prediction of the visual outcome is essential for patients' counselling and for weighing the risks against the benefits of surgery.

In the past 15 years, many studies of different methodological qualities have addressed this issue. Also, several factors have been found to be associated with postoperative VA, but the results are not consistent. The purpose of this study was to review the literature on potentially predictive factors for postoperative VA, in idiopathic ERM, both in terms of methodological quality and of results.

Materials and methods

Search strategy and selection

A structured literature search in PubMed and Embase was performed on October 14th 2013 and a search filter with synonyms for 'epiretinal membrane', 'surgery' and 'VA' executed in 'title and/or abstract' was applied. No further limitations were used. The results of this query are shown in Tables S1 and S2.

Title and abstract screening of all retrieved articles was performed independently by two authors (LS and RvdV) using prespecified criteria. Studies were included if all following criteria were fulfilled: (1) adults with an idiopathic ERM; (2) treatment with vitreoretinal surgery; (3) measurement of preoperative factors; and (4) reporting of postoperative visual function. Criteria for exclusion were: (1) non-original research/review; (2) studies with less than five adults with idiopathic ERM; (3) studies describing techniques or guidelines; (4) studies in which surgical parameters are the primary measures of outcome; (5) studies with no separate analysis for idiopathic ERM; and (6) studies not in English, German, French, Spanish or Russian. Full-text screening on relevance was performed independently by the three authors (LS, RvdV and RvL) using the same in- and exclusion criteria (Figure 1).

Quality assessment

The quality of the selected articles was appraised independently by two authors (LS and RvL). A standardized checklist of predefined criteria, based on Moons et al. (Table S3) was used.⁶ The risk of bias was assessed for four items: selection bias (e.g. clear description of in- and exclusion criteria and indication for surgery), detection bias for the prognostic factor and for the outcome

(e.g. clear description of the method of measuring and the same setting for all participants), and treatment (e.g. reporting and standardization of surgical procedures). Retrospective studies have a higher risk of bias because of non-standardized procedures and were therefore ranked as moderate risk of bias as a maximum score for the population and outcome variables. All discrepancies were resolved by consensus discussion. Studies were considered to be of good quality when the potential bias was low or moderate for at least two of the four scored items. Assessment of all studies is presented in Table 1.



Figure 1 - Flowchart

Results

General

In total, we retrieved 1927 studies of which 60 met the selection criteria. After reviewing the fulltext, 34 publications remained that met all inclusion criteria. Reference checking yielded one extra article.⁷ The main reason for exclusion after reading the full-text was that preoperative factors were not analysed in relation to postoperative VA but in relation to other preoperative factors. The risk of bias in these 35 studies was assessed. Nineteen studies were selected based on the quality assessment with a total of 934 eyes and follow-up ranging from three to twelve months (Table 1).

Characteristics of these eligible studies and their correlation coefficients of the studied preoperative factors with postoperative VA are shown in Table 2. VA after surgery was statistically significant better than preoperative VA in all included studies.⁷⁻²⁵

Patient characteristics

Age and gender

The influence of age on postoperative VA was analysed in five studies.^{9,12,15,23,24} Nitta et al. found that a younger age was statistically significantly associated with visual improvement of 0.3 logMAR or more from baseline in patients with hyperfluorescent on fundus autofluorescence (FAF).²³ None of the other studies confirmed this association.^{9,12,15,24} Gender was studied by Falkner-Radler et al. but a statistically significant effect on postoperative VA was not found.¹²

Duration of symptoms

Four studies examined the effect of symptom duration on postoperative VA.^{9,16,23,25} Asaria et al. reported a negative correlation of the duration of symptoms with postoperative VA and with improvement of VA after three months of follow-up.⁹ Thus, the longer the symptoms were present, the lower the postoperative VA and the less gain in VA. The other three studies did not find a statistically significant correlation.^{9,16,25}

	Author	Design	F/U	Рор	Prog	Out	Treat
1	Mayer et al. (2013) ²²	pros	≥				
2	Brito et al. (2014) ²⁵	pros	≥				
3	Shiono et al. (2013) ²⁴	pros	≥				
4	Kinoshita et al. (2012) ¹⁷	pros	≥				
5	Koutsandrea et al. (2007) ⁸	pros	≥				
6	Nitta et al. (2013) ²⁶	pros	≥				
7	Inoue et al. (2010 and 2011) ^{13,27} *	pros	≥				
8	García-Férnandez et al. (2013) ²⁰	pros	≥				
9	Cobos et al. (2013) ¹⁹	retro	≥				
10	Mitamura et al. (2009) ¹⁰	retro	≥				
11	Shimozono et al. (2012) ¹⁸	retro	≥	•			
12	Kunikata et al. (2011) ¹⁴	retro	≥				
13	Suh et al. (2009) ¹¹	pros	<				
14	Kim et al. (2012) ¹⁵	retro	≥			•	
15	Falkner-Radler et al. (2010) ¹²	pros	<		•		•
16	Asaria et al. (2008) ⁹	pros	<	•			•
17	Kim et al. (2013) ¹⁶	pros	≥		•	•	
18	Itoh et al. (2013) ²¹	retro	≥		•		•
19	Niwa et al. (2003) ⁷	?	≥		•		•
20	Kwon et al. (2009) ²⁸	retro	2	•		•	
21	Massin et al. (2000) ²⁹	retro	<		•		
22	Shimada et al. (2011) ³⁰	?	≥	•	•	•	•
23	Kim et al. (2010) ³¹	retro	≥	•		-	•
24	Kinoshita et al. (2011) ³²	retro	?	•	•		•
25	Tilanus et al. (1997) ³³	retro	±				
26	Gao et al. (2012) ³⁴	retro	?	•	•	•	•
27	Geerts et al. (2004) ³⁵	retro	≥	•	•		•
28	Koerner et al. (1999) ³⁶	retro	±				
29	Moisseiev et al. (2011) ³⁷	retro	?	•		•	•
30	Gomes et al. (2009) ³⁸	retro	<		•	?	
31	Wong et al. (2005) ³⁹	pros	≥	•		•	•
32	Ameline-Chamuleau et al. (1996) ⁴⁰	?	<			?	
33	De Bustros et al. (1988) ⁴¹	retro	≥		•	•	•
34	Rice et al. (1986) ²	retro	±	•	•	•	•
35	Gunten et al. (1994) ⁴²	retro	±	•	•	•	•

Table 1 – Critical appraisal of potentially eligible studies

* Same data published in 2011 and in 2010

Design = study design; pros = prospective; retro = retrospective; ? = not described; F/U = follow-up time: \geq = 6 months or more in all subjects, \pm = 6 months or more in most subjects, < = less than 6 months in most subjects; Pop = study population (selection bias); Prog = prognostic factor (detection bias); Out = outcome (detection bias); Treat = treatment

e low risk of bias; 💛 = moderate risk of bias 🕈 = high risk of bias;? = risk of bias cannot be assessed

Ophthalmological examination

Preoperative visual acuity

Preoperative VA in relation to postoperative VA was investigated in nine studies.^{8,9,12–14,17,20,24,25} Eight studies found that better preoperative VA was associated with better postoperative VA.^{9,12–14,17,20,24,25} A stepwise multiple regression analysis was performed in two studies including inner segment/outer segment junction (IS/OS) integrity in one study and photoreceptor outer segment length and age in the other study. Both showed an independent and positive association of preoperative VA with postoperative VA after six and after twelve months, respectively.^{13,24} Koutsandrea et al. were the only study that did not find a statistically significant relation between pre- and postoperative VA.⁸

Preoperative VA in relation to visual improvement was studied in four studies.^{9,13,14,23} Three studies showed a statistically significant higher gain in VA in subjects with poorer preoperative VA after six and twelve months.^{9,13,23} This effect remained statistically significant in a multivariate analysis.¹³ Kunikata et al. could not find a relation with improvement in VA after three months.¹⁴

Metamorphopsia

Retinal deformation in ERM can cause symptoms of metamorphopsia. Metamorphopsia was investigated as a potential prognostic factor for postoperative VA in two studies.^{12,17} In one study, the severity of metamorphopsia was measured with M-charts that give a score for horizontal and for vertical metamorphopsia.¹⁷ The preoperative vertical metamorphopsia score was correlated with postoperative VA at twelve months and with the improvement of VA. A higher metamorphopsia score was associated with worse postoperative VA and with less improvement of VA. Falkner-Radler et al. did not find a statistically significant influence of the duration or the subjective grading of metamorphopsia measured with the Amsler grid on postoperative VA at three months.¹²

Preoperative metamorphopsia scores were not correlated with preoperative VA in both studies.^{12,17}

Table 2 - Characteristics of the eligible studies and their correlation coefficients of the studied preoperative factors with postoperative visual acuity

Study	Design	Ν	Inclusion criteria other than iERM	Mea (Log	an VA MAR)	No. of ey	phakic /es	CFT (µm)		Intact IS/OS		F/U (mos)
				pre	post	pre	post	pre	post	pre	post	
Mayer et al. (2013) ²²	Pros	31	 BCVA <20/32 and/or symptoms > 6 mos 			26/31	17/31					12
Brito et al. (2014) ²⁵	Pros	20	- pseudophakic	0.58	0.36	0/20	0/20	480	391	7/20	12/20	6
Shiono et al (2013) ²⁴	Pros	41		0.18	0.06	36/41	3/41	376	343			6
Kinoshita et al. (2012) ¹⁷	Pros	49	- metamorphopsia	0.38	0.09	43/49	0/49	418		35/49		12
Koutsandrea et al. (2007) ⁸	Pros	20	- BCVA ≤20/40	0.72	0.34	20/20	15/20	472	249			12
Nitta et al. (2013) ²⁶	Pros	37	- hyperfluorescent lines on FAF	0.46				449				12
Inoue et al. (2010 and 2011) ^{13,27}	Pros	45	- BCVA ≤20/32 - F/U 12 mos	0.42	0.09	44/45	2/45	457		34/45		12
García-Fernández et al. (2013) ²⁰	Pros	77	- F/U 12 mos	0.47	0.29	63/77	0/77	503	361			12
Cobos et al. (2013) ¹⁹	Retro	51	- F/U 6 mos	0.60	0.28	30/51	24/51	413		29/51	30/51	6
Mitamura et al. (2009) ¹⁰	Retro	70		0.35	0.14*	66/70	0/70	441*	292*	33/70	53/70	6
Shimozona et al. (2012) ¹⁸	Retro	50	- F/U 6 mos	0.28	0.10	47/50	0/50	356	303	50/50	48/50	6
Kunikata et al. (2011) ¹⁴	Retro	73		0.23	0.13	61/73	22/73	371	300			6
Suh et al. (2009) ¹¹	Pros	101	- F/U 3 mos	0.54^{\dagger}	0.18^{+}	91/101	55/101			54/101	64/101	3
Kim et al. (2012) ¹⁵	Retro	84	- F/U 12 mos			73/84	9/84	408		59/84		12
Falkner-Radner et al. (2010) ¹²	Pros	41		0.56	0.39	32/41	0/41	436	380	14/41		3
Asaria et al. (2008) ⁹	Pros	27		0.49								3
Kim et al. (2013) ¹⁶	Pros	52		0.32	0.18	37/52	37/52	372		34/52		6
Itoh et al. (2013) ²¹	Retro	46	- F/U 6 mos	0.28	0.01	41/46	1/46	463				6
Niwa et al. (2003) ⁷	?	29	- F/U 6 mos	0.39	0.09	24/29	0/29	411	268			6

Table 2 – Continued

Study	Age S	Symptom duration	VA	MMF	CFT	ΑΜΤ	Separate retinal layers	ELM integrity	IS/OS integrity	COST F integrity	AF mfERG	Other factors [∫]
Mayer et al. (2013) ²²							-		NR			
Brito et al. (2014) ²⁵		Х	NR		Х			Х	Х	0.	295 [‡]	Foveal contour
Shiono et al (2013) ²⁴	х		0.439)	х		PROS: -0.414					OFT ONT
Kinoshita et al. (2012) ¹⁷			0.418	8 0.311	Х				Х			
Koutsandrea et al. (2007) ⁸			Х		Х						Х	
Nitta et al. (2013) ²⁶	+	Х	+									
Inoue et al. (2010 and 2011) ^{13,27}			0.451	<u>_</u>	х				-0.271			Pseudohole Retinal cysts
García-Fernández et al. (2013) ²⁰			+									
Cobos et al. (2013) ¹⁹									+			
Mitamura et al. (2009) ¹⁰					Х				NR			
Shimozona et al. $(2012)^{18}$					х					NR		COST line defect
Kunikata et al. (2011) ¹⁴			0.44		0.24							
Suh et al. (2009) ¹¹					> 0.25	> 0.25						
Kim et al. (2012) ¹⁵	Х				0.475				0.302		0.302	
Falkner-Radner et al. (2010) ¹²	х		NR	Х	Х				NR			Gender, ILM profile, foveal contour
Asaria et al. (2008) ⁹	Х	0.23 [‡]	0.34 [‡]									
Kim et al. (2013) ¹⁶		х			х		GCL + IPL, INL: NR		Х			Parafoveal: OPL, ONL, PRL
Itoh et al. (2013) ²¹										COST line defect: 0.27 [‡]		ELM line defect, IS/OS line defect
Niwa et al. (2003) ⁷											0.543	

N = number of eyes; VA = visual acuity; MMF = metamorphopsia; LogMAR = Logarithm of the Minimum Angle of Resolution; CFT = central foveal thickness; IS/OS = inner segment/outer segment; F/U = follow up time; pre = preoperatively; post = postoperatively; mos = months; AMT = average macular thickness ELM = external limiting membrane; COST = cone outer segment tips; mfERG = multifocal electroretinogram; PROS = photoreceptor outer segment length; OFT = outer foveal thickness; ONT = outer nuclear layer thickness; ILM = inner limiting membrane; GCL + IPL = ganglion cell layer and inner plexiform layer thickness; INL = inner nuclear layer thickness; ORT = outer plexiform layer thickness; PRL = photoreceptor layer thickness; NR = not reported: factor was statistically significant but correlation coefficient was not reported; X = factor was studied but not statistically significant; + = statistically significant difference with Mann-Whitney-U test

* calculated afterwards; ⁺ median instead of mean; ¹ not statistically significant; ⁺ R² instead of simple regression coefficient

Optical coherence tomography

Central foveal thickness

The central foveal thickness (CFT) is the distance between the vitreoretinal surface and the retinal pigment epithelium (RPE) measured at the foveal centre on OCT. As ERM causes retinal thickening, many studies investigated this factor in relation with postoperative VA.^{8,10-18,24,25} Four studies found a statistically significant worse postoperative VA in patients with higher preoperative CFT values in a univariable analysis.^{11,14-16} This could not be confirmed by six other studies.^{8,10,13,17,18,24} A multivariate analysis performed with age, IS/OS integrity and multifocal electroretinogram parameters by Kim et al. showed no statistically significant effect of preoperative CFT on postoperative VA.¹⁵

Three studies also analysed the association between preoperative CFT and visual improvement.^{10,13,18} Only Mitamura et al. found that greater preoperative CFT is related to less improvement in VA. The other two studies did not find an association.¹⁰

Suh et al. also studied the average macular thickness, defined as the average thickness of a 1-mm circle centred on the fovea, in relation to postoperative VA and VA improvement, and stratified for preoperative IS/OS integrity.¹¹ A statistically significant correlation was found for VA three months after surgery, but not for VA improvement.¹¹

Thickness of separate layers

With the introduction of the spectral-domain OCT, the retina can be studied in much more detail (Figure 2). Two studies measured the thickness of separate retinal layers on OCT and analysed their associations with postoperative VA at six months.^{16,24} Kim et al. focused on the location close to the foveal centre where all retinal layers are present and measured the thickness of the ganglion cell layer (GCL) together with the inner plexiform layer (IPL), the inner nuclear layer (INL), the outer plexiform layer (OPL), the outer nuclear layer (ONL) and the photoreceptor layer (PRL).¹⁶ Shiono et al. measured only the foveal layers: the ONL, the outer foveal thickness and the photoreceptor segments (PROS) length.²⁴ The PRL and the outer foveal thickness both refer to the distance between the external limiting membrane (ELM) and the RPE. The PROS length is the distance between the IS/OS junction and the RPE. Only the preoperative thickness of the GCL plus IPL and of the INL was significantly associated with postoperative VA in the first study.¹⁶ The thinner the inner layers, the better the postoperative VA. This effect remained statistically significant in a multiple regression analysis for the INL thickness only. No associations were found with improvement in VA. The study of Shiono et al. revealed a statistically significant better postoperative VA for greater PROS lengths in a multiple regression analysis, including age and preoperative VA.²⁴ An association between preoperative ONL and PRL/outer foveal thickness measured at the fovea or at the parafovea and postoperative VA could not be found in both studies.^{16,24}



Figure 2 - Foveal optical coherence tomography parameters; GCL + IPL = ganglion cell layer and inner plexiform layer; INL = inner nuclear layer; OPL = outer plexiform layer; ONL = outer nuclear layer; ELM = external limiting membrane; IS/OS = inner segment/outer segment junction; COST = cone outer segment tips; RPE = retinal pigment epithelium

External limiting membrane integrity

ELM integrity is defined as the continuation of the hyper-reflective line corresponding to the ELM. A relation between ELM integrity and VA is described for retinal detachment, macular holes and age-related macular degeneration.⁴³⁻⁴⁵ In one study that examined this factor in ERM surgery, it was categorized into three groups: intact, minor disruption (< 200 μ m) or large disruption (> 200 μ m).²⁵ No statistically significant association with postoperative VA was found.²⁵ Shimozono et al. also planned to study ELM integrity but all subjects had a continuous ELM preoperatively.¹⁸

Itoh et al. analysed the ELM defect diameter as a predictor for postoperative VA but a statistically significant correlation was not found.²¹

Inner segment/outer segment integrity

Alignment of the discs in photoreceptor outer segments is essential for normal visual functioning and this may be represented by an intact IS/OS junction on OCT.^{39,46} IS/OS integrity was defined as the continuation of the hyper-reflective line corresponding to the IS/OS junction. The predictive value of the IS/OS integrity on the postoperative VA was studied in eight studies using different rankings for IS/OS assessment.^{10,12,13,15,16,19,25,32} In five studies, IS/OS was categorized in two groups: intact and irregular/disrupted/missing.^{13,15,16,19,37} Two studies graded IS/OS integrity as intact, irregular/disrupted and missing/invisible^{10,12} and one study as intact, minor disruption (< 200 μ m) and large disruption (> 200 μ m).²⁵ Five studies found a statistically significant worse postoperative VA in patients with preoperative disruption of the IS/OS layer on OCT.^{10,12,13,15,19} This effect on postoperative VA after twelve months remained statistically significant in a stepwise multiple regression analysis, including preoperative VA and OCT parameters performed in two studies.^{13,15} Kim et al. also included multifocal electroretinogram parameters in the multiple regression analysis.¹⁵ In contrast, three studies did not find a statistically significant effect of preoperative IS/OS integrity on postoperative VA.^{16,17,25} Shimozono et al. also planned to study IS/OS integrity, but this was not possible as all subjects had a continuous IS/OS junction preoperatively.¹⁸

Preoperative IS/OS integrity in relation to visual improvement was investigated in six studies.^{10,12,13,15,19,22} Three studies reported a statistically significant higher gain in VA after six and twelve months for patients with a continuous IS/OS junction preoperatively^{13,19,22} Falkner-Radler et al. compared eyes with an intact or disrupted IS/OS junction to those with an invisible junction and found that eyes with an intact or disrupted IS/OS junction experienced more visual improvement after three months than eyes in which the IS/OS junction was not visible.¹² A statistically significant relation between preoperative IS/OS integrity and visual improvement could not be confirmed by two studies.^{10,16} Itoh et al. studied IS/OS defect diameter but no statistically significant correlation with postoperative VA was found.²¹

Cone outer segment tips integrity

The cone outer segment tips (COST), also known as Verhoeff membrane, are visible on OCT as a hyper-reflective line between the IS/OS junction and the RPE (Figure 2). Disruption of the COST line might be a sign of photoreceptor damage and is considered as a potential predictor for postoperative VA in two studies.^{18,21} A continuous COST line on OCT preoperatively was associated with better VA six months after surgery.^{18,21} The correlation between the preoperative defect diameter of the COST line with postoperative VA showed a strong statistically significant association.²¹

Other retinal changes

Preoperative foveal contour on OCT is found not to affect postoperative VA after three or six months in two studies.^{12,25} ILM profile evaluated on OCT as normal, or mildly or severely distorted, does not seem to affect postoperative VA after three months.¹² The preoperative presence or absence of retinal cysts or macular pseudoholes on OCT is also not related to postoperative VA after twelve months.¹³

Fundus autofluorescence

One study investigated whether FAF is useful for the prediction of postoperative VA after six months.²⁵ Autofluorescence mainly results from lipofuscin in the RPE, which is derived from incompletely digested photoreceptor discs.⁴⁷ Photoreceptor cell loss due to an ERM will lead to decreased lipofuscin levels, and as a consequence, an increase in foveal hypo-autofluorescence can be seen on FAF. A three-grade classification based on signal intensity and the extent of the hypofluorescent area was used. Preoperative foveal autofluorescence and postoperative VA were statistically significant correlated. Eyes with an enlarged hypofluorescent area encompassing the foveal and parafoveal area had lower VA six months after surgery.²⁵

Multifocal electroretinogram

An objective assessment of visual function can be obtained by multifocal electroretinogram (mfERG). The potential predictive value of mfERG parameters on postoperative VA was investigated in two studies.^{8,15} The amplitude and the implicit time of the negative and the positive peak of the biphasic mfERG response were studied in both. The amplitude and the implicit time of the positive peak were found to be statistically significant related to postoperative VA after twelve months in a univariable analysis by Kim et al.¹⁵ In multiple regression analysis, only the implicit time remained statistically significant. No statistically significant associations between mfERG parameters and postoperative VA after six months were found by Koutsandrea et al.⁸

Discussion

We examined the literature on predictive factors for VA after ERM surgery and found that preoperative VA was consistently associated, IS/OS integrity was probably associated and severity of metamorphopsia, COST integrity and FAF are possibly associated with postoperative VA.

The finding that a better preoperative VA predicts a better postoperative VA is plausible. In these cases, the ERM apparently causes a mild functional disturbance, or the ERM was present for a short period of time. From a clinical point of view, it is more interesting to look for improvement in VA as an outcome measure, in contrast to absolute VA and evaluate what the potential improvement in VA is in a patient with an ERM and a VA of 0.3 on a Snellen chart. In subjects with lower preoperative VA more visual improvement can be expected because they have more to gain after surgery. However, this only holds if their lower VA is not a result of irreversible damage. To distinguish low VA because of irreversible anatomical damage and low VA because of reversible functional disturbance, a prognostic model including more than preoperative VA is needed. At this moment, merely qualitative associations were reported. Only Kunikata et al. reported on a prognostic model including VA and CFT.¹⁴

Optical coherence tomography parameters to predict surgical outcome are objective and easy to reproduce. The introduction of the frequency-domain OCT made it possible to depict the retina in much more detail and provided the opportunity to study OCT parameters other than CFT. Integrity of the IS/OS layer appears to be a relevant parameter as well as integrity of the COST and PROS length, but confirmation by other studies is necessary. IS/OS integrity is consistently reported to correlate with preoperative and with postoperative VA in the included studies. Associations with VA are also found in untreated ERM eyes and in other retinal diseases as lamellar macular hole, central serous retinopathy and Stargardt disease.^{48–52} PROS length has been shown to correlate with VA in patients with diabetic macular oedema, retinitis pigmentosa and after surgery for ERM.^{53–55}

A statistically significant influence of CFT on postoperative VA or visual improvement was found in four studies and all used time-domain OCT (TD-OCT).^{10,11,14,15} Studies that did not find such an effect obtained CFT measurements by spectral-domain or high-definition OCT except for Koutsandrea et al. who also used TD-OCT.^{8,12,13,16–18,24,25} The use of different OCT devices may explain these different results. We cannot explain the differences in findings for IS/OS integrity.

IS/OS and COST integrity and PROS length seem to be the most promising predicting factors but all refer to the outer retinal layers while the ERM is located on the inner retina. Kim et al. were the only to study the parafoveal inner layers and found that thinner GCL plus INL and thinner IPL were statistically significantly associated with better VA after surgery.¹⁶ The pathological mechanism that can elucidate these results in relation to the ERM-associated symptoms, such as visual loss and metamorphopsia, is still unknown, but possible theories have been proposed. Ooto et al. studied metamorphopsia and foveal microstructure in ERM and normal eyes and suggested that changes in the INL can explain the occurrence of lowered VA and metamorphopsia.⁵⁶ Like Kim et al., they hypothesized that ERM contraction leads to stretching of the INL or to oedema which may disorganize the cell bodies that comprise the INL.¹⁶ This might inhibit normal functioning of the synaptic junctions and lower photoreceptor sensitivity, leading to metamorphopsia. Visual loss may result from aberrations in the retina induced by thickening of the GCL and the INL.^{16,56,57} Indications for inner retinal damage are supported by two studies that investigated ERG parameters and found the positive or b-waves to be more affected than the negative or a-waves, which indicates Müller or bipolar cells dysfunction.^{7,15} Both conclude from these results that impairment of the inner retina precedes photoreceptor layer damage.

Other studies speculate about mechanisms to explain ERM-induced symptoms by outer retinal changes. The junctional complexes between the Müller cells and the photoreceptor cell have atypical projections that extend beyond the ELM.⁵⁸ Therefore, ERM-mediated traction on the inner retina is likely to reach the ELM at the fovea and may cause not only retinal thickening but also varying degrees of distortional forces in the photoreceptor layer.^{55,59} This anatomical destruction of the photoreceptor layer may subsequently lead to disturbance of the COST line and shortening of foveal PROS length.⁵⁵ Okamoto et al. studied structural changes in the photoreceptor cell layer on high-resolution images obtained by adaptive optics scanning laser ophthalmoscopy in patients with idiopathic ERM compared to normal subjects.⁶⁰ Compared with normal eyes, ERM eyes showed an abnormal cone mosaic pattern with multiple thin, straight and hyporeflective lines in the photoreceptor layer, the so-called microfolds. Patients with foveal microfolds had more severe metamorphopsia measured with M-charts and greater average CFT detected by spectral-domain OCT. The mean cone density did not differ between ERM and normal eyes suggesting that cone loss due to ERM is unlikely or minimal.

These findings may indicate that tractional forces on the inner retina can reach the photoreceptor layer via the Müller cells and that visual symptoms may be caused by anatomical
damage of the inner retina as well as the outer retina. Parameters comprising the photoreceptor layer might well predict VA after surgery, although it may also implicate irreversible damage with worse postoperative results. However, restoration of IS/OS junction is also reported.^{10,11,25}

Prognostic studies are investigations of future events or the evaluation of associations between risk factors and health outcomes in populations of patients.^{6,61} The results of such studies tell us about the clinical course of a disease and help us in the decision-making of patient's management. They do not provide evidence of a causal relationship. The ultimate goal of a prognostic study is to formulate a prediction model and estimate the sensitivity and specificity of this model. Kim et al. report the predictive value of preoperative first-order positive peak implicit time of an ERG as predictor for final BCVA >20/25.¹⁵ No other parameters were included in this model. Unfortunately, ERG is not easily obtained in clinical practice. Itoh et al. present an equation that predicts postoperative BCVA at twelve months based on the preoperative BCVA in a multivariable model including COST line defect. Unfortunately, they did not report the number of subjects included in this analysis. This finding should be confirmed by others.

To our knowledge, this is the first review on predictors for postoperative VA in idiopathic ERM. The main strengths of this study are the systematic literature search and the methodological quality assessment. However, the risk of bias in the potentially eligible studies was rather high for several reasons. The risk of selection bias was high because a clear definition of the study population could not be obtained from most studies as in- and exclusion criteria and surgical indications were poorly reported. The risk of detection bias of predictors, however, was low in most studies because measurement of the predictors was standardized. The timing of the postoperative VA measurement was not the same for all subjects in some studies, increasing the risk of detection bias for the outcome. The effect of potential predictors may differ over time and as a consequence comparisons between subjects with different follow-up time will be unreliable. There are also limitations to this review. First, the nineteen included studies were heterogeneous, and effect sizes of associations were usually not reported. For that reason, we were unable to perform a formal meta-analysis. Also, some recently described factors, like COST integrity, were only reported once and further research is required to draw firm conclusions.

The role of cataract should be mentioned. Most subjects were phakic preoperatively and underwent vitrectomy with concomitant cataract surgery so that the final visual outcome is not likely to be affected by (progressive) cataract formation. Postoperative VA is then, however, the combined effect of the vitrectomy and the cataract extraction. This will interfere with a possible association between pre- and postoperative VA. However, this should not be a problem when studying an association between anatomical parameters of the retina and postoperative VA, because these parameters are independent of lens status. So, for prognostic studies, concomitant cataract surgery is not a problem for the analysis. For an individual patient, the grade of cataract is of course relevant for the result of the surgery.

The aim of this systematic review was to give a critical appraisal of the current literature on predictors for clinical outcome after surgery for idiopathic ERM. In total, 35 relevant studies were identified, but the quality of the studies varied. Preoperative VA is the only variable to be consistently associated with postoperative VA. IS/OS integrity on OCT is probably associated and the severity of metamorphopsia, COST integrity and FAF are possibly associated with postoperative VA. CFT is not associated with postoperative VA. Further studies of good methodological quality are needed to confirm these findings. An overall prediction model, including different parameters is still awaited. Table S1 - PubMed search strategy

#1	(((("macular"[Title/Abstract]) OR "epiretinal"[Title/Abstract]) OR "preretinal"[Title/Abstract]) OR
	"cellophane"[Title/Abstract]) OR "opaque"[Title/Abstract]
#2	((((("membrane"[Title/Abstract]) OR "membranes"[Title/Abstract]) OR "pucker"[Title/Abstract])
	OR "puckers"[Title/Abstract]) OR "fibrosis"[Title/Abstract]) OR "maculopathy"[Title/Abstract]
#3	#1 AND #2
#4	(("ERM" [Title/Abstract]) OR "retinal folds"[Title/Abstract]) OR "retinal folding"[Title/Abstract]
#5	#3 OR #4
#6	(((("peeling"[Title/Abstract]) OR "vitrectomy"[Title/Abstract]) OR "ppv"[Title/Abstract]) OR
	"surgery"[Title/Abstract]) OR "surgical"[Title/Abstract]
#7	("visual"[Title/Abstract]) OR "functional"[Title/Abstract]
#8	((((((("outcome"[Title/Abstract]) OR "outcomes"[Title/Abstract]) OR "acuity"[Title/Abstract])
	OR "function"[Title/Abstract]) OR "functions"[Title/Abstract]) OR "functioning"[Title/Abstract])
	OR "improvement"[Title/Abstract]) OR "improvements"[Title/Abstract]) OR
	"improve"[Title/Abstract]) OR "improves"[Title/Abstract]) OR "improved"[Title/Abstract]) OR
	"improving"[Title/Abstract]) OR "recovery"[Title/Abstract]) OR "recover"[Title/Abstract]) OR
	"recovers"[Title/Abstract]) OR "recovered"[Title/Abstract]) OR "recovering"[Title/Abstract]
#9	#7 AND #8

#10 #5 AND #6 AND #9

Table S2 – Embase search strategy

#1	(((('macular':ab,ti) OR 'epiretinal':ab,ti) OR 'preretinal':ab,ti) OR 'cellophane':ab,ti) OR
	'opaque':ab,ti
#2	((((('membrane':ab,ti) OR 'membranes':ab,ti) OR 'pucker':ab,ti) OR 'puckers':ab,ti) OR
	'fibrosis':ab,ti) OR 'maculopathy':ab,ti
#3	#1 AND #2
#4	(('ERM':ab,ti) OR 'retinal folds':ab,ti) OR 'retinal folding':ab,ti
#5	#3 OR #4
#6	(((('peeling':ab,ti) OR 'vitrectomy':ab,ti) OR 'ppv':ab,ti) OR 'surgery':ab,ti) OR 'surgical':ab,ti
#7	('visual':ab,ti) OR 'functional':ab,ti
#8	((((((((((((((((()(())())))))))))) OR 'outcomes':ab,ti) OR 'acuity':ab,ti) OR 'function':ab,ti) OR
	'functions':ab,ti) OR 'functioning':ab,ti) OR 'improvement':ab,ti) OR 'improvements':ab,ti) OR
	'improve':ab,ti) OR 'improves':ab,ti) OR 'improved':ab,ti) OR 'improving':ab,ti) OR 'recovery':ab,ti)

OR 'recover':ab,ti) OR 'recovers':ab,ti) OR 'recovered':ab,ti) OR 'recovering':ab,ti

- #9 #7 AND #8
- #10 #5 AND #6 AND #9

Type of bias	Considered items for the assessment of potential bias	Risk of bias
Selection bias	 Study participation Well-defined source population for idiopathic macular pucker In- and exclusion criteria are adequately described Indication for surgery is adequately described 	Low Moderate High Uncertain
Detection bias (prognostic factor)	 Prognostic factor measurement Clear definition of prognostic factors is provided Clear description of method of prognostic factor measurement Method of measurement of prognostic factor is adequately valid and reliable Method and setting of prognostic factor measurement are the same for all subjects Continuous variables are reported or adequate cut-off points are used 	Low Moderate High Uncertain
Detection bias (outcome)	 Outcome measurement Clear definition of outcome is provided including duration of follow-up Clear description of method of outcome measurement Method of measurement of outcome is adequately valid and reliable Method and setting of outcome measurement are the same for all subjects 	Low Moderate High Uncertain
Treatment	 Treatment Clear description of treatment and surgical variables Treatment the same for all subjects Indications are described if different treatments are given 	Low Moderate High Uncertain

Table S3 – Standardized checklist of predefined criteria for quality assessment

CHAPTER 2.2

Prognostic factors associated with visual outcome after pars plana vitrectomy with internal limiting membrane peeling for idiopathic epiretinal membrane

Kamil G. Laban, Laura M. Scheerlinck, Redmer van Leeuwen

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Abstract

Purpose: Pars plana vitrectomy with internal limiting membrane (ILM) peeling for idiopathic epiretinal membrane has shown varying results. More data are needed on the factors associated with visual outcome.

Methods: We extracted baseline clinical characteristics, optical coherence tomography (OCT) characteristics and 3-month postoperative best-corrected visual acuity (BCVA). Linear regression analysis was used to evaluate whether baseline and OCT characteristics are associated with BCVA at 3-months as well as BCVA difference.

Results: Out of 82 operated eyes, 66 (80%) had 3-month follow-up, and 47 (71%) showed 3month postoperative improvement. Preoperative BCVA was an independent determinant of postoperative BCVA (r = 0.31; p < 0.01) and BCVA difference (r = 0.68; p < 0.01). Other baseline and OCT characteristics showed no independent associations with postoperative outcome.

Conclusion: Better preoperative BCVA predicts better postoperative BCVA. Other baseline and OCT characteristics are not associated with visual outcome 3 months after surgery.

Introduction

Idiopathic epiretinal membrane (iERM) can lead to severe loss in visual acuity (VA) and metamorphopsia. Although pars plana vitrectomy (PPV) with internal limiting membrane (ILM) peeling for iERM has been shown successful in many cases, a substantial number of patients do not show VA improvement, and some patients even show a decrease in VA after surgery.^{2,62–65} Therefore, many studies have looked for potential predictors of postoperative VA.⁶⁶ Associations with postoperative VA have been reported for preoperative VA^{2,39,41,62,66,67}, shorter duration of symptoms^{2,41,62}, integrity of photoreceptor inner segment/outer segment (IS/OS) line^{67–71} and integrity of foveal cone outer segment tips (COST) line^{72,73}, measured with optical coherence tomography (OCT). Also, a low preoperative VA has been associated with a larger improvement in VA compared to a higher preoperative VA^{2,39}. Other possible determinants such as the presence of cystoid macular edema (CME)⁷⁴, lens status⁶², intraoperative complications⁶², macular thickness^{69,75}, photoreceptor outer segment (PROS) length^{16,24} and inner nuclear layer thickness^{16,24}, have shown inconsistent results or results that have not been reproduced. To improve counselling of patients and better specify indications for PPV, more data are needed on factors predicting visual outcome.

Methods

This study was conducted at the University Medical Center Utrecht, the Netherlands, a tertiary referral center for patients with iERM. The study was performed in accordance with the ethical standards laid down by the Declaration of Helsinki and its later amendments. For the purpose of this study we included all patients receiving PPV with iERM and ILM peeling between June 1, 2011 and May 31, 2013. Patients were excluded if ERM was secondary to another retinal pathology, in case of ERM recurrence, in case of vitreomacular traction and in the presence of diabetic retinopathy affecting vision. ERM after previous macula-on retinal detachment was not excluded.

After referral from secondary hospital care, indication for surgery was made after clinical examination. Patients were eligible for surgery if they had progressive and symptomatic visual impairment or metamorphopsia leading to binocular complaints.

Surgical intervention in all patients consisted of 20-, 23- or 25-gauge PPV with ERM peeling and subsequent ILM peeling by 1 of 4 vitreoretinal surgeons. ILM peeling was assisted by the use of 2.5 mg/ml infracyanine green to confirm complete removal. By discretion of the surgeon, phakic patients with some degree of cataract received combined surgery including phacoemulsification with intraocular lens implantation.

Patients were examined preoperatively and postoperatively, at day 1 and 7, and after 1 and 3 months. Longer follow-up was not consistent. Clinical examination included best-corrected distance visual acuity (BCVA) measured by Snellen charts. Data were collected on age, gender, symptoms of iERM (including metamorphopsia), duration of symptoms, lens status, and ophthalmologic history.

Postoperative outcome variables were postoperative BCVA, BCVA difference, and occurrence of complications including cataract progression or formation. Postoperative BCVA at the final follow-up was extracted separately to verify the associations.

Optical coherence tomography

Preoperatively, OCT was performed using Cirrus HD-OCT (Carl Zeiss Meditec AG, Jena, Germany) or Spectralis SD-OCT (Heidelberg Engineering GmbH, Heidelberg, Germany). The scans covered a 6 x 6 mm area with 2 mm depth. OCT scans were assessed by 1 grader (K.G.L.) and in case of doubt by a consensus meeting with 2 others (L.M.E.S and R.v.L). Measurements were performed using a complementary software measuring tool (Carl Zeiss, Meditec, version 6.5 Cirrus HD-OCT software or Heidelberg Engineering, version 5.4.6 Spectralis SD-OCT software) to determine the COST lesion length, central foveal thickness (CFT), outer plexiform layer thickness, outer nuclear layer thickness, outer foveal thickness (OFT), and PROS length (Figure 1A). Distances were measured in micrometers. CFT was defined as the distance between the retinal pigment epithelium (RPE) and the vitreoretinal surface at the foveal center [10,11,13-15,18,20], OFT was defined as the distance between RPE and the external limiting membrane (ELM) ²⁴, and PROS length was defined as the distance between the RPE and the IS/OS junction ²⁴. The integrity of the ELM, IS/OS line, COST line, and RPE was assessed and categorized as 'continuous', 'disrupted', or 'not well defined' (Figure 1B). The presence of pseudoholes (including lamellar holes) and CME were noted (Figure 1C). Also, parafoveal thickness was automatically assessed using raster scans (Figure 2), and included central thickness, superior thickness, temporal thickness, inferior thickness, and nasal thickness.



Figure 1 - OCT characteristics. **a** Example of an epiretinal membrane (marked with arrowhead) with retained integrity of retinal lines. Measurements were taken in micrometers of central foveal thickness (a), outer plexiform layer (b), outer nuclear layer (c), outer foveal thickness (d), and photoreceptor outer segment length (e), as shown. **b** Example of CME presence. **c** Example of disrupted ELM, IS/OS and COST (marked with arrowheads). RPE retained integrity.



Figure 2 - Optical coherence tomography raster scan with retinal thickness measurements of the right eye. Measurements are in micrometers. CT = central thickness; ST = superior thickness; TT = temporal thickness; IT = inferior thickness; NT = nasal thickness.

Outcomes

The primary outcome was BCVA 3-months after surgery and the secondary outcome was BCVA difference, defined as BCVA at 3-months minus baseline BCVA.

Statistical analysis

BCVA measurements were converted to logarithm of the minimum angle resolution (LogMAR) VA for analysis. Values are presented in number with percentage (%), means with standard deviations (± SD), or medians with interquartile ranges (IQR). One-way ANOVA and univariable linear regression were used to test the correlation of baseline and OCT characteristics with preoperative BCVA, 3-month postoperative BCVA or BCVA difference. A p value <0.05 was considered to be statistically significant. Multivariable linear regression analyses were performed to evaluate if baseline characteristics and OCT characteristics were independent predictors for postoperative BCVA and BCVA difference.

Results

In total, the medical charts of 105 eyes in 103 patients were reviewed. We excluded 8 eyes due to recurring ERM after previous ERM peeling, 7 eyes diagnosed with coexisting vitreomacular traction, 6 due to secondary ERM after macula-off retinal detachment, and 2 eyes due to macular degeneration. Eventually, 82 eyes of 80 patients were included in this study. Sixteen patients (19.5%) were lost to follow-up, leading to 66 eyes of 65 patients with a 3-month analysis. ERM and ILM were successfully removed in all operated eyes. Patients lost to follow-up did not differ from included patients in baseline characteristics and OCT parameters, except for a higher COST-lesion length.

Baseline characteristics

Baseline characteristics and associations are presented in Table 1. Mean \pm SD preoperative BCVA was 0.41 \pm 0.26 LogMAR, and 0.27 \pm 0.21 LogMAR for postoperative BCVA. PPV only was performed in 27 pseudophakic eyes (40.9%) and in 21 phakic eyes (31.8%), and 18 eyes (27.3%) underwent combined surgery with phacoemulsification and intraocular lens implantation. At 3 months postoperatively, clinically significant cataract or posterior capsule opacification was reported in 8 eyes (12.1%), CME in 5

eyes (7.6%), macular hemorrhage in 1 eye (1.5%), and retinal atrophy in 1 eye (1.5%). Mean \pm SD threemonth BCVA was 0.26 \pm 0.23 LogMAR in a subgroup analysis excluding 21 phakic eyes at risk of postoperative cataract. Perioperative complications included retinal hemorrhage in 6 eyes (9.1%); high intraocular pressure in 3 eyes (4.5%); and vitreous hemorrhage in 1 eye (1.5%). However, these were not considered to affect BCVA at 3 months. At 3 months postoperatively, 47 patients (71.2%) showed improvement of BCVA compared to preoperative BCVA.

		All eyes
Variable		66
Age (years)	median (IQR)	70 (65-74)
Males	n (%)	30 (45.5)
Metamorphopsia	n (%)	39 (59.1)
Duration symptoms (months)	median (IQR)	11 (6-24)
Pseudophakia	n (%)	27 (40.9)
History of retinal detachment (without		
macular involvement)	n (%)	10 (15.2)
Combined surgery	n (%)	19 (28.7)
Preoperative BCVA Three month Postoperative BCVA Three month BCVA difference Three month improvement Maximum BCVA	mean (sd) mean (sd) mean (sd) n (%) mean (sd)	0.41 (0.26) 0.27 (0.21) -0.14 (0.28) 47 (71.2) 0.17 (0.16)
Time of maximum BCVA (months postoperatively) Maximum BCVA difference	median (IQR) mean (sd)	4 (3-8) -0.24 (0.25)
Improvement at maximum BCVA	n (%)	59 (89.4)

Table 1 - Baseline characteristics of included eyes

Values are expressed as median (IQR), n (%) or mean ± SD.

A lower preoperative BCVA was statistically significantly associated with less metamorphopsia at baseline (r = 0.26, p = 0.04). Also, preoperative BCVA was statistically associated with three-month postoperative BCVA (r = 0.31, p < 0.01; Figure 3A), and BCVA difference (r = 0.68, p < 0.01; Figure 3B). This means that a better preoperative BCVA results in a better postoperative BCVA, and a lower preoperative BCVA results in a greater BCVA improvement. The other clinical characteristics showed no

statistically significant associations with 3-month postoperative BCVA or BCVA difference in univariable and multivariable analysis adjusted for preoperative BCVA (Table 2).

Mean \pm SD BCVA at final follow-up was 0.17 \pm 0.16 LogMAR with a median (IQR) follow-up of 4 months (3-8) after surgery. An improvement was found in 59 eyes (89.4%). Univariable and multivariable analyses revealed no independent associations of baseline characteristics and BCVA or BCVA difference at the final follow-up (data not shown).

		Preo	perative	Posto	perative	В	CVA
	All eyes	В	CVA	В	CVA	diffe	erence
Variable	66	r	P-value	r	P-value	r	P-value
Age (years)	70 (65-74)	0.16	0.21	0.07	0.59	0.21	0.09
Males	30 (45.5)	0.04	0.72	0.03	0.79	0.07	0.58
Metamorphopsia	39 (59.1)	0.26	0.04	0.09	0.48	0.18	0.24
Duration symptoms							
(months)	11 (6-24)	0.13	0.32	0.10	0.45	0.21	0.12
Pseudophakia	27 (40.9)	0.14	0.25	0.16	0.20	0.01	0.93
History of retinal							
detachment (without							
macular involvement)	10 (15.2)	0.22	0.07	0.02	0.90	0.23	0.06
Preoperative BCVA	0.41 (0.26)	-	-	0.31	< 0.01	0.68	< 0.01

Table 2 - Univariable correlations with preoperative best-corrected visual acuity (BCVA), three-month postoperative BCVA, and difference between three-month postoperative and preoperative BCVA

Values are expressed as median (IQR), n (%) or mean ± SD. r = Linear regression coefficient.



Figure 3 - Linear regression plot of preoperative BCVA with 3-month postoperative BCVA (**a**) and BCVA difference (**b**, defined as three-month postoperative BCVA minus preoperative BCVA). A better preoperative BCVA leads to a better postoperative BCVA (**a**) and a lower preoperative BCVA results in a greater BCVA improvement. BCVA was measured in logMAR scale.

Optical coherence tomography

OCT characteristics and associations are presented in Table 3. In total 61 eyes (92%) were measured by Cirrus HD-OCT and 5 eyes (8%) by Spectralis SD-OCT. Raster measurements of all parafoveal areas, CFT, OFT, and PROS-length showed an association with preoperative BCVA (p < 0.01), reflecting lower preoperative BCVA in patients with thickened parafoveal areas and greater PROS-lengths. Preoperative OCT measurements showed no statistically significant associations with 3-month postoperative BCVA in univariable analysis or in multivariate analysis adjusted for preoperative BCVA. Higher values for central raster thickness and CFT were associated with a greater BCVA difference (r = 0.30, p = 0.02; and r = 0.32, p < 0.01, respectively). However, in a multivariable analysis including preoperative BCVA, this association lost its statistical significance for central raster thickness (r = 0.03, p = 0.77), and CFT (r = 0.10, p = 0.35). The integrity of ELM, IS/OS and COST lines was not found to be statistically significantly associated with preoperative BCVA, 3-month postoperative BCVA or BCVA difference.

Univariable and multivariable analyses revealed no independent associations of OCT characteristics with BCVA at the final follow-up. Multivariable analysis revealed no independent associations of OCT characteristics with BCVA difference adjusted for preoperative BCVA (data not shown).

	All eyes	Preope	rative BCVA	Postope	erative BCVA	BCVA	difference
OCT Variable	66	r	P-value	r	P-value	r	P-value
Signal strength	8 (7-8)						
Continuous RPE	66 (100)						
Continuous ELM	49 (74.2)	0.08	0.56	0.14	0.28	0.05	0.69
Continuous IS/OS	45 (68.2)	0.05	0.67	0.10	0.43	0.14	0.29
Continuous COST	12 (18.2)	0.02	0.91	0.02	0.89	0.01	0.98
COST lesion length in μm	992 (683)	0.36	0.02	0.08	0.63	0.27	0.08
Central thickness in μ m	492 (92)	0.42	< 0.01	0.16	0.21	0.30	0.02*
Superior thickness in μm	451 (79)	0.35	< 0.01	0.16	0.21	0.22	0.09
Temporal thickness in μ m	449 (79)	0.32	0.01	0.21	0.10	0.14	0.26
Inferior thickness in µm	434 (67)	0.35	< 0.01	0.24	0.06	0.15	0.25
Nasal thickness in μm	447 (62)	0.44	< 0.01	0.24	0.06	0.24	0.05
CFT in µm	444 (143)	0.35	< 0.01	0.04	0.78	0.32	< 0.01*
Outer plexiform layer in μm	31 (26)	0.26	0.05	0.17	0.21	0.13	0.33
Outer nuclear layer in µm	222 (80)	0.12	0.35	0.01	0.94	0.12	0.33
Outer foveal thickness in μm	89 (21)	0.38	< 0.01	0.20	0.11	0.21	0.10
PROS-length in µm	61 (21)	0.37	< 0.01	0.15	0.23	0.24	0.06
Pseudohole	11 (16.7)	0.13	0.29	0.08	0.51	0.20	0.11
CME	21 (31.8)	0.11	0.36	0.17	0.17	0.03	0.84

Table 3 - Optical coherence tomography (OCT) characteristics and univariable associations with preoperative best-corrected visual acuity (BCVA), three-month postoperative BCVA, and difference between three-month postoperative and preoperative BCVA.

Values are expressed as median (IQR), mean ± SD or n (%). r = Linear regression coefficient.

*Not statistically significant in multivariable analysis adjusted for preoperative BCVA; (p > 0.05).

Discussion

The results of our study show that preoperative VA has a prognostic value for postoperative BCVA and BCVA difference. Other baseline and OCT parameters were not independently associated with 3-month postoperative BCVA or BCVA difference.

The predictive value of preoperative BCVA for postoperative BCVA has been reported several times with consistent results.^{2,39,41,62,66,67,71,75,77} Our results show a similar association indicating that preoperative BCVA is a reproducible prognostic factor for postoperative BCVA. A better preoperative BCVA results in a better postoperative BCVA. A lower preoperative BCVA results in a greater BCVA is preoperative BCVA. Therefore, even patients with low BCVA could benefit from iERM surgery.

Previously, multiple preoperative factors have been proposed as predictors for visual outcome after ERM surgery. Although predictive values of some factors have been reproduced in different studies, substantial variation in results exists. Duration of symptoms has been studied as determinant for postoperative outcome.^{2,24,25,41,62,67,72,77,78} Similar to other studies^{16,25,78}, we did not find an association

between duration of symptoms and postoperative VA. A possible explanation could be the subjective nature of these symptoms with unreliable estimation of symptom duration.⁷² Also, 28% of the included eyes in this study had some degree of cataract before surgery. This might have affected VA and influenced the severity and duration of symptoms. In concordance with previous results^{16,24,67,77}, we did not find an effect of age and gender on postoperative VA.

Until now, the most consistent results on prognostic OCT parameters have been reported for IS/OS integrity. An intact IS/OS line seems to be associated with better postoperative VA in most studies.^{67–72} However, other studies did not find this association.^{16,17,25} In our study, we were unable to reproduce the association between IS/OS line integrity and postoperative VA. This may be explained by the difficult interpretation of the IS/OS line. Also, the use of different rating scales of IS/OS line integrity reduces inter-study comparison. In our study, 68% of the analyzed eyes had intact IS/OS lines preoperatively. This was similar to the range of intact IS/OS junction in other studies^{16,17,19,68,71,72}, although some studies had lower intact IS/OS line rates (between 34 and 47%).^{25,67,70} Central retinal thickness and CFT have been investigated in multiple studies and associations have been described.^{16,69,72,75} However, in our study as well as other studies, this association was not found.^{17,24,70,71,76} Also, CFT has been associated with BCVA difference in one study⁷⁰, but similar to two other studies^{71,76}, we did not find this association.

ELM integrity was investigated in one small study²⁵, but similar to our results, an association with postoperative BCVA was not found. COST line integrity has been investigated previously.^{73,76} One study found that an intact COST line was associated with better postoperative BCVA⁷⁶, while the second study found that a smaller COST line lesion length was associated with a better postoperative BCVA. In our study no associations were found. One study⁷⁶ had a different COST line disruption rate in their population (48% vs. 88%), and both studies had different mean COST line lesion lengths (323µm⁷⁶ and 893µm⁷³ respectively), compared to our study (992 µm). PROS length has been found to be a prognostic factor for postoperative BCVA in one small prospective case study²⁴, while in our study we did not find this association. Although the methodology was similar to our study, patients with better preoperative BCVA were included in this study²⁴, possibly influencing the relationship with postoperative BCVA. The current study is the first to our knowledge to investigate parafoveal area sector-thickness as direct determinant for postoperative BCVA. The parafoveal thickness might be a better reflection of the full effect of an ERM on retinal thickness than the CFT, which is measured in the foveal area only. However, no associations were found for parafoveal area and postoperative BCVA.

A possible explanation for the discrepancy between our results and previous findings is the difficulty in the assessment of the different OCT parameters. Often, the evaluation of line integrity is not straightforward and prone to subjective decisions. Also, we evaluated prognostic factors for a follow-up time of 3 months, while most studies used a longer follow-up time, which may have affected the associations. However, while the degree of improvement in VA will be different with a longer follow-up, we do not think that the direction of the change in VA will differ. Therefore, we believe that the strength

of the association is lower with shorter follow-up, but the direction of the association does not change. We discuss this limitation below. According to this study and the inconsistencies in the literature, OCT parameters are not yet useful in clinical decision-making. More studies are needed, preferably in a large cohort with standardized OCT readings.

The strengths of our study are the large study sample and the inclusion of almost all OCT parameters that have been reported in the literature. Previous studies have focused on a few parameters at a time and often did not report on others, with a potential for publication bias. The study limitations are inherent to its retrospective nature. First, the measurement of postoperative outcome was not standardized. However, because well-trained professionals performed the VA measurements unaware of preoperative (OCT) characteristics, we do not expect this to have biased our results. Second, due to follow-up release after 3 months in case of favourable outcome, we were unable to extract unbiased data from a follow-up longer than 3 months. Although improvement of BCVA within up to 1 year has been described⁶², a 3-month follow up has been reported appropriate to indicate prognostic values of variables and has been found to be comparable with 6 months of follow-up.^{67,69} Also, in phakic eyes, cataract progression will have more influence on postoperative BCVA after 6 months than after 3 months of follow-up.⁶⁹ In this study we also analysed BCVA at the final follow-up [median (IQR) 4 (3-8) months postoperatively] to validate our results. Similar to our results with 3-month follow-up, only preoperative BCVA was independently associated with postoperative BCVA and BCVA difference.

Conclusion

Apart from preoperative VA, a broad range of baseline and OCT parameters were not associated with BCVA at 3 months after surgery for iERM. These results confirm the literature inconsistencies and warrant further studies to develop a prognostic model for visual outcome after ERM surgery.

CHAPTER 2.3

Prognostic model for visual outcome after idiopathic epiretinal membrane surgery

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Submitted

ABSTRACT

Purpose: Idiopathic epiretinal membranes (iERM) can cause severe vision loss and metamorphopsia. Although pars plana vitrectomy has been shown successful in many cases, prediction of individual visual outcome is still very difficult. Our aim was to develop a model that can predict visual change after vitrectomy for iERM.

Methods: In this prospective cohort study, clinical, optical coherence tomography, fundus autofluorescence (FAF) and microperimetry parameters were obtained at baseline and 6 months after vitrectomy. Linear regression analysis was used to evaluate associations between baseline characteristics and change in best corrected visual acuity (BCVA) 6 months after vitrectomy. A 10-fold cross-validation with the least absolute shrinkage and selection operator was carried out to correct for overfitting.

Results: In total, 39 eyes were included. Preoperative factors that predicted visual change were preoperative BCVA (β = -0.731), the presence of an iERM or vitreomacular traction in the fellow eye (β = 0.159), and a hyperfluorescent FAF (β = 0.084). This model could explain 71.8% of the variation in change in BCVA. A prediction model with omission of FAF could explain 70.1% of the variation.

Conclusion: We developed a prediction model with readily available parameters explaining 72% of the change in BCVA after iERM surgery.

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Introduction

Pars plana vitrectomy for idiopathic epiretinal membrane (iERM) is considered in patients with visual loss, disturbing metamorphopsia, diplopia, or binocular complaints.^{2,63,79} Counseling of patients and discussing the risk-benefit ratio of surgery is essential. Unfortunately, prediction of individual visual outcome is still very difficult.^{13,14,66,80} Therefore, surgery is usually indicated in eyes with documented deterioration of visual function. Nevertheless, early surgical intervention has been advocated for eyes with good visual acuity, and likely less irreversible retinal damage.^{81,82}

According to literature, preoperative visual acuity is the best predictor for visual improvement.^{13,17,24,66,80,83} In addition, numerous preoperative parameters derived from optical coherence tomography (OCT), such as the integrity of the inner segment/outer segment (IS/OS) junction, have been studied.^{13–15,17,19,21,24,25,66,80,83} However, studies yielded contradictory results and the predictive value of OCT parameters is disappointing.^{13–15,17,19,21,24,25,66,80,83}

The aim of this study was to develop a prognostic model that can predict individual change in BCVA after pars plana vitrectomy (PPV) with peeling of the iERM and the internal limiting membrane (ILM). For this purpose, we performed a prospective cohort study with standardized assessment of a wide range of preoperative parameters.

Methods

Subjects

This prospective cohort study was carried out at the University Medical Center Utrecht, a tertiary referral center for vitreoretinal surgery. After referral from secondary hospital care, the indication for surgery was based on the patients' symptoms and signs at the surgeon's discretion. Patients with loss of visual acuity or disturbing metamorphopsia were eligible for surgery. Consecutive patients with an iERM between February 5th 2013 and March 17th 2015 who were scheduled for surgery were included. Eyes with an iERM in combination with a macular pseudohole (MPH) or lamellar macular hole (LMH) were included. Exclusion criteria were high myopia (< -6.0 diopters), secondary ERMs, the presence of vitreomacular traction (VMT), or pre-existing macular or optic nerve diseases.

Surgery

Surgical treatment consisted of three-port 25-gauge PPV with removal of the iERM and subsequent ILM-peeling by two experienced vitreoretinal surgeons (PS and RvL). ILM peeling was assisted by the use of 2.5 mg/ml infracyanine green (ICG; Laboratoires SERB, Paris, France)

dissolved in a 5% glucose solution to confirm complete removal. By discretion of the surgeon, phakic patients with some degree of cataract underwent combined surgery including phacoemulsification with intraocular lens implantation.

Examinations

Patients were examined preoperatively and 1, 3 and 6 months postoperatively. At each visit, patient's symptoms were recorded, including subjective visual loss, monocular and binocular metamorphopsia, diplopia, binocular complaints, and restrictions in daily life. Ophthalmological examinations of both eyes comprised of best-corrected distance visual acuity (BCVA) measured by Snellen charts. Ocular dominance was tested by the distance hole-in-the-card test. OCT was performed using Optos spectral domain-OCT (Optos OCT/SLO, Optos Plc., Dunfermline, UK) and consisted of a horizontal and vertical scan through the fovea. The foveal thickness and the thickness of the outer plexiform layer (OPL), the outer nuclear layer (ONL), the outer foveal layer (OFL; distance from external limiting membrane to the retinal pigment epithelium), and the photoreceptor outer segment layer (PRL; distance from the junction of inner segment/outer segments (IS/OS) to the retinal pigment epithelium) were measured manually at the center of the fovea. Assessed on spectral domain-OCT were the integrity of the external limiting membrane (ELM), the IS/OS and the cone outer segment tips (COST) line, and the presence of cystoid macular edema (CME), a LMH or a MPH (defined according to the International Vitreomacular Traction Study Group) (Figure 1).⁸⁴ The integrity of the ELM, IS/OS junction and COST line was graded as continuous or disrupted. Retinal thickness was automatically assessed based on retinal topography (Optos OCT/SLO), and included central thickness and superior, temporal, inferior and nasal guadrant thickness.



1. Classification of an idiopathic epiretinal membrane (iERM) with macular puckering (**A**), an iERM with a macular pseudohole (**B**), and an iERM with a lamellar macular hole (**C** and **D**).

Fundus autofluorescence (FAF; excitation 488nm and emission 500nm) was acquired with Spectralis spectral domain-OCT with confocal scanning laser ophthalmoscopy (Heidelberg Engineering GmbH, Heidelberg, Germany). FAF was graded as hyperfluorescent or normofluorescent based on the presence or absence of a hyperfluorescent spot in the fovea. Microperimetry (Optos OCT/SLO; Optos Plc., Dunfermline, UK) was performed by one examiner in a dark room at least 15 minutes following pupil dilatation with 0.5% tropicamide and 5% phenylephrine and with occlusion of the non-tested eye. Subjects had to maintain fixation on a central target. A customized pattern covering the central 11° with the following features was used: Goldman III stimulus size, 200-millisecond stimulus duration, a 1,500-millisecond interval between stimuli presentation and a 4-2 strategy on a 10 cd/m² background. Retinal sensitivity was tested at 21 points; 1 stimulus in the fovea at 0.0°, 4 stimuli at 1.0°, 12 stimuli at 3.5°, and 4 stimuli 5.5°. The stimulus level ranged between 0 and 20 decibel (dB).

Postoperative outcome measure was the difference between BCVA 6 months after vitrectomy and preoperative BCVA.

Statistical analysis

Statistical analysis was carried out using Rstudio software (version 0.99.892.0; RStudio, Inc., Boston, MA, United States). Decimal BCVA was converted into logarithm of the minimum angle resolution (LogMAR) for analysis. All descriptive data are presented as means with standard deviations except for duration of symptoms, which is presented as median with range because of the skewed distribution. The T-test was used for categorical preoperative variables and univariable linear regression analysis for continuous preoperative variables. Preoperative parameters with a *P*-value \leq 0.10 in the univariable analysis that met the assumptions for linear regression analysis, were included in a multivariable linear regression model with difference in BCVA as an outcome measure. A forward and backward selection method based on Akaike's Information Criterion was used for model development. To avoid overfitting a 10-fold crossvalidation with the least absolute shrinkage and selection operator (LASSO) from the R package "glmnet" was carried out.^{85,86} The 10-fold cross validation method randomly divides the data into 10 parts. Nine parts are used as a training set to fit the model and 1 part as a validation set to assess the predictive accuracy. This cross-validation process is repeated 10 times, with each of the subsamples used exactly once for model validation. The results are then averaged to produce a single estimate of the coefficients.

Results

General

In total, 41 eyes of 41 patients were enrolled in this study. Two eyes were excluded because of clinically significant cataract during follow-up. Baseline characteristics of the 39 included patients are summarized in Table 1.

Mean preoperative BCVA was 0.33 LogMAR (range 0.01-0.72) and mean postoperative BCVA was 0.17 LogMAR (range -0.08-0.59). Visual improvement > 0.20 LogMAR (2 Snellen lines) was observed in 17 eyes (44%) and improvement >0.10-0.20 LogMAR in 8 eyes (21%). Nine eyes (23%) experienced no significant change in BCVA (-0.10 – 0.10 LogMAR) and 4 eyes (10%) showed a loss in visual acuity of >0.10-0.20 LogMAR. Visual loss of > 0.20 LogMAR was observed in 1 eye (3%), which could not be explained by ophthalmological examination and OCT. The individual change in BCVA 6 months after surgery in relation to preoperative BCVA is presented in Figure 2.

Characteristics	Patients
No. eyes	39
Age (years)*	68.0 ± 7.5
Men	20 (51%)
Preoperative BCVA, LogMAR*	0.33 ± 0.20
Duration of symptoms, months	24 (2-120)
Dominant eye affected [#]	9 (23%)
Fellow eye affected	12 (31%)
Presence of macular pseudohole	7 (18%)
Presence of lamellar macular hole	4 (10%)
Preoperative cystoid macular edema	9 (23%)
Disruption of the IS/OS junction	7 (18%)
Disruption of the COST line	25 (64%)
Central foveal thickness on topography, µm*	460.5 ± 105.6
Outer foveal layer, µm*	80.0 ± 22.9
Photoreceptor outer segment layer, µm*	45.0 ± 22.2
Hyperfluorescence on FAF	13 (33%)
Mean sensitivity on microperimetry, dB*	13.5 ± 1.7

Table 1 – Baseline characteristics of patients treated by vitrectomy for idiopathic epiretinal membranes.

BCVA, Best-corrected visual acuity; LogMAR, logarithm of the minimum angle resolution; IS/OS, inner segment/outer segment; COST, cone outer segment tips; FAF, fundus autofluorescence

* Mean ± standard deviation

[#] Ocular dominance testing was inconclusive in 2 patients



Figure 2. Baseline best-corrected visual acuity and change in best-corrected visual acuity in LogMAR 6 months after vitrectomy for idiopathic epiretinal membrane for all patients.

In total, 15 out of 20 phakic eyes underwent concurrent lens extraction and intraocular lens implantation. No perioperative or postoperative complications were noted. Postoperative CME 6 months after surgery was present in 11 patients (28%) and in 7 of these patients CME was already present at presentation.

Thirteen (33%) patients had a hyperfluorescent FAF. Of these patients, 5 had a MPH, 2 a LMH, 2 CME, 1 a MPH with CME, 2 a LMH with CME, and 1 had no MPH or LMH or CME. One patient with a MPH had no hyperfluorescent FAF.

Preoperative BCVA

Preoperative BCVA was better in patients who experienced subjective restrictions in daily life and if the dominant eye was affected. Mean preoperative BCVA was 0.24 \pm 0.17 LogMAR in patients with restrictions in daily life and 0.39 \pm 0.20 LogMAR in patients without restrictions (*P* = 0.014). Mean preoperative BCVA was 0.21 \pm 0.14 LogMAR if the dominant eye was affected and 0.38 \pm 0.20 LogMAR if the non-dominant eye was affected (*P* = 0.009). Restrictions in daily life and whether the dominant eye was affected were also associated (*P* = 0.026). Better preoperative BCVA correlated with better mean sensitivity on microperimetry (β = -0.058, *P* = 0.001). Preoperative BCVA was worse in eyes with higher preoperative CFT values on topography ($\beta = 0.001$, P = 0.023).

Preoperative BCVA was not associated with symptoms, gender, age, the duration of symptoms, thickness of the separate retinal layers, disruption of the IS/OS junction or the COST line, hyperfluorescence on FAF, and the presence of a MPH, a LMH, CME, or an iERM or VMT in the fellow eye.

Difference in BCVA

Mean postoperative BCVA improved to 0.16 LogMAR (range 0.59 - -0.08) with a mean change in BCVA of -0.16 LogMAR (range -0.51 - 0.27 LogMAR). Lower preoperative BCVA was associated with lower postoperative BCVA (β = 0.281, *P* = 0.017) and with more visual improvement (β = -0.723, *P* < 0.001).

Preoperative factors with a *P*-value \leq 0.10 in the univariable analysis with change in BCVA as an outcome are shown in Table 2. Lower preoperative BCVA and higher CFT values were associated with more visual improvement. The presence of an iERM or VMT in the fellow eye, whether the dominant eye was the affected eye, disruption of the IS/OS junction, the presence of a LMH, higher values for OFL and PRL, better mean sensitivity on microperimetry, and hyperfluorescence on FAF were associated with less change in BCVA. Difference in BCVA was not associated with symptoms, gender, age, the duration of symptoms, thickness of the separate retinal layers, disruption of the IS/OS junction or the COST line, and the presence of a MPH or CME.

Mean difference in BCVA in 15 patients that underwent concomitant cataract extraction with intraocular lens implantation was similar to 19 patients who were pseudophakic before iERM surgery (respectively -0.20 \pm 0.18 LogMAR and -0.16 \pm 0.22 LogMAR, *P* = 0.545).

Multivariable model development

A multivariable linear regression model with change in BCVA 6 months after vitrectomy as an outcome included all preoperative factors with a *P*-value ≤ 0.10 in the univariable analysis (Table 2). Preoperative BCVA, the presence of an iERM or VMT in the fellow eye, and a hyperfluorescent FAF were independent predictive factors with respect to change in BCVA. Regression coefficients, 95%-confidence intervals (CI) and *P*-values of this model are shown in Table 3. More visual improvement can be expected in eyes with low preoperative BCVA, without iERM or VMT in the fellow eyes, and without a hyperfluorescent FAF. The adjusted R² of this model was 0.718, which means that 71.8% of the difference in BCVA can be explained by these factors.

As FAF imaging is not available in all clinics we repeated the analysis omitting FAF in the multivariable model. The regression coefficients, 95%-CI and *P*-values of this model are presented in

Table 4. The adjusted R^2 of a model including preoperative VA and the presence of an iERM or VMT in the fellow eye was 0.701.

Model evaluation

A 10-fold cross-validation with the LASSO was applied to correct for overfitting. The single estimates for the regression coefficients of the two multivariable models are shown in Table 3 and 4. LASSO regression did not retrieve other predictive factors and had only a minor effect on the correlation coefficients (Table 3 and 4). As LASSO methods do not provide 95%-CI or *P*-values, we could not report them.

Table 2 – Association of preoperative factors with change in best-corrected visual acuity six months after vitrectomy for idiopathic epiretinal membranes.

Preoperative variable	β	<i>P</i> -value		
Preoperative BCVA	-0.723	< 0.001		
Fellow eye affected	0.156	0.022		
Presence of LMH	0.230	0.033		
Dominant eye affected	0.149	0.049		
Central foveal thickness on topography (µm)	-0.001	0.007		
Outer foveal layer	0.003	0.042		
Photoreceptor outer segment layer	0.003	0.030		
Hyperfluorescence on FAF	0.195	0.003		
Mean sensitivity on microperimetry (dB)	0.055	0.002		
BCVA, Best-corrected visual acuity; LMH, lamellar macular hole; FAF, fundus autofluorescence				

Mult	ivariable regression m	LASSO regression mode	
β	95% - Cl	P-value	β
-0.003	-0.080 - 0.073	0.904	-0.004
-0.731	-0.9150.546	<0.001	-0.726
0.159	0.078 - 0.241	<0.001	0.158
0.084	0.004 - 0.165	0.040	0.084
	Mult β -0.003 -0.731 0.159 0.084	β 95% - Cl -0.003 -0.080 - 0.073 -0.731 -0.9150.546 0.159 0.078 - 0.241 0.084 0.004 - 0.165	Multivariable regression model β 95% - Cl P-value -0.003 -0.080 - 0.073 0.904 -0.731 -0.9150.546 <0.001

Table 3 – Multivariable and LASSO regression model of preoperative variables and difference in bestcorrected visual acuity 6 months after vitrectomy for idiopathic epiretinal membranes.

LASSO, least absolute shrinkage and selector operator; CI, confidence interval; BCVA, best-corrected visual acuity; FAF, fundus autofluorescence.

Table 4 – Multivariable and LASSO regression model of preoperative variables excluding fundus autofluorescence for the difference in best-corrected visual acuity 6 months after vitrectomy for idiopathic epiretinal membranes.

	LASSO regression model					
Preoperative variable	β	95% - Cl	P-value	β		
Intercept	0.028	-0.044 - 0.100	0.430	0.027		
Preoperative BCVA	-0.766	-0.9460.585	<0.001	-0.760		
Fellow eye affected	0.190	0.112 - 0.267	<0.001	0.187		
LASSO, least absolute shrinkage and selector operator; CI, confidence interval; BCVA, best-corrected visual acuity.						

Discussion

The aim of this study was to provide a prognostic model that can predict individual change in BCVA following vitrectomy with ILM-peeling for iERM. Many studies have focused on one or a few potential predictive factors and performed univariable analyses. However, since preoperative VA is such a strong determinant of postoperative VA, multivariable analyses including preoperative VA are essential for studying the additional predictive value of preoperative variables.

Two previous studies provided a multivariable model for change in BCVA and found preoperative BCVA^{13,80}, disruption of the IS/OS junction¹³ or attenuation of the foveal ellipsoid zone⁸⁰, and the presence of a MPH as predictive factors.⁸⁰ We could not confirm their results with respect to integrity of the IS/OS junction. However, a reliable comparison is difficult as different gradings are applied.^{13,80} In the present study, the IS/OS junction was graded as continuous or disrupted. In contrast, Inoue et al. and Sheales et al. each used other classifications including more subtle, but difficult to ascertain, abnormalities of the IS/OS junction.^{13,80}

In the same studies, less visual improvement was found in eyes with a MPH 3 months after surgery⁸⁰ but not 12 months after surgery, while the proportion of eyes with a MPH was comparable with our data.¹³ Sheales et al. report on better preoperative BCVA in eyes with a MPH suggesting that metamorphopsia rather than decreased visual acuity had been the indication for surgical treatment in these eyes.⁸⁰ In our cohort, preoperative BCVA was not better in eyes with a MPH and change in BCVA

was extremely variable. The discrepancy in results might result from a real variation in the course of VA recovery or may be a change finding due to small numbers.

In the present study, a hyperfluorescent FAF was associated with less change in BCVA. All but one patient with a hyperfluorescent FAF had a MPH, a LMH, CME or a combination. Conversely, only LMH was associated with less visual change, which did not remain statistically significant in a multivariable model including FAF. The interpretation of this finding is unclear. Autofluorescence mainly results from accumulation of lipofuscin in the RPE, which is derived from incompletely digested photoreceptors.^{47,87} In healthy eyes, the amount and distribution of lipofuscin is reflected by the intensity of autofluorescence.^{47,87} However, an ERM may induce a masking effect due to retinal thickening and/or dispersion of macular pigment.²⁵ Accordingly, the presence of an ERM is usually accompanied by hypofluorescence.²⁵ On the other hand, any retinal defect may show hyperfluorescence by decreasing the masking effect or as a result from increased accumulation of lipofuscin derived from damaged photoreceptors, as is seen in a full-thickness or a LMH.^{47,87–89} CME can lead to either hyper- or hypofluorescence on FAF.^{47,87} A limitation to the interpretation of this association is the lack of quantitative grading of FAF, which is yet inherent to this imaging method.

The adjusted R² of the prediction model including preoperative BCVA, the presence of an iERM or VMT in the fellow eye, and a hyperfluorescent FAF was 0.718 versus 0.701 of a model without FAF as a predictor. FAF imaging has a low predictive value and considering its interpretation difficulties, one might question its additive value in clinical practice.

Glial cells, mainly derived from Müller cells and microglia, play a pivotal role in the pathogenesis of iERM formation.^{90–92} Müller cells are activated by any retinal stress, including inflammation or retinal damage due to tractional forces.^{90–92} Depending on the stimulus, Müller cells can hypertrophy, proliferate or differentiate into different cell types. Up to now, the pathophysiology of iERM is not elucidated, but as various stimuli can lead to ERM formation, there may be different underlying mechanisms.

Our finding that the presence of an iERM in both eyes is associated with less visual improvement may be a reflection of such a specific underlying mechanism. It may be an indication of strong vitreomacular adhesion, which can lead to anomalous posterior vitreous detachment accompanied by fierce tractional forces and/or a (partial) vitreoschisis. Consequently, these eyes might be prone to develop an iERM. In addition, complete removal of the ERM together with the ILM may be more difficult in these patients which may prevent complete visual recovery.^{93,94} As previously mentioned, proliferative gliosis can be triggered by several stimuli, e.g. low grade chronic inflammation and breakdown of the blood-retina barrier.⁹⁰⁻⁹² The presence of an iERM in both eyes might be an indication for such underlying subclinical pathologies affecting both eyes. However, this is speculation since we have no data to support this.

In our cohort, patients with the dominant eye affected experienced more restrictions in daily life even though they had a better preoperative BCVA. This suggests that the indication for surgery is set at an earlier stage of the disease. Up to now, many different OCT parameters have been studied and varying associations with postoperative visual outcome were reported.^{13–15,17,19,21,24,25,66,80,83} The contradictory results may be a consequence of the differences in grading, e.g. of the IS/OS junction, or may be an indication of the difficulty in the assessment of these parameters. Or it may suggest that their prognostic value is limited in conjunction with other, stronger predictors. In our cohort, OCT parameters that were associated with visual change in univariable analyses were deleted from multivariable analyses including preoperative visual acuity.

In literature, both absolute postoperative BCVA and change in BCVA have been used as outcome measure of prognostic studies. One should be aware of this difference in the comparison of results. We consider change in BCVA to be more relevant in counseling of patients. Depending on the preoperative BCVA, the intention to perform surgery may be different. In patients with still good preoperative BCVA, the aim is maintenance of visual acuity, while in patients with decreased BCVA, the intention of surgery is visual improvement.

The strengths of this study are its prospective design, which enabled standardized assessment of a large number of pre- and postoperative parameters. The risk of selection bias is minimal as preoperative factors are measured in eligible patients before measuring the outcome.

There are also limitations to this study. The time of follow-up was limited to 6 months, while further improvement in visual acuity has been described in some studies 12 months after vitrectomy.^{13,15,17,66,82} Although visual acuity may increase in time, we do not expect this to affect the direction or the strength of the associations found in this study.

Our sample size is small, albeit comparable with many similar studies.^{13,14,17,66,79,80} By using LASSO regression, we were able to develop a robust model with reliable regression coefficients. As the prognostic value of prediction models strongly depends on the study cohort, validation in another population is required for the generalizability of this model.

In conclusion, predictive factors for change in BCVA 6 months after vitrectomy for iERM are preoperative visual acuity, the presence of an iERM or VMT in the fellow eye, and a hyperfluorescent FAF. Using these parameters, that are easy to obtain in clinical practice, 72% of the variation in postoperative change in BCVA can be predicted. Confirmation of these predictive factors in other cohorts is required.

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CHAPTER 3

Rhegmatogenous retinal detachment

CHAPTER 3.1

Incidence, risk factors and clinical characteristics of unexplained visual loss after intraocular silicone oil for macula-on retinal detachment

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Abstract

Purpose: To investigate the incidence, risk factors, and clinical characteristics of unexplained visual loss after macula-on rhegmatogenous retinal detachment (RRD).

Methods: Retrospective cohort of patients with primary macula-on rhegmatogenous retinal detachment treated by vitrectomy with gas or silicone oil (SO) tamponade in 2011 and 2012. Outcome was unexplained visual loss (>2 Snellen lines) 2 months after the last vitrectomy.

Results: Incidence of unexplained visual loss was 0.7% (1/151) in patients treated by gas and 29.7% (11/37) in patients treated by SO (P = 0.001). Visual loss occurred both during SO tamponade and after removal. Cases underwent optical coherence tomography, perimetry, microperimetry, fluorescein angiography, and visual evoked potentials. Patients with unexplained visual loss after SO tamponade showed a small scotoma within the central 2° on microperimetry. Duration of SO tamponade was the only statistically significant factor related to the incidence of unexplained visual loss (P = 0.001).

Conclusion: Incidence of SO-related visual loss was 30% with duration of tamponade as the only risk factor. This study is the first to apply microperimetry in these patients, which showed a distinct pattern of a small central scotoma. Therefore, microperimetry can be of great value in the diagnostic workup of patients with unexplained visual loss after vitrectomy.

Introduction

Silicone oil (SO) is widely used in vitreoretinal surgery as an endotamponade for complex retinal detachments (RDs) associated with proliferative vitreoretinopathy (PVR) or an increased risk of PVR formation.^{1–5} It provides a prolonged tamponade and its optical clarity facilitates good postoperative assessment and laser photocoagulation. Silicone oil is usually removed once reattachment is accomplished because of the risk of oil emulsification, cataract, glaucoma, and keratopathy in case of long-lasting SO tamponade.^{3–6} Newer SO formulations have higher viscosities and carry lower risks of emulsifying with the same success rates.^{2,7,8}

However, several case series have addressed another SO-related complication. Profound visual loss is described in patients with rhegmatogenous retinal detachment (RRD) without macular involvement treated by vitrectomy and SO tamponade. Patients with good visual acuity at the time of surgery lost vision during SO tamponade or after SO removal without any apparent explanation.^{9–16} Christensen and Ia Cour compared visual outcomes of patients treated by vitrectomy with gas or SO tamponade for RD without macular involvement.¹⁰ They found unexplained visual loss only to occur after SO use with an incidence of 30%. Up to date, the pathophysiological mechanism of this phenomenon remains unclear. The aim of this study was to investigate the incidence, risk factors, and clinical characteristics of unexplained visual loss in patients presenting with a primary macula-on RRD treated by vitrectomy with gas or SO tamponade.

Methods

Subjects

In this retrospective cohort study, medical records were reviewed of all patients who underwent surgery for a macula-on RRD. Initial surgeries were performed in 2011 or 2012 at an academic tertiary referral center. The study followed the tenets of the Declaration of Helsinki. Exclusion criteria included scleral buckling surgery only, age <18 years, previous intraocular surgery except for cataract extractions, redetachement with macular involvement, or follow-up less than three weeks postoperatively.

Preoperative data were obtained from medical charts and included age, gender, ophthalmological and medical history, visual acuity, macular status based on the surgical report, presence and grade of PVR (grade C or D), and lens status. Also, surgical parameters and the occurrence of perioperative complications were recorded. Postoperative data included visual acuity 2 months after vitrectomy, duration of SO tamponade, intraocular pressure, and postoperative complications.

Surgery

Surgery was performed by one of four experienced vitreoretinal surgeons. Intraocular surgery consisted of a 20-, 23- or 25-gauge pars plana vitrectomy. On surgeon's discretion, Perfluorodecalin (Bausch and Lomb) and intravitreal Kenakort 40 mg/mL (triamcinolone acetonide; Bristol-Myers Squibb, Anagni, Italy) was used. For tamponade with gas, either SF₆ or C₃F₈ was used and for SO tamponade Siluron 2000 was used (2000 centistokes; Fluoron GmbH, Ulm, Germany). Patients were mostly treated by the same surgeon if they had to undergo several vitreoretinal procedures.

Outcome measures

The primary end point was best-corrected visual acuity (BCVA) 2 months after the last vitrectomy in patients treated by gas tamponade or 2 months after SO removal in patients treated by SO tamponade. Visual loss was defined as a loss of two or more Snellen lines in BCVA compared with baseline. In case of visual loss, medical records were reviewed for potential causes, such as cataract formation or progression, secondary capsular opacification, macular or corneal edema, vitreous hemorrhage, epiretinal membrane formation, optic nerve abnormalities, or vascular occlusions. In the absence of an explanation and without improvement of BCVA within 6 months, visual loss was considered to be unexplained.

Examinations

Best-corrected visual acuity was assessed by Snellen charts by well-trained professionals. Subjects with unexplained visual loss underwent spectral domain optical coherence tomography (OCT) using Cirrus high definition (Carl Zeiss Meditec, Inc, Dublin, CA) to exclude structural retinal causes such as epiretinal membrane formation or macular edema. A scanning protocol of a 5-line raster scan through the fovea was used with a raster length of 6 millimeter, a scan density of 0.25, and a scan angle of 0°. Automated 24-2 visual field testing (Carl Zeiss Meditec, Inc) was performed to investigate optic nerve damage together with an OCT scan of the nerve fiber layer if visual field defects were present. Fluorescence angiography was performed to exclude any vascular abnormalities. Pattern-reversal visual evoked potentials were tested in patients suspected of an optic neuropathy and were elicited by checkerboard stimuli with large 1 (60 minutes of arc; minutes) and small 0.25 (15 minutes) checks at 1 meter viewing distance. Luminance and contrast of the stimulus were standardized for all patients.

Subjects without abnormalities on these examinations were selected to undergo microperimetry and OCT (Spectral OCT/SLO; OPKO-OTI, Miami, FL). Patients were examined in a dark room at least 15 minutes after pupil dilatation with 0.5% tropicamide and 5% phenylephrine and with occlusion of the nontested eye. They were asked to maintain fixation on a central target. A customized pattern centered on the central 11° was used and incorporated the following features: Goldmann III stimulus size, 200-millisecond stimulus duration, a 1,500-millisecond interval between stimuli presentation and a 4-2 strategy on a 1.27 cd/m² background (Figure 1). Retinal sensitivity was tested at 21 points; 1 stimulus in the fovea at 0.0°, 4 stimuli at 1.0°, 12 stimuli at 3.5°, and 4 stimuli 5.5°. The stimulus level ranged between 0 dB and 20 dB.

Retinal layer thickness on OCT (OPKO-OTI) in eyes that underwent microperimetry was measured manually on a horizontal line b-scan through the fovea by one examiner (LS) at 1 mm from the fovea at the nasal and the temporal side. Total retinal thickness and thickness of each layer separately was assessed, including the ganglion cell layer together with the inner plexiform layer, the inner nuclear layer (INL), the outer plexiform layer (OPL), the outer nuclear layer (ONL) and the photoreceptor layer (PRL; distance from ELM to retinal pigment epithelium).



Figure 1 - Customized pattern for microperimetry covering the central 11° of the retina to test retinal sensitivity. This figure is an example of a fellow eye with normal retinal sensitivities at all stimuli and a visual acuity of 20/20.

Data analysis

Best-corrected visual acuity measurements were converted to logarithm of the minimum angle resolution (logMAR) visual acuity for analysis. Statistical analysis was performed using SPSS version 20.0 for Windows (SPSS Inc, Chicago, IL). The Pearson $[chi]^2$ or Fisher's exact test was used for univariate analysis of categorical variables. The means were compared using the Student's t-test for normally and Mann–Whitney U test for abnormally distributed variables for the comparison between gas and SO tamponade groups. Differences with P < 0.05 were considered to be statistically significant. Logistic regression analysis was performed to identify risk factors for unexplained visual loss.

Results

General results

In total, 193 eyes with macula-on RD were included and 151 eyes of those were treated by vitrectomy with gas tamponade and 44 eyes with SO tamponade. Two SO-treated eyes were excluded due to uncertainty about the macular status and one eye due to an occlusion of the cilio-retinal artery before surgery confirmed by fluorescein angiography. Four eyes of four patients were excluded because of redetachment after SO removal with uncertainty about the macular status.

Median age was 60 years (range, 32 years–83 years) for patients with gas tamponade and 59 years (range, 36 years–82 years) for those with SO tamponade. In the gas group 58% were male compared to 76% in the SO group. Median preoperative visual acuity was 0.10 logMAR (Snellen

equivalent, 20/25) in both tamponade groups. Median postoperative visual acuity was 0.10 logMAR (Snellen, 20/25) for gas-treated patients and 0.40 logMAR (Snellen, 20/50) for SO-treated patients. Median time of outcome measurement was 52 days after vitrectomy in gas-treated eyes (range, 20 days–155 days) and 55 days after SO removal for SO-treated eyes (range, 20 days–92 days).

In the 151 eyes treated by gas tamponade, C_3F_8 was used in 88 eyes (58%), SF_6 in 61 eyes (40%), and air in 2 eyes (1%). Only 1 of these eyes had a redetachment within 2 months after vitrectomy. Indications for SO tamponade (n = 37) were RRD with high risk of PVR formation in 21 eyes (e.g., giant tears or multiple defects) or RRD with the presence of PVR in 7 eyes. In 9 eyes, SO was used because of a redetachment without macular involvement after previous pars plana vitrectomy with gas tamponade or scleral buckling. Median duration of SO tamponade was 16 weeks.

Postoperative lens status in the 151 gas-treated eyes was phakic in 65 eyes, pseudophakic in 85 eyes, and aphakic in 1 eye. In 21 eyes, pars plana vitrectomy was combined with cataract extraction with intraocular lens implantation. Of the 37 eyes treated by SO tamponade, 35 eyes were pseudophakic and 2 eyes were phakic after SO removal.

Visual loss

A loss in BCVA of >=2 Snellen lines occurred in 21 of the 151 gas-treated eyes (13.9%) and in 20 of the 37 SO-treated eyes (54.1%). In the gas tamponade group, visual loss was a result of cataract formation (12 eyes), cystoid macular edema (2 eyes), epiretinal membrane formation (1 eye), and corneal opacifications (4 eyes). Two eyes had improvement within 6 months. Visual loss could not be explained and did not improve within 6 months in 1 eye (0.7%).

Of the patients treated by SO tamponade, 20 (54%) experienced visual loss, which could be explained in 9 eyes. Reasons for a decreased BCVA were cataract formation (one eye), secondary capsular opacification (five eyes), cystoid macular edema (one eye), and vitreous hemorrhage (one eye). Postoperative BCVA of 1 eye improved within 6 months. Visual loss remained unexplained and without improvement in 11 eyes (29.7%) and occurred during SO tamponade in 8 eyes and after SO removal in 3 eyes. In particular, no structural abnormalities were present on OCT, such as disruption of the inner segment/outer segment junction or retinal pigment epithelium. The incidence of unexplained visual loss was 29.7% in patients treated by SO tamponade compared with 0.7% in patients treated by gas tamponade, which was a statistically significant difference (P < 0.001).

Risk factors for unexplained visual loss after silicone oil tamponade

Characteristics of patients with unexplained visual loss and of patients without visual loss are shown in Table 1. Patients with explained visual loss are excluded. Median preoperative visual acuity was statistically significantly better in patients with unexplained visual loss, with 0.05 logMAR (Snellen, 20/22) and 0.15 logMAR (Snellen, 20/29) respectively (Mann–Whitney U test, P = 0.026). In the 17 eyes without visual loss, a vitreous hemorrhage was present in 3 eyes and residual intraocular gas from previous pars plana vitrectomy in 3 other eyes. Median postoperative visual acuity was 0.15 logMAR

(Snellen, 20/29; range, 20/50–20/20) in patients without visual loss and 1.00 logMAR (Snellen, 20/200; range, 2/200–20/66) in patients with unexplained visual loss (Mann–Whitney U test, P < 0.001).

The mean duration of SO tamponade in patients with unexplained visual loss was 18 weeks. In contrast, mean duration was 13 weeks in patients without visual loss, which was statistically significantly shorter (Student's t-test, P = 0.005).

There were no statistical differences between both groups with respect to age, gender, intraocular pressure, the use of perfluorocarbon liquids, ILM peeling, surgeons, and systemic comorbidity (Table 1).

Univariable logistic regression analysis was performed to identify risk factors for unexplained visual loss. SO duration was the only statistically significant factor (odds ratio, 1.3; P = 0.017). Age, gender, and intraocular pressure were no risk factors for unexplained visual loss.

Examinations in patients with unexplained visual loss after silicone oil tamponade

Patients' characteristics are shown in Table 2. No structural abnormalities like epiretinal membrane formation or cystic macular edema were seen on OCT at the time of diagnosis. Fluorescence angiography performed in nine patients revealed no signs of vascular causes such as arterial occlusions or macular edema. Ten patients underwent visual field examination, which showed a decreased central sensitivity with a median of 12 dB (range, 0 dB–27 dB) and without arcuate scotoma suspect for glaucomatous damage.

Microperimetry was performed in 10 patients, and all showed the same distinct abnormality of a small scotoma in the central 2° (Figure 2). Retinal sensitivity at 0° and 1° was drastically decreased with a median sensitivity of 0.0 dB (range, 0.0 dB–8.8 dB). Retinal sensitivity at 3.5° and 5.5° was not or only slightly lowered with a median sensitivity of 13.9 dB (range, 4.5 dB–14.9 dB). Median retinal sensitivity at 0° and 1° was statistically significantly correlated with BCVA (in logMAR) at the time of microperimetry (Spearman's rho = -0.860; P = 0.003). In three patients, retinal sensitivity at 3.5° and 5.5° on microperimetry was decreased and in those visual evoked potentials were tested. The P100 latencies in the affected eyes were increased compared with patients' unaffected eyes but within normal limits. Amplitudes were decreased for both checkerboard stimuli in the affected eyes but also for the large stimuli in the unaffected eyes of two patients. Based on these results, a distinction between a maculopathy and an optic neuropathy cannot be made.

Data of retinal layer thickness on a horizontal line OCT scan through the fovea (OPKO-OTI) is shown in Table 3. Follow-up ranged from 5 months to 36 months. Total nasal and temporal retinal thickness was statistically significantly reduced in affected eyes compared with unaffected eyes (P =0.013 and P = 0.047, respectively). The ganglion cell layer along with inner plexiform layer was the only layer, which was statistically significantly thinner in affected eyes (P < 0.001). The ONL on the nasal side was statistically significantly thicker (P = 0.037). No qualitative changes such as disruption of the inner segment/outer segment junction or retinal pigment epithelium layer were noticed (Figure 2). Microcystic edema was found in 2 of 11 patients at 5 months and 6 months after SO removal.

No visual loss (n = 17)	Unexplained visual loss (n = 11)	P-value
59.7 ± 14.2	55.0 ± 11.0	0.073
12 (71)	8 (73)	1.000
0.15 ± 0.25	0.05 ± 0.15	0.017
20/28 (20/100-20/20)	20/22 (20/40-20/20)	
0.15 ± 0.22	1.00 ± 0.60	<0.001
20/28 (20/40-20/20)	20/200 (2/200-20/63)	
100%	100%	NA
0%	0%	NA
5/3/4/5	4/1/5/1	0.535
12 (71) 5 (29)	6 (55) 5 (45)	0.444
1 (6) 16 (94)	0 (0) 11 (100)	1.000
25 ± 13	32 ± 22	0.082
13 (76) 4 (24)	6 (55) 5 (45)	0.409
13 ± 4.4	18 ± 5.1	0.005
10 (59) 4 (24) 2 (12)	6 (55) 2 (18) 2 (18)	1.000
	$(n = 17)$ 59.7 ± 14.2 $12 (71)$ 0.15 ± 0.25 $20/28 (20/100-20/20)$ 0.15 ± 0.22 $20/28 (20/40-20/20)$ 100% 0% $5/3/4/5$ $12 (71)$ $5 (29)$ $1 (6)$ $16 (94)$ 25 ± 13 $13 (76)$ $4 (24)$ 13 ± 4.4 $10 (59)$ $4 (24)$ $2 (12)$ $1 (6)$	(n = 17)(n = 11) 59.7 ± 14.2 55.0 ± 11.0 $12 (71)$ $8 (73)$ 0.15 ± 0.25 0.05 ± 0.15 $20/28 (20/100 - 20/20)$ $20/22 (20/40 - 20/20)$ 0.15 ± 0.22 1.00 ± 0.60 $20/28 (20/40 - 20/20)$ $20/200 (2/200 - 20/63)$ 100% 100% 0% 0% 0% 0% $5/3/4/5$ $4/1/5/1$ $12 (71)$ $6 (55)$ $5 (29)$ $5 (45)$ $1 (6)$ $0 (0)$ $16 (94)$ $11 (100)$ 25 ± 13 32 ± 22 $13 (76)$ $6 (55)$ $4 (24)$ $5 (45)$ 13 ± 4.4 18 ± 5.1 $10 (59)$ $6 (55)$ $4 (24)$ $2 (18)$ $2 (12)$ $2 (18)$ $1 (6)$ $1 (9)$

Table 1 - Characteristics of patients treated by SO tamponade with and without unexplained visual loss

IQR, interquartile range.

No.	Indication	BCVA	BCVA 1	BCVA before	BCVA 2 months	Duration of	Highest IOP	Investigations
		before	month with	SO removal	after SO	SO (weeks)	during SO	
		SO	SO		removal*		(mmHg)	
1	Re-RD	20/20	20/30	20/50	20/200	17	22	OCT, FA, VF, MP
2	Multiple	20/20	20/40	20/125	20/400	19	33	OCT, FA, VF, OCT
	defects							NFL, MP
3	Re-RD	20/20	20/70	20/100	20/63	24	50	OCT, FA, VF, OCT
								NFL, MP
4	Multiple defects	20/20	20/100	-	20/200	12	30	oct, fa, vf, mp
5	Re-RD	20/25	20/25	20/100	20/100*	15	46	OCT, FA, VF, OCT
								NFL, MP
6	Giant tear	20/20	20/70	2/200	20/400*	26	32	OCT, FA, VF, OCT
								NFL, MP, VEP
7	Re-RD	20/25	20/800	20/400	20/70*	17	18	OCT, MP
8	Multiple	20/30	20/40	20/100	20/125	21	24	OCT, FA, VF, OCT
	defects							NFL, MP, VEP
9	PVR	20/40	20/40	20/40	2/200	30	33	OCT, VF, OCT NFL,
								MP, VEP
10	Multiple	20/25	20/25	20/20	20/100	17	32	OCT, FA, VF, OCT
	defects							NFL, MP
11	Giant tear	20/40	-	20/50	20/400*	17	58	OCT, FA, VF, OCT
								NFL

Table 2 - Characteristics of patients with unexplained visual loss after intraocular SO for macula-on RRD

*Cataract extraction with intraocular lens implantation during silicone oil removal procedure.

Re-RD, redetachment; FA, fluorescence angiography; VF, visual field examination; MP, microperimetry; OCT NFL, optical coherence tomography of the nerve fibre layer; VEP, visual evoked potentials.



Figure 2 - Microperimetry and OCT of two eyes that suffered from unexplained visual loss after SO tamponade after RD without macular involvement. Visual acuity of both patients is 20/126. Retinal sensitivity is severely decreased within the central 2° and is normal to slightly decreased at the other stimuli. The OCT scans show no structural abnormalities.

	Nasal thic Media	kness in μm n (range)		Temporal thi Median		
Layers	Affected eyes (n = 8)	Fellow eyes (n = 8)	P-Value	Affected eyes (n = 8)	Fellow eyes (n = 8)	P-Value
Total	290 (260-315)	325 (280-370)	0.013	283 (250-320)	315 (275-360)	0.047
GCL + IPL	45 (35-50)	98 (75-115)	< 0.001	48 (30-55)	93 (75-110)	<0.001
INL	48 (35-60)	40 (35-50)	0.144	45 (35-50)	40 (30-50)	0.478
OPL	28 (20-95)	28 (20-85)	0.854	25 (15-40)	23 (20-25)	0.275
ONL	88 (25-105)	65 (15-80)	0.037	90 (65-105)	75 (65-85)	0.142
PRL	60 (55-85)	65 (55-75)	0.739	63 (55-80)	65 (50-80)	0.921

Table 1 - Retinal layer thickness on OCT in patients with unexplained visual loss

GCL + IPL, ganglion cell layer together with inner plexiform layer; INL, inner nuclear layer; OPL, outer plexiform layer; ONL, outer nuclear layer; PRL, photoreceptor layer thickness (distance between external limiting membrane and retinal pigment epithelium)

Discussion

The occurrence of some dramatic cases with unexplained visual loss triggered our investigation into this disorder. The observed incidence of almost 30% in this period in our population may be a chance finding caused by a clustering of cases. However, the incidence rate in this formal cohort study resembles the figure of a previous incidence study of Christensen and la Cour.¹⁰ All other reports in the literature are case series, precluding incidence estimations. To better assess the risk of SO-related visual loss, more cohort studies are needed, preferably including the use of microperimetry to establish the diagnosis.

The association between unexplained visual loss after vitrectomy and SO tamponade has been reported several times before mainly in case series.^{9–16} To our knowledge, there are no cases reported after gas tamponade. The duration of SO tamponade was the only factor in our cohort that was statistically significantly related to the incidence of SO-related visual loss, which is another indication for a causal relationship. Median duration of SO tamponade in our patients with visual loss was 4 months, which is comparable to other studies and is not considered long-term tamponade.^{9–16}

The occurrence of SO-related visual loss is reported after the use of SO of various viscosities produced by different pharmaceutical companies.^{9–16} It is therefore not likely that visual loss is related to a specific brand or viscosity of SO.

Patients with SO-related visual loss showed a severely decreased central sensitivity on microperimetry. A central scotoma on visual field examination was also found in three case series.^{11,14,16} However, microperimetry has never been described before in these patients, as far as we know. This central scotoma is different from the microperimetry pattern seen after RD with macular involvement and similar visual acuity (Figure 3). This makes microperimetry a useful test to discriminate visual loss due to SO or due to other causes, such as macular detachment. In addition, microperimetry may demonstrate cases with a combination of both macular detachment and SO-associated visual loss.



Figure 3 - Microperimetry examination of an eye after RD with macular involvement treated by vitrectomy and gas tamponade with visual acuity of 20/200. Retinal sensitivity is decreased at all stimuli.

In two case series of together six patients, multifocal electroretinography was performed and showed substantially reduced central macular function in all patients.^{9,13} Flash visual evoked potentials were tested in one study and were normal in all three patients.⁹ These findings suggest a retinal origin. In our study, we performed pattern in three patients and the lowered amplitudes in combination with normal latencies could result from either optical nerve or retinal damage. Based on the results of the multifocal electroretinography and the size of the scotoma on microperimetry, a maculopathy seems to be most likely although further research is required. Also, glaucomatous optic neuropathy is unlikely as an arcuate scotoma, and excavation of the optic nerve head are not seen in these patients.

Several hypotheses about the pathophysiology of this phenomenon have been proposed. One theory concerns the dissolution of macular pigments in SO during tamponade. Lipophilic substances, that is, retinol and cholesterol, have been found in SO after removal. Lutein and zeaxanthin, both lipophilic, may also dissolve in SO, which in turn may render the macula more vulnerable to phototoxic damage.^{12,16–18} Another hypothesis refers to the lost buffering capacity of the vitreous cavity. Normally, the vitreous body serves as an infinite buffer for electrolytes and water-soluble factors. With the intraocular presence of SO, this buffer may be insufficient, leading to impaired homeostasis. Potassium is found to accumulate in the retina in porcine eyes with oil tamponade, which may cause metabolic exhaustion and eventually degeneration of the Müller cells.¹⁹ Asaria et al. found elevated levels of cytokines in the aqueous compartment around the SO.²⁰ It is unknown whether this affects retinal function. Increased phototoxicity at the time of the oil removal procedure was postulated.²¹ This, however, cannot account for visual loss during the tamponade.

A recent study reported on the long-term findings in 4 patients with SO-related visual loss after 4 to 9 years.¹⁴ All patients showed microcystic macular edema in the inner nuclear layer and thinning of the ganglion cell layer on OCT. These characteristics are also described in optic neuropathies of various etiologies and are propagated to be a sign of retrograde synaptic degeneration.^{22–24} Based on these findings, they suggest that SO-related visual loss results from a retrograde maculopathy caused by an optic neuropathy due to phototoxic damage of the ganglion cells in the retinal nerve fiber layer.¹⁴ In our

patients, follow-up ranged from 5 months to 36 months, and microcystic edema was found in 2 of 11 patients at 5 months and 6 months after SO removal. It may be that it takes many years for these cysts to form. However, other authors have shown that microcystic macular edema on OCT is not specific for optic neuropathies and is also seen in other pathologies such as epiretinal membranes, age-related macular degeneration, primary open angle glaucoma, and uveitis.^{25,26}

Thinning of inner retinal layers is previously described after the use of SO in eyes with unexplained visual loss but also in healthy eyes receiving SO.^{10,27} Reduction in the ganglion cell layer and the inner plexiform layer implicates neurodegenerative damage, which is also found in eyes with glaucoma, diabetic retinopathy, and multiple sclerosis.²⁸⁻³¹ Because this thinning is also found in eyes without SO-related visual loss, it seems that the presence of intraocular SO in general leads to retinal changes.

The main strengths of this study are the large sample size and the formal risk analysis of visual loss after gas and SO tamponade. Furthermore, this is the first study applying microperimetry to characterize SO-related visual loss. The study limitations are inherent to its retrospective nature. Postoperative visual acuity was not measured at exactly the same points in time and ranged from 20 days to 155 days after the last vitrectomy. Also, we do not have a full examination of all eyes with visual loss and no microperimetry examination of the one eye with unexplained visual loss after gas tamponade. Moreover, the use of multiple surgeons and multiple surgical techniques may affect postoperative visual acuity. Unexplained visual loss after macula-on RRD is associated with SO tamponade and has, in our cohort, an incidence of almost 30%. It can occur during SO tamponade and after SO removal, and the duration of tamponade seems to be a risk factor. Patients with SO-related visual loss show a distinct pattern on microperimetry. Therefore, microperimetry can be of great value in the diagnostic workup of these dramatic cases.

CHAPTER 3.2

Functional and structural changes in the retina following intraocular silicone oil tamponade

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Submitted

Abstract

Purpose: to investigate whether intraocular silicone oil (SO) tamponade is associated with functional and structural retinal changes in patients with both macula-on and macula-off rhegmatogenous retinal detachment (RRD).

Methods: prospective cohort study of patients with RRD treated by vitrectomy with gas or SO tamponade at the University Medical Center Utrecht. Outcome was best corrected visual acuity (BCVA), retinal sensitivity on microperimetry, and inner retinal layer thickness on spectral domain optical coherence tomography (SD-OCT) 2 months after surgery.

Results: in total 40 eyes were included; 10 eyes with macula-on RRD and gas, 10 eyes with macula-on RRD and SO, 10 eyes with macula-off RRD and gas, and 10 eyes with macula-off RRD and SO. Median retinal sensitivity on microperimetry and the thickness of the ganglion cell layer together with the inner plexiform layer on OCT were lower following SO tamponade compared to gas tamponade for macula-on and macula-off RRD (p < 0.037).

Conclusion: Foveal sensitivity was decreased and the inner retina was thinner in eyes after SO tamponade compared to gas tamponade. These effects were observed in patients with macula-on as well as macula-off RRD. Although further investigation is warranted to validate our results and to study potential underlying mechanisms, retinal surgeons need to be aware of these findings after the use of SO tamponade.

Introduction

Silicone oil (SO) is a biochemically inert polymer that is widely used as an intraocular tamponade after vitreoretinal surgery.^{1,3,32} Indications for its use include complex retinal detachments with proliferative vitreoretinopathy (PVR), giants retinal tears or trauma.^{1,3,32} Compared to gas, which dissolves spontaneously, SO has the advantage of prolonged tamponade. Although SO is considered to be safe, well-tolerated and not affecting retinal physiology, an unexplained severe visual loss has been described following intraocular SO use.^{9–13,16,27,33,34} Silicone oil related visual loss (SORVL) is characterized by a profound and irreversible visual loss occurring during SO tamponade or shortly after SO removal, without abnormalities on optical coherence tomography (OCT) or fluorescein angiography.^{9–13,16,27,33,34} It is found in 30 per cent of eyes with macula-on RRD and in 50 per cent of eyes with macula-on giant retinal tears.^{10,33,34}

Previously, we showed that microperimetry is a sensitive test to demonstrate a deep central scotoma in eyes with SORVL.³⁴ We also noted that the central scotoma on microperimetry in SORVL is different from the microperimetry pattern seen in eyes with a macula-off RRD with similar visual acuity.³⁴ Therefore, microperimetry is a good diagnostic tool for SORVL both following macula-on and macula-off RRD.

Remarkably, intraocular SO may affect retinal structure even without symptoms of SORVL. Thinning of the ganglion cell layer and the inner plexiform layer on OCT was observed following SO tamponade for macula-on RRD, in comparison with gas tamponade for macula-on RRD or healthy fellow eyes.^{10,27,34} Additionally, we found that magnesium levels in retro-oil fluid are lower during SO tamponade for RRD in eyes not suffering from SORVL, indicating a potential influence of SO on magnesium homeostasis.³⁵ Both findings indicate that SO tamponade may affect retinal structure and function, even in the absence of clinical symptoms.

The aim of this observational study was to investigate whether SO tamponade may induce functional and structural changes in the retina. The choice for type of tamponade is made by the surgeon at the time of surgery, based on the different properties of the tamponade agents and the characteristics of the retinal detachment. Therefore, randomisation for type of tamponade is not feasible. We compared microperimetry and OCT findings following gas tamponade and SO tamponade, in patients with macula-on as well as macula-off RRD.

Methods

Patients

This prospective cohort study was carried out from March 19, 2014 through May 5, 2015, at the University Medical Center Utrecht, a tertiary referral center. Patients with a RRD who were scheduled for vitrectomy with gas or SO tamponade were recruited. From these consecutive patients, 10 were selected for each group (macula-on with gas; macula-on with SO; macula-off with gas; macula-off with SO). Exclusion criteria were pre-existing diseases affecting the macula or the optic nerve, redetachment with

macular involvement, and age <18 years. Since our aim was to study the effect of SO on macular function and retinal layer thickness, we excluded patients with structural abnormalities on the postoperative OCT-scan that presumably affected visual acuity (e.g. macular oedema, subfoveal fluid, epiretinal membrane). This study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the University Medical Center Utrecht. Written informed consent was obtained from all patients.

Surgery

Intraocular surgery was performed by three experienced vitreoretinal surgeons and consisted of a 20or 25-gauge pars plana vitrectomy (Alcon Constellation Vision System; Alcon Laboratories Inc.). Perfluorodecalin (Bausch and Lomb, USA), intravitreal Kenakort 40mg/ml (triamcinolone acetonide, Bristol-Myers Squibb, Italy) and infracyanine green (Laboratories SERB, Paris) were used at surgeon's discretion. The internal limiting membrane (ILM) was peeled in the presence of PVR at the discretion of the surgeon. Air, SF₆ or C₃F₈ was used for gas tamponade and Siluron[®] 2000 for SO tamponade (Fluoron GmbH, Germany, 2000 centistokes).

Examinations

Best corrected visual acuity (BCVA) was obtained preoperatively and 2 months after the last vitrectomy. This was 2 months after the primary vitrectomy with gas tamponade or 2 months after SO removal. Microperimetry and OCT were performed 2 months after the last vitrectomy in all patients. Patients with a macula-on RRD also underwent an OCT preoperatively. In patients with SO tamponade, microperimetry and OCT were also performed monthly during SO tamponade.

BCVA was assessed using Snellen charts. Spectral domain-OCT and microperimetry (Optos OCT/SLO; Optos Plc., Dunfermline, UK) was performed by one examiner in a dark room at least 15 minutes following pupil dilatation with 0.5% tropicamide and 5% phenylephrine and with occlusion of the non-tested eye. Subjects had to maintain fixation on a central target. A customized pattern covering the central 11° with the following features was used: Goldman III stimulus size, 200-millisecond stimulus duration, a 1,500-millisecond interval between stimuli presentation and a 4-2 strategy on a 10 cd/m² background. Retinal sensitivity was tested at 25 points; 1 stimulus in the fovea at 0.0° , 4 stimuli at 1.0° , 8 stimuli at 3.5° , and 12 stimuli 5.5° (Figure 1A). The stimulus level ranged between 0 and 20 decibel (dB). The means of all stimuli at $0.0^{\circ} + 1.0^{\circ}$ (inner ring), at 3.5° (middle ring) and at 5.5° (outer ring) were calculated for data analysis.

Retinal layer thickness on spectral domain-OCT (Optos OCT/SLO) was measured manually on a horizontal scan through the fovea. The thickness of the ganglion cell layer together with the inner plexiform layer (GCL + IPL) was measured at 1 mm from the fovea at the nasal and at the temporal side.

Outcome measures

Outcome measures were BCVA; mean retinal sensitivity on microperimetry of the inner ring; and GCL + IPL thickness on OCT. Measurements took place 2 months following the primary vitrectomy with gas tamponade or 2 months following the SO removal procedure.

Data analysis

Statistical analysis was carried out using SPSS version 21.0 (SPSS Inc, Chicago, Illinois, USA). BCVA was converted into logarithm of the minimum angle resolution (LogMAR) visual acuity for analysis. All descriptive data are presented as medians and ranges because of small sample sizes. The Mann–Whitney U test was used to compare the predefined outcome measures between the gas treated and the SO treated eyes with stratification for macular status. Differences with p < 0.05 were considered to be statistically significant. As it concerns exploratory data analysis, no adjustments for multiple testing were performed.

Results

Fifty-eight eyes from 58 patients were examined. Three eyes were excluded due to redetachment with macular involvement and 1 eye because of permanent SO tamponade. Nine eyes with macula-off RRD and gas tamponade and 5 eyes with macula-off RRD and SO tamponade were excluded due to postoperative abnormalities on OCT that presumably affected visual acuity; epiretinal membrane (n=5), subfoveal fluid (n=4), macular oedema (n=2), and other structural abnormalities (n=3).

In total, 40 eyes of 40 patients were included: 10 eyes with macula-on RRD and gas tamponade, 10 eyes with macula-on RRD and SO tamponade, 10 eyes with macula-off RRD and gas tamponade and 10 eyes with macula-off RRD and SO tamponade. Baseline and other clinical characteristics are shown in Table 1. There was one peroperative complication. In one eye with a macula-off RRD and SO tamponade a SO bubble moved into the anterior chamber during SO injection which was not complicated with elevated intraocular pressure or corneal decompensation postoperatively.

Postoperative visual acuity

The associations between postoperative BCVA and the type of tamponade for macula-on and maculaoff RRD are shown in Figure 2. Although the mean postoperative BCVA tended to be worse after silicone oil tamponade, both for macula-on and macula-off RRD, this was not statistically significant in both groups.

Microperimetry

Postoperative median sensitivity of the inner, the middle and the outer ring are shown in Table 2. The postoperative retinal sensitivity of the inner ring for individual patients are shown in Figure 2.

	Маси	ıla-on	Macula-off	
	Gas	Silicone oil	Gas	Silicone oil
No. of patients	10	10	10	10
Age, years [*]	62 (45-72)	62 (30-74)	62 (54-75)	61 (51-74)
Men	6	9	8	9
Preoperative BCVA, LogMAR [*]	0.11 (-0.06-0.19)	0.20 (-0.02-0.40)	1.78 (0.52-2.48)	1.30 (0.09-2.48)
Previous surgery [†]				
- vitrectomy	0	1	0	1
- scleral buckling	0	0	0	1
PFCL use	5	8	5	10
ILM peeling	0	3	0	3
Indication silicone oil				
- PVR ≥ grade C1		3		4
- giant retinal tear		3		1
- multiple/inferior breaks		4		5
Duration of SO tamponade, months *		2.9 (1.2-3.9)		3.4 (2.4-5.1)
Time since RRD, months [*]	2.3 (1.9-7.5)	4.8 (4.2-6.0)	2.2 (1.6-9.6)	6.6 (5.1-8.7)

Table 1 - Clinical characteristics of patients treated by vitrectomy for rhegmatogenous retinal detachment according to macular status and intraocular tamponade.

Median (range)

[†] Previous surgery for RRD; these patients were treated by vitrectomy and SO tamponade due to a redetachment

BCVA, best-corrected visual acuity; LogMAR, logarithm of the minimum angle resolution; PVR, proliferative vitreoretinopathy; PFCL, perfluorocarbon liquid; ILM, internal limiting membrane; SO, silicone oil; RRD, rhegmatogenous retinal detachment



Figure 2 - Best corrected visual acuity (LogMAR) and central retinal sensitivity (dB) of the inner ring (mean of the 5 stimuli at 0° and 1°) on microperimetry, 2 months after vitrectomy and gas tamponade or after silicone oil (SO) removal for rhegmatogenous retinal detachment (RRD). Individual patients are represented by the black dots. Values in the grey box are the medians of each group. Presented *P*-values are from the Mann-Whitney U test between gas and SO tamponade for macula-on and macula-off RRD separately.

In macula-on RRD patients, the median sensitivity of the inner ring was 11.8 dB following SO tamponade, which was statistically significantly lower than the median of 15.6 dB following gas tamponade (p = 0.003). To exclude sensitivity loss due to ILM-peeling, we also calculated the median central retinal sensitivity excluding 3 eyes with ILM-peeling and SO tamponade. Median sensitivity of the inner ring further decreased to 8.0 dB (range 0.4-15.2 dB).

In macula-off RRD patients, the median sensitivity of the inner ring was 11.6 dB in the SO group and 15.0 dB in the gas group (p = 0.037). Median sensitivity of the inner ring in the 7 eyes with SO tamponade without ILM-peeling was also 11.6 dB (range 0.8-17.6 dB).

Abnormalities on microperimetry were only observed following SO tamponade: in 5 eyes with macula-on RRD and in 2 eyes with macula-off RRD. Microperimetry showed a small central scotoma in 4 patients and more subtle abnormalities in 3 patients, which were not present on previous microperimetry examinations. Retinal sensitivity and BCVA did not correlate well in these patients. Not all patients with a central scotoma had a low BCVA and subtle abnormalities on microperimetry were accompanied by both low and normal BCVA. Examples of individual patients are shown in Figures 1 and 3.

Retinal layer thickness on OCT

Median values for the GCL + IPL thickness are shown in Table 2. The thickness of the GCL + IPL was statistically significantly lower after SO tamponade compared to gas tamponade for macula-on and macula-off RRD for both the temporal and the nasal side (p < 0.027).

Minimal disruption of the inner segment/outer segment (IS/OS) layer on OCT was seen in 3 eyes with macula-off RRD and gas and 2 eyes with macula-off RRD and SO tamponade. These irregularities on OCT did not correspond with microscotomas on microperimetry.

Table 2 - Retinal sensitivity on microperimetry and retinal layer thickness on optical coherence tomography two months after vitrectomy or after silicone oil removal for rhegmatogenous retinal detachment.

	Macula-on			Macula-off		
	Gas	Silicone oil	p [†]	Gas	Silicone oil	p [†]
No. of patients	10	10		10	10	
Microperimetry						
Inner ring (dB) [*]	15.6 (14.8-18.4)	11.8 (0.4-18.4)	.003	15.0 (11.6-17.2)	11.6 (0.8-17.6)	.037
Middle ring (dB) [*]	16.0 (14.5-17.5)	15.6 (8.0-17.5)		15.8 (13.3-18.3)	13.6 (10.0-18.0)	
Outer ring (dB) *	15.3 (14.3-17.2)	15.1 (13.8-16.5)		15.3 (12.3-18.2)	13.8 (9.7-17.5)	
Optical coherence tomography						
GCL + IPL thickness (μ m) *						
- Nasal	88 (65-120)	63 (50-100)	.023	90 (75-110)	75 (45-105)	.017
- Temporal	93 (40-110)	60 (40-70)	.003	85 (60-105)	60 (35-100)	.027
		6 × 1 × 1			C	

dB, decibel; inner ring, mean of the 5 stimuli at 0° and 1°; middle ring, mean of the 8 stimuli at 3.5°; outer ring, the mean of the 12 stimuli at 5.5° GCL + IPL, ganglion cell layer together with inner plexiform layer measured at 1 mm from the fovea

* Median (range)[†] p-value from Mann–Whitney U test between gas and silicone oil tamponade stratified for macular status. All tested P-values are shown.



Figure 1 - Postoperative microperimetry following vitrectomy for rhegmatogenous retinal detachment (RRD). A deep central scotoma was present in 2 patients after a macula-on RRD and in 2 patients after macula-off RRD and silicone oil (SO) tamponade. (A) Typical microperimetry following macula-on RRD and gas tamponade with good retinal sensitivity at all stimuli and good best-corrected visual acuity (BCVA). (B) Right eye of a 74-year old man following macula-on RRD and 3-month SO tamponade with low BCVA (20/200) and a small central scotoma. Already during SO tamponade BCVA had worsened (20/125) and subtle abnormalities on microperimetry were present (not shown). (C) Left eye of a 29year-old man with a normal BCVA before surgery and during SO tamponade for a macula-on RRD, presented with a loss in visual acuity to 20/800 and a central scotoma with eccentric fixation following SO removal. The duration of SO tamponade was 3 months. (D) Typical microperimetry following macula-off RRD and gas tamponade and low visual acuity. (E) Right eye of a 63-year old man 2 months following macula-off RRD and SO tamponade. During SO tamponade, BCVA worsened from 20/63 to 20/200 and microperimetry revealed a central scotoma (not shown). Visual acuity improved after SO removal to 20/50 with only slight improvement in 2 central stimuli on microperimetry. (F) Left eye of a 50-year-old man with macula-off RRD who had a BCVA of 20/63 during SO tamponade. Following SO removal after 3.5 months, BCVA had decreased to 20/100 and microperimetry revealed a central scotoma which was not present during SO tamponade.



Figure 3 - Subtle microperimetry abnormalities with varying best-corrected visual acuity (BCVA) following silicone oil (SO) tamponade for macula-on rhegmatogenous retinal detachment. (A) Left eye of a 62-year old man with SO tamponade for 3.5 months for a macula-on RRD who presented with a severe visual loss and microperimetry abnormalities following SO removal. One month after SO removal, BCVA was 20/400 and microperimetry showed a central scotoma similar to Figure 1B (0-8 dB). Two months following SO removal, microperimetry had improved significantly but visual acuity remained unchanged. (B) Left eye of a 57-year old man with a retinal sensitivity similar to (Left), but with a much better postoperative visual acuity of 20/26 following a 3-month SO tamponade for a macula-on RRD. (C) Right eye of a 67-year old man with a 2-month SO tamponade for a macula-on RRD with slightly decreased central retinal sensitivity and a postoperative visual acuity of 20/22.

Discussion

This study suggests that SO tamponade has consequences for macular function and structure, apart from the previously described SORVL. Even though median BCVA was not decreased, central retinal sensitivity was significantly diminished following SO tamponade compared to gas tamponade both for macula-on and macula-off RRD.

Previous studies evaluating microperimetry after RRD focused on associations between morphological changes and retinal sensitivity.^{36–39} Our aim, however, was to study the effect of SO on retinal sensitivity in eyes without morphological changes. By exclusion of patients with abnormalities on OCT that may affect macular anatomy and function (e.g. an epiretinal membrane or macular oedema), anatomical and functional outcomes could be compared as reliable as possible in current practice. In line with our findings, a study on microperimetry after scleral buckling surgery observed no differences in retinal sensitivity between macula-on and macula-off RRD.³⁷

A disagreement between BCVA and central retinal sensitivity was previously reported after peeling of the ILM.⁴⁰ Although postoperative BCVA was similar for patients with and without ILM-peeling, a greater and faster recovery was measured by microperimetry in patients without ILM-

peeling.⁴⁰ In our study, a severely decreased retinal sensitivity was observed irrespective of ILM-peeling. Microperimetry may be more sensitive to detect subtle signs of retinal damage than visual acuity measurements. On the other hand, visual acuity and retinal sensitivity reflect two different aspects of visual function. Visual acuity testing relies on the ability to resolve a spatial pattern, while retinal sensitivity tested by microperimetry is based on the ability to discriminate signals of low contrast.⁴¹ Intraocular SO may influence these features of visual function differently. Unfortunately, contrast sensitivity measurements were not included in this study. These could have been of additional value in order to better understand the disagreement between visual acuity and retinal sensitivity. Contrast sensitivity was found to be affected following macula-on and macula-off RRD in comparison with healthy fellow eyes.^{42,43}

In concordance with previous results, we observed the GCL + IPL to be significantly thinner after SO tamponade compared to gas tamponade.^{10,27,34} Thinning of the macular inner retinal layers is linked to several neurodegenerative disorders involving Müller cell degeneration, such as glaucoma, diabetes mellitus, Alzheimer's disease, and Parkinson's disease.^{31,44,45} Whether a neurodegenerative process is involved in eyes with SO tamponade, with or without SORVL, is unknown.

Electrophysiological examinations performed in eyes suffering from SORVL are unrevealing. Multifocal and pattern electroretinography predominantly demonstrate varying degrees of macular dysfunction.^{11,13,16,33} In some of these eyes, visual evoked potentials indicate additional optic nerve involvement or an isolated optic neuropathy.^{11,13,16,33} The mechanism by which SO may induce this dysfunction is still to be resolved.

The main strengths of this study are its prospective nature and the use of microperimetry. Microperimetry used in this study runs simultaneously with a scanning laser ophthalmoscope, which enables to correct for fixation instability and to secure reliable retesting. In patients with SO tamponade, we performed microperimetry each month during tamponade in order to measure retinal sensitivity prior to the development of a central scotoma. This allowed for reliable assessment of macular function even in the presence of a central scotoma and fixation difficulties. Consequently, blinding of the perimetrist was not feasible, since retesting of the macular area requires the inclusion of previous testing, which is different for gas and SO patients. Also, intraocular SO is noted during microperimetry examination.

Several remarks should be made with respect to the results of this study. The number of patients was small, which allows for chance findings. Moreover, others should confirm our results, since unknown factors may interfere with the surgical results of our clinic. The cases with SORVL could not be linked to a particular surgeon or type of procedure (e.g. ILM-peeling), in line with our previous study on this subject.³⁴

The time of follow-up was longer for patients with SO tamponade compared to patients with gas tamponade, as it included the duration of SO tamponade. Time since last vitrectomy however, was around 2 months in all groups. Since patients with SO tamponade had more time to recover from RRD, any adverse effects would have resulted in better visual outcomes. We observed poorer visual

outcomes, which may be an underestimation of the real effect. Neither do we think that our findings can be explained by the fact that patients with SO tamponade had 2 vitrectomies, since visual loss and central scotomas were also observed during SO tamponade prior to the second surgery.

Another limitation of this study is the possibility of confounding by indication. To exclude this confounding, randomisation for gas or SO tamponade would be appropriate. However, the decision on what type of tamponade is used, is made by the surgeon at the time of surgery and depends on the estimated risk of redetachment considering multiple factors including presence of PVR and size of retinal tear. A randomised clinical trial performed in 1992 by the Silicone Study Group, randomised eyes with RRD and PVR grade C3 or more to vitrectomy and either gas (C₃F₈) or SO (1000 centistokes) tamponade.³ Macular attachment was achieved in about 80%, regardless of tamponade. Subgroup analysis indicated that eyes with anterior PVR may benefit from SO tamponade.³² Considering the reported incidence of SORVL of around 30%, this should be taken into account in the trade-off between the pros and cons of gas and SO tamponade.^{10,33,34} With the current knowledge, randomisation for gas or SO tamponade, and the occurrence of SORVL if treated by SO tamponade. However, this category is hard to define and, in our opinion, randomisation would therefore not be feasible in current practice.

This study shows that foveal sensitivity is lower and the inner retina is thinner is eyes after SO tamponade compared to gas tamponade. These effects were observed following both macula-on and macula-off RRD. Although further investigation is warranted to validate our results and to study potential underlying mechanisms, retinal surgeons need to be aware of these findings after the use of SO tamponade.

CHAPTER 3.3

Electrophysiology in eyes with silicone oil related visual loss

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Submitted

Abstract

Purpose: Silicone oil related visual loss (SORVL) is a serious complication of silicone oil tamponade and is characterized by an unexplained profound visual loss with a deep central scotoma. The aim of this study is to investigate whether SORVL is a maculopathy or an optic neuropathy.

Methods: In total, 9 eyes with silicone oil related visual loss were included; 7 eyes with macula-on rhegmatogenous retinal detachment (RRD) and 2 eyes with macula-off RRD. All patients underwent multifocal electroretinogram (mfERG), pattern electroretinogram (pERG), and visual evoked potentials (VEP).

Results: Implicit times of the first positive peak (P1) on mfERG were prolonged in ring 1 and 5 in all patients and in ring 4 in all but one patient. P1 implicit times of ring 2 and 3 yielded varying results. P1 Response densities of P1 were within normal limits for ring 1 to 5 in all patients, except for one patient. Implicit times on VEP were prolonged in the affected eyes of two patients and in both eyes in one patient.

Conclusions: SORVL is characterized by prolonged implicit times in ring 1, 4 and 5 on mfERG, suggesting a retinal dysfunction. In 3 patients, these mfERG findings were accompanied by abnormal VEP recordings.

Introduction

Silicone oil (SO) is widely used in vitreoretinal surgery as an endotamponade for complex rhegmatogenous retinal detachments (RRD).^{1,3,46} Compared to gas, which dissolves spontaneously, SO has the advantage of prolonged tamponade. Although SO is considered to be safe, well tolerated and not affecting retinal physiology, an unexplained visual loss has been described following intraocular SO use. This SO-related visual loss (SORVL) is characterized by a profound visual loss, which can occur during SO tamponade or shortly after SO removal and cannot be explained by complications such as cystoid macular edema, hyper- or hypotony, or epiretinal membranes.^{9–11,13,15,16,33,34,47} It is found in 30 to 53 per cent of eyes with macula-on RRD.^{10,33,34,48} Previously, we showed that microperimetry is a good diagnostic tool for SORVL, following both macula-on and macula-off RRD, as it demonstrates a typical small and deep central scotoma in eyes with SORVL.^{34,49}

The pathophysiology of this dramatic complication is unknown. Many hypotheses have been put forward, but the localization of the functional defect is still under debate.^{9-11,13,15,16,33,34,47,48} Case series that performed electrophysiological examinations in eyes with SORVL report diverging results indicative of either a maculopathy, an optic neuropathy, ganglion cell death or a combination.^{9,11,13,15,16,33,47,48} Predominantly a macular dysfunction of varying degrees is observed with or without optic nerve dysfunction.^{9-11,13,15,16,33,447,48} An isolated optic neuropathy was found in 4 eyes of a total of 31 eyes.^{9,11,13,15,16,33,47,48} In most eyes, macular function was tested by means of pattern electroretinogram (pERG).^{11,16,33} In the minority, a multifocal electroretinogram (mfERG) or a combination of pERG and mfERG was performed.^{9,13,15,47,48}

The aim of this study is to determine whether SORVL is a maculopathy or an optic neuropathy. For this purpose, mfERG, pERG and visual evoked potentials (VEP) were performed in 9 patients with SORVL. The mfERG is able to detect local electrical responses from the posterior retina and is useful for the assessment of macular function or local retinal functional defects.⁵⁰ The responses evoked by pERG have been suggested to arise in the retinal ganglion cells, driven by the macular photoreceptors and corresponding retinal cells.⁵¹ VEP testing provides diagnostic information on the functional integrity of the postretinal visual pathway including the optic nerve, optic radiations, and occipital cortex.⁵² Yet, VEP responses can also be abnormal secondary to poor optics or poor retinal function.⁵²

Methods

Subjects

Patients with SORVL associated with both macula-on as well as macula-off RRD and who were still visiting our clinic, were identified in retrospect. SORVL was defined as an unexplained visual loss in BCVA of 2 or more Snellen lines during SO tamponade or within 2 months after SO removal. No abnormalities, such as macular edema or epiretinal membrane, were seen on OCT, while a deep central scotoma was present on microperimetry (Optos OCT/SLO; Optos Plc., Dunfermline, UK) (Figure 1). The study was conducted at the University Medical Center Utrecht, the Netherlands and approved by its

Ethics Committee. The study followed the tenets of the Declaration of Helsinki and its later amendments.

In total, 9 patients with unilateral SORVL were included; 7 patients after macula-on RRD and 2 patients after macula-off RRD. All cases had a primary RRD without recurrent detachment. Median age at the time of the electrophysiological examinations was 64.1 years (range 30.5-74.6 years). Of these patients, 8 were male and 1 was female. Median best corrected visual acuity at the time of testing was 20/200 in Snellen with a range from 20/650 to 20/25). Median duration of SO tamponade was 15.0 weeks (range 12.0-21.3 weeks). Median time between SO removal and electrophysiological examinations was 9.1 months (range 3.7-52.4 months). Clinical characteristics of all patients are summarized in Table 1.



Figure 1 – Customized pattern of microperimetry covering the central 11 degrees of the macula. **A.** An eye treated by gas tamponade for a macula-on rhegmatogenous retinal detachment (RRD) with normal retinal sensitivities at all stimuli and a visual acuity of 20/25. **B.** An eye with silicone oil related visual loss (patient 6) two months after silicone oil removal after a RRD without macular involvement and a visual acuity of 20/200. Retinal sensitivity is severely decreased within the central 2 degrees and is normal to slightly decreased at the other stimuli. Visual acuity improved to 20/125 at the time of electrophysiological examinations.

No.	Sex	Age, years*	Eye	Macula	Indication for SO tamponade	SO tamponade duration, months	Lens status*	Time since SO removal, months*	BCVA, Snellen*
1	М	30	LE	On	PVR C1	2.8	Phakic	7.5	20/650
2	М	47	LE	On	Defects inferior	3.3	Cataract	9.1	20/200
3	F	59	LE	On	PVR B	3.1	Pseudophakic	3.7	20/25
4	М	64	LE	On	Multiple defects	3.5	Pseudophakic	11.9	20/200
5	М	66	RE	On	Multiple large defects	4.4	Pseudophakic	52.4	20/200
6	М	74	RE	On	Multiple defects	3.2	Pseudophakic	3.9	20/125
7	М	53	LE	On	Defects inferior	4.0	Pseudophakic	4.4	20/125
8	М	65	RE	Off	Multiple defects	4.9	Pseudophakic	12.0	20/40
9	М	71	LE	Off	Giant retinal tear	3.4	Pseudophakic	12.9	20/400

Table 1 – Clinical characteristics of patients with silicone oil related visual loss after rhegmatogenous retinal detachment

SO, silicone oil; BCVA, best-corrected visual acuity; SORVL, silicone oil related visual loss; RE, right eye; LE, left eye * at the time of electrophysiological examinations

Examinations

All patients underwent mfERG, standard pERG, large field pERG and pattern reversal VEP (Espion Gold system; Diagnosys UK Ltd, Cambridge UK) in a centre of expertise for rare visual disorders, the Bartiméus Institute for the visually impaired, Zeist. For mfERG and pERG we used Dawson, Trick, and Litzkow fibre electrodes on both eyes.⁵³ The ends of the fibres were attached to the skin, as close as possible to the nasal and temporal corners of the eye, so that the fibre itself floated on the cornea. Reference electrodes were placed on the left and right temples. The ground electrode was positioned on the forehead above the nose. MfERG sweep recording time was 109 seconds with small recording periods of 15 seconds. For each patient 4 sweeps were recorded, analyzed and combined. The luminance of the stimulus elements were 830 cd/m2 in the light state and 8 cd/m2 in the dark state (Michelson contrast > 98%). For the VEP measurements one active midline electrode was placed 2 cm above the inion referenced to a frontal midline electrode. All tests were performed according to ISCEV standards except for pERG and pattern reversal VEP being recorded with dilated pupils to eliminate the influence of the pupil diameter on the amount of light and to correct for differences in pupil size which can occur after vitrectomy.^{50–52} The patient's pupils were dilated with 0.5% tropicamide and refractive errors were corrected for the test distance in each case. Fixation was monitored by visual inspection.

Data analysis

For comparison of the data we calculated the interocular difference in implicit times by subtracting the value from the fellow eye from that of the affected eye and the interocular ratio of the response density

for mfERG or the amplitude for pERG by dividing the value for the affected by that of the fellow eye. No statistical analysis was carried out, as it concerns exploratory data on a small number of patients.

MfERG - Reliability of the signal of the affected eye was checked by calculating the correlation of the waveforms of both eyes. Signals $R^2 < 0.8$ were rejected as no response. The implicit time of the first positive peak (P1) for each of the 61 hexagons was calculated with Espion's 'Absolute' marker place algorithm. Signals were filtered with Espion V6 Software (Diagnosys, LLC, Cambridge UK) 'FFT: Intensity 3'. Reference values for mfERG interpretation are based on 20 age-matched controls that underwent mfERG in The Rotterdam Eye Hospital, with the same equipment under the same circumstances, for diagnostic workup but in whom a retinal disorder was excluded. Ring values for interocular absolute implicit time differences and response densities fraction was calculated. Values within the limits of mean ± 2 standard deviations of the controls were defined as normal.

PERG - Reliability of the signal of the affected eye was checked by calculating the correlation of the waveforms of both eyes. Signals $R^2 < 0.8$ were rejected as no response. Interocular difference in implicit times for the P50 was found by searching for the highest correlation between the waveforms in shifting the response of the affected eye between -20ms and 20ms in the range 20ms - 80ms. This was done after drift removal and using a 30Hz Gaussian filter. N95 interocular difference in implicit times difference was searched in the range 50ms – 150ms using a 30Hz Gaussian filter.

VEP - P100 implicit time for each eye was defined by the time position of the maximum of a fitted 2^{nd} order curve. Reference values were calculated from a group of 80 controls (range 30 – 75 years) of The Rotterdam Eye Hospital and Bartiméus Zeist. Mean P100 implicit time ± 2 standard deviations of the controls was defined as normal for the absolute values (\leq 117ms) and for the interocular differences (\leq 11ms).

Results

Multifocal electroretinogram

Results of the mfERG are shown in Table 2 with abnormal values indicated in bold. Figure 2 shows the individual values for interocular difference in implicit time and response density ratio of 9 patients with SORVL. Implicit times of the P1 were prolonged in ring 1 (R1) and ring 5 (R5) in all patients and in ring 4 (R4) in all but 1 patient. Implicit times of ring 2 (R2) and ring 3 (R3) yielded varying results. Response densities were within normal limits for R1 to R5 in all patients, except for 1 patient. A patient with a macula-off RRD showed a decreased response density ratio in R1 and normal values for the other rings. Figure 3 shows an example of a typical multifocal electroretinogram of a patient with SORVL.

			mfERG										
			Δ Implicit time P1, ms*					Response density ratio P1 [#]					
No.	Eye	Macula	Ring 1	Ring 2	Ring 3	Ring 4	Ring 5	Ring 1	Ring 2	Ring 3	Ring 4	Ring 5	
1	LE	On	2.5	2.6	-1.4	2.1	4.70	0.73	0.72	0.68	0.83	0.55	
2	LE	On	4.2	2.0	4.0	2.7	3.96	1.20	0.80	0.89	0.81	0.81	
3	LE	On	2.5	1.5	0.3	2.2	3.78	0.89	0.93	0.83	0.74	0.77	
4	LE	On	2.5	1.0	0.6	0.9	2.08	0.62	0.65	0.68	0.68	0.64	
5	RE	On	5.0	0.3	-1.1	5.8	3.71	1.11	1.20	1.15	1.21	1.07	
6	RE	On	3.3	2.0	4.2	2.9	6.55	1.00	1.15	1.13	1.01	0.83	
7	LE	On	3.4	1.4	0.8	2.0	3.83	0.89	1.08	0.93	0.90	0.85	
8	RE	Off	3.4	5.4	-3.0	3.6	6.29	0.55	0.80	0.93	0.90	0.95	
9	LE	Off	3.3	0.6	2.8	2.7	2.81	0.52	1.00	0.99	1.04	0.93	
Mea	n cor	ntrols ⁺	0.7	0.5	0.4	0.4	0.33	0.80	0.84	0.82	0.82	0.82	
SD c	ontro	ols [†]	0.6	0.5	0.4	0.4	0.29	0.13	0.12	0.15	0.14	0.15	

Table 2 – Multifocal electroretinogram results of patients with silicone oil related visual loss after rhegmatogenous retinal detachment

mfERG, multifocal electroretinogram; P1, first positive peak, SD, standard deviance

* Interocular difference in implicit times of the P1 in milliseconds calculated by subtracting fellow eye from the affected eye [#] Interocular ratio of the amplitude of P1 of the affected eye divided by the fellow eye

⁺ Reference values are based on 20 age-matched controls that underwent mfERG in The Rotterdam Eye Hospital for diagnostic workup but in whom a retinal disorder was excluded

Values that deviate more than 2SD from the mean of controls are indicated in bold

Pattern electroretinogram

Table 3 shows the interocular difference in implicit time and the amplitude ratio for the P50 and the N95 component of the standard and the large field pERG. Reliable measurements of the P50 were available for 7 eyes and of the N95 for 6 eyes. Interocular differences in implicit times detected by pERG do not seem to be related to the values found by mfERG. Standard and large field pERG retrieved varying results for interocular amplitude ratios of the P50 and the N95 component. Interocular amplitude ratios of the P50 and the N95 component on standard and the large field pERG were inconsistent. Figure 4 shows pERG recordings of both eyes of 2 patients.

Visual evoked potentials

Table 3 presents the implicit times of the P100 of VEP recordings of both eyes and the interocular difference in implicit time. VEP testing yielded a detectable response in all eyes. Implicit times were prolonged in the affected eyes of patient 1 and 5 and in both eyes in patient 4. Differences in implicit time between eyes recorded by VEP do not seem to be related to differences in implicit time found by mfERG. A representative VEP response is shown in Figure 5.



Figure 2 – Interocular difference in implicit time in milliseconds and response density ratio of the first positive peak in ring 1 to ring 5 on multifocal electroretinogram. Each dot represents a patient with silicone oil related visual loss. The shaded grey areas indicate the mean values \pm 2 standard deviations measured in 20 age-matched controls. Values for interocular difference in implicit times were significantly higher in eyes with silicone oil related visual loss in ring 1, 4 and 5 and interocular response density ratios were within normal limits. One patient with a macula-off rhegmatogenous retinal detachment had a lower response density ratio in the central hexagon (ring 1).



Figure 3 – Example of a typical multifocal electroretinogram of a patient with silicone oil related visual loss in his left eye. **A**. Good responses are obtained at all hexagons. The horizontal arrow in the enlarged response indicates the implicit time of the first positive peak (P1). The vertical arrow indicates the response density. **B**. Response densities are comparable in both eyes. **C**. The colored waveforms represent the responses of the affected eye. These colors correspond to the colors of the hexagons. The P1 of the fellow eye of all rings are indicated with the dashed lines. P1 implicit times were significantly prolonged in ring 1, 4 and 5 of the affected left eye. The exact values of the affected are shown in the colored box and of the fellow eye in the grey box. **D**. Indication of the delay in P1 implicit time per ring of this patient. P1 implicit times were prolonged in ring 1, 4, and 5 and normal in ring 2 and 3.

			VEP			Standard pERG				Large field pERG			
			Impl	icit tir	ne P100		P50 N95				P50	N95	
No.	Eye	Macula	RE	LE	Δ, ms*	Δ, ms*	Ratio, µV [#]	Δ, ms*	Ratio, μV [#]	Δ, ms*	Ratio, µV [#]	Δ, ms*	Ratio, µV [#]
1	LE	On	103	122	19	0	0.88	-3	0.95	1	0.96	0	0.84
2	LE	On	106	107	1								
3	LE	On	98	95	-3	1	1.07	5	1.08	2	1.01	1	1.15
4	LE	On	124	128	4	-1	0.52			1	0.59		
5	RE	On	120	113	7	2	1.33	1	1.16	2	0.91	4	1.27
6	RE	On	108	106	2	4	0.50	5	1.35	2	1.22	0	1.20
7	LE	On	92	95	3	2	0.72	1	1.08	1	0.72	4	0.62
8	RE	Off	111	113	-2	0	1.43	-2	2.05	-1	1.19	2	0.87
9	LE	Off	113	112	-1								

Table 3 – Visual evoked potentials and pattern electroretinogram results of patients with silicone oil related visual loss after rhegmatogenous retinal detachment

VEP, visual evoked potentials; pERG, pattern electroretinogram; RE, right eye; LE, left eye

* Interocular difference in implicit times in milliseconds calculated by subtracting fellow eye from the affected eye

[#] Interocular ratio of the amplitude of the affected eye divided by the fellow eye

Abnormal values for the implicit time of the VEP are indicated in bold. Reference values are based on 80 age-matched controls. Mean P100 implicit time ± 2 standard deviations of the controls was defined as normal for the absolute values (≤ 117 ms) and for the interocular differences (≤ 11 ms).

No reference values were available for standard and large field pERG


Figure 4 - Large field pattern electroretinogram of a patient with silicone oil related visual loss in his left eye. The signal in the affected eye (**A**) has more noise than the fellow eye (**B**). Large field pattern electroretinogram of a patient with silicone oil related visual loss in his left eye. The signal in the affected eye (**C**) has more noise and a lower amplitude than the fellow eye (**D**).



Figure 5 – Typical pattern reversal visual evoked potentials recording of a patient with silicone oil related visual loss in his left eye (**A**) and his fellow eye (**B**). The boxes indicate the normal range of the P100 implicit time and amplitude based on the mean ± 2 standard deviations measured in 200 controls.

Discussion

This study demonstrates that eyes with SORVL have consistently prolonged implicit times in R1, R4 and R5 on mfERG, with response densities mainly within normal limits. These findings advocate a retinal dysfunction in SORVL. In a minority of cases this was accompanied by abnormal VEP recordings.

Our finding of prolonged P1 implicit times in R1, R4 and R5 in all patients with SORVL are indicative of a retinopathy. A delay in implicit time may be an early indicator of macular damage and may precede reduction in response density, as has been described in patients with diabetes.^{54,55} P1 implicit times were also found to be increased in eyes with a low visual acuity due to retained intraocular iron in absence of clinical signs of siderosis.⁵⁶ The P1 mainly arises from the bipolar cells and prolonged implicit times may reflect abnormal synaptic transmission rather than cell loss.^{57–59} This might explain the absence of structural abnormalities on OCT.

We only included patients with unilateral SORVL and therefore we cannot exclude that our findings result from other effects than SORVL. Prolonged implicit times may result from the vitrectomy or the RRD itself. However, a study that performed mfERG in porcine eyes demonstrated that implicit times and response densities of all peaks were not affected by vitrectomy or experimental retinal detachment.⁶⁰ Secondly, P1 implicit time is also found to gradually extend with increasing myopia.^{61,62} In the present study, we looked at interocular differences and since spherical equivalents are highly correlated within individual patients we do not assume that this affects our conclusions. Furthermore, we corrected refractive errors for test distance. Thirdly, our findings may represent side-effects of SO use in general. However in that case, we would presume to have found a more generalized effect on mfERG.

In previous studies, a total of 6 out of the 14 eyes with SORVL was reported to have a reduced function of the macula, based on decreased response densities.^{9,13,15,47,48} Tode et al. performed mfERG in 3 eyes with SO tamponade for macula-on RRD without visual loss and in 6 eyes with SORVL following macula-on RRD.⁴⁸ Response densities were reduced during SO tamponade and 6 weeks after removal but had recovered in all 9 eyes at 14 to 70 months after SO removal.⁴⁸ Different time intervals between SO removal and electrophysiological examinations might explain the discrepancy in findings, since response densities may improve over time.⁴⁸ On the other hand, our mfERG protocol including 4 short recording periods and the thorough data analysis of the combined recordings may yield less variable results. Unfortunately, other studies did not provide much information on their test protocols and did not report on implicit times for mfERG, which hampers reliable comparison to our data.^{9,13,15,47,48}

Factors affecting stimulus luminance can influence electrophysiological investigations. In the present study, pupils were fully dilated in both eyes to correct for differences in pupil size which can occur after vitrectomy. In addition, lens and media opacities can lower response densities on mfERG due to light scattering but do not affect implicit times.^{63,64} Any adverse

effects could have resulted in decreased response densities in affected or fellow eyes with severe opacities but not in altered implicit times on mfERG.

SORVL is characterized by an unexplained severe visual loss during SO tamponade or after SO removal for RRD in the absence of structural abnormalities. A deep central scotoma was previously described and we demonstrated that microperimetry is an appropriate diagnostic tool.³⁴ Also, we found that features of SORVL can be observed after macula-on as well as macula-off RRD.^{34,49} However, definite criteria for SORVL are still lacking. By means of microperimetry, retinal sensitivity was measured in the central 11 degrees, which corresponds to the hexagons of R1 and R2 of the mfERG. On microperimetry, retinal sensitivity was particularly decreased within the central 2 degrees (Figure 1). Anatomically, this correlates with our mfERG findings of consistently prolonged implicit times in R1. The microperimetry pattern does not cover the area of R4 and R5 on mfERG which does not allow for comparison of these data.

A new hypothesis has been added to the debate on the functional origin of SORVL by Tode et al. In contrast to others, they found physiological VEP recordings and response densities on mfERG.^{9-11,13,15,16,33,34,47} Spectral domain-OCT revealed reduced thickness of the nerve fiber layer (NFL), the ganglion cell layer (GCL) and inner plexiform layer (IPL) in eyes with SORVL, with a thinned NFL in 3 of the 6 eyes on optic disc OCT. Based on these findings, they propose that ganglion cell death underlies SORVL and not a retinopathy or an optic neuropathy. However, thinning of the GCL and IPL is not only described in SORVL but also after the use of intraocular SO with no demonstrated visual loss.^{10,27,34} Furthermore, similar pERG recordings for both eyes in some individuals in the present study advocate against ganglion cell death as the primary cause of SORVL. Still, it might be an additional component in some patients. However, retinal dysfunction, as observed in SORVL, hinders reliable interpretation of electrophysiological examinations that test the postretinal visual pathway.⁶⁵

Abnormalities on VEP recordings were not related to the severity or the extent of macular dysfunction detected by mfERG. Based on these findings, we cannot conclude whether these abnormalities on VEP are secondary to macular dysfunction or a sign of optic nerve involvement. Histopathological studies demonstrated the presence of emulsified SO in the optic nerve in 13-24% of the eyes treated by SO tamponade for various vitreoretinal disorders.⁶⁶⁻⁶⁹ The duration of SO tamponade in these eyes ranged from 2 months to 12 years. These findings could not be confirmed by Knecht et al. in post-mortem eyes that received SO tamponade for 50 days and they proposed that other factors, e.g. high intraocular pressure during SO tamponade, should be involved in this migration process.⁷⁰ Wickham et al. suggested that the migration of SO into the optic nerve potentially underlies SORVL.⁶⁹ It is unknown whether emulsified SO in the optic nerve could affect optic nerve function and consequently pattern reversal VEP recordings. Neither do we know whether SO migrated into the optic nerve in the eyes investigated in the present study.

Reliable interpretation of VEP is challenging in eyes with macular dysfunction because of the reduced amplitude of the foveal component and a relatively increased parafoveal component.⁷¹ Consequently, VEP implicit time can be mistakenly interpreted as prolonged if the parafoveal component masks the foveal component. In the present study, we fitted a parabolic function through the P100 waveform in order to obtain reliable curves of VEP recordings.

The strengths of this study are the large number of cases, the standardized assessment of mfERG, standard and large field pERG and VEP and its thorough analysis. The main limitation is that we did not perform mfERG in eyes that had SO without SORVL. Therefore we cannot ascertain that our findings are specific for SORVL and do not reflect retinal damage induced by the use of SO itself.

In conclusion, this study demonstrates that SORVL is characterized by prolonged implicit times in R1, R4 and R5 on mfERG, suggesting a retinal dysfunction. In some patients, these mfERG findings were accompanied by abnormal VEP recordings. A study comparing mfERG in patients treated by SO tamponade both with and without SORVL is required to ensure whether these findings characterize SORVL, or whether they are side effects of SO tamponade.

CHAPTER 3.4

Electrolyte composition of retro-oil fluid and silicone oilrelated visual loss

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Abstract

Purpose: Up to one-third of patients with intra-ocular silicone oil (SO) tamponade for complex macula-on retinal detachment may experience an unexplained visual loss during or after SO tamponade. Although the underlying mechanism is unknown, previous studies suggested that accumulation of retinal potassium could be involved. Hence, this study tested the hypothesis that intra-ocular potassium levels are elevated during silicone oil tamponade.

Methods: A prospective cohort study was carried out from 13 October, 2013 through 5 March, 2015. Potassium, sodium, magnesium, chloride, calcium, lactate dehydrogenase (LDH) and glucose levels were measured in retro-oil fluid and paired serum from 16 patients undergoing oil removal, including 2 patients with SO-related visual loss (SORVL). Vitreous humour and paired serum from 27 patients with macular hole (n = 19) or floaters (n = 8) served as controls.

Results: Median potassium levels in retro-oil fluid and vitreous humour were similar. Magnesium and chloride levels were lower in retro-oil fluid compared with vitreous humour (p < 0.01) and LDH levels were elevated in retro-oil fluid (p < 0.0001). One of the two patients with SORVL revealed abnormal high potassium and magnesium levels. The other patient had normal levels.

Conclusion: Potassium levels are not increased in retro-oil fluid during SO tamponade, making the 'potassium accumulation' hypothesis unlikely. The disturbance in magnesium concentration during SO tamponade warrants further investigation.

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Introduction

Silicone oil (SO) is a biochemically inert polymer that is widely used as a prolonged intra-ocular tamponade for the repair of complex retinal detachments associated with proliferative vitreoretinopathy.^{1,3} Although considered to be safe, well tolerated, and not affecting retinal physiology, up to a third of patients treated by SO tamponade for retinal detachments without macular involvement may suffer from SO-related visual loss (SORVL).^{9–13,34,72} This irreversible, profound and unexplained visual loss can occur during SO tamponade or immediate after SO removal and cannot be explained by complications such as cystoid macular oedema, hyper- or hypotony, or epiretinal membranes.^{9–13,34,72} Evaluation by visual field tests or microperimetry typically reveals a small deep central scotoma and a severely decreased central macular function can be detected by multifocal electroretinography.^{11,34,72}

In contrast to gas tamponade, SO tamponade is generally accompanied by thinning of the ganglion cell layer and the inner plexiform layer visible by optical coherence tomography (OCT) that is observed in patients with SORVL, but also in patients with normal visual acuity.^{10,27,34}

Currently, the pathophysiology of this intriguing adverse event remains unknown. SOmediated retinal toxicity or aberrant levels of potassium in the ocular fluid between the SO and the retina (termed retro-oil fluid) have been suggested to play a role.^{19,72} Retinal electrolyte homeostasis is normally regulated by Müller cells, with the vitreous fluid serving as an infinite buffer.⁷³ However, electrolytes hardly dissolve in SO which could lead to accumulation in the limited retro-oil fluid volume and consequently in the retina, leading to retinal toxicity and subsequent visual loss.^{11,12,19}

In order to better understand the underlying mechanisms of this severe complication, we investigated the electrolyte concentrations in retro-oil fluid and vitreous humour, both in patients with and without SORVL. In the context of retinal thinning, lactate dehydrogenase (LDH) was measured as an indicator of tissue damage. Reference values for electrolytes, glucose and LDH in vitreous humour of human eyes in-vivo were hitherto lacking. Here we provide, for the first time, reference values for these substances in living human eyes.

Material and methods

Patients

We prospectively enrolled 16 patients undergoing removal of SO after rhegmatogenous retinal detachment surgery at the University Medical Center Utrecht, The Netherlands, between 13 October, 2013 and 5 March, 2015. Patients that underwent primary vitrectomy for macular hole (n = 19) or floaters (n = 8) served as controls. This study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the University Medical Center Utrecht. Written informed consent was obtained from all patients.

Sample collection

Surgery for oil removal was performed by 25-gauge or 20-gauge vitrectomy. Prior to balanced salt solution infusion and oil extrusion, an undiluted sample of the ocular fluid between the SO and the retina (the retro-oil fluid) was aspirated just above the optic disc by a 25-gauge soft-tip cannula connected with a 40-cm tube to a 5-ml syringe. In patients that underwent primary vitrectomy for macular hole or floaters, an undiluted vitreous humour sample was obtained with the vitreous cutter. Sample volumes ranged from 100 to 400 μ L. Serum samples were obtained from all patients at the time of surgery. All samples were immediately stored at -80°C until analysis.

Measurement of electrolytes, glucose and lactate dehydrogenase levels

The levels of potassium (K⁺), magnesium (Mg²⁺), chloride (Cl⁻), sodium (Na⁺), calcium (Ca²⁺), glucose and LDH were determined in retro-oil fluid, vitreous humour and paired serum using the Beckman-Coulter AU5811 chemistry analyser (Brea, CA, USA). K⁺, Na⁺ and Cl⁻ were measured by indirect ion-selective electrodes. Mg²⁺, Ca²⁺, glucose, LDH, as well as total protein and total triglyceride concentrations were determined by colorimetric methods.

Patients with SORVL

Silicone oil-related visual loss was defined as an unexplained loss in best-corrected visual acuity of two or more Snellen lines during SO tamponade or within 2 months after SO removal and the presence of a central scotoma on microperimetry. Two of the 16 patients treated by SO tamponade presented with SORVL. In patient 1, visual acuity deteriorated during SO tamponade from 0.50 to 1.00 logarithm of the minimum angle resolution (LogMAR), and a central scotoma on microperimetry was present before SO removal (Figure 1A-1B). Silicone oil (SO) was removed after 4.9 months. Patient 2 had visual loss from 0.50 to 1.00 LogMAR and a central scotoma on microperimetry after SO removal, which was not present during SO tamponade (Figure 1C-1D). The duration of SO tamponade was 3.7 months. Both patients were treated for a primary rhegmatogenous retinal detachment with macular involvement.

Although not all SO patients underwent microperimetry to test whether a central scotoma was present, visual acuity measurements revealed no additional patients suspected of SORVL.



Figure 1 - Microperimetry results for patient 1 and 2 during silicone oil (SO) tamponade and 2 months after SO removal. In patient 1, a small central scotoma was detected during SO tamponade (A) and persisted after SO removal (B). In patient 2, microperimetry revealed a central scotoma 2 months after SO removal (D) which was not seen during SO tamponade (C). Visual acuity had deteriorated from 0.50 to 1.00 LogMAR in both patients.

Statistical analysis

Statistical analysis was carried out using SPSS version 21.0 (SPSS Inc, Chicago, IL, USA). Descriptive statistics were used to present demographic and clinical characteristics. Best-corrected visual acuity was converted into LogMAR visual acuity for analysis. All data are presented as medians and ranges. Differences in electrolyte, glucose and LDH concentrations between both groups were evaluated with a Mann-Whitney-U test with a Bonferroni-Holm correction for multiple testing. Differences with p < 0.05 were considered statistically significant.

Results

General results

The median age of 16 SO patients was 63.5 years and of 27 controls 66.5 years. Twelve (75%) of the 16 SO patients and 10 (37%) of the 27 controls were men. Seven (44%) patients were treated by SO tamponade after failure of retinal detachment surgery. The macula was involved in 11 (69%) patients. Median postoperative visual acuity for SO patients was 0.70 LogMAR (Snellen equivalent 20/100, range 20/200-20/20). The median duration of SO tamponade was 4.0 months (range 1.2-5.2 months).

The median concentrations and ranges of electrolytes, glucose and LDH in ocular fluid and serum are summarized in Table 1. Median K⁺ levels in retro-oil fluid (4.49 mmol/l) were similar to K⁺ levels in vitreous humour (4.72 mmol/l; p = 0.145). Median levels of Mg²⁺ (0.64 mmol/l) and Cl⁻ (120.0 mmol/l) were significantly lower in retro-oil fluid compared to vitreous humour (0.82 and 124.3 mmol/l, respectively; p < 0.01), while median LDH levels were elevated in retro-oil fluid (29.1 versus 15.8 U/l; p < 0.0001). Median Na⁺, Ca²⁺ and glucose levels did not differ between retro-oil fluid and vitreous humour. Serum levels of electrolytes, glucose and LDH were similar in both groups. Total protein concentration was < 2.0 g/l and total triglyceride concentration was < 2.0 mmol/l in retro-oil fluid and vitreous humour, which is in line with previous results ⁷⁴.

To correct for the circulating electrolyte concentrations, we also compared the ocular fluid-to-serum ratio between the two groups (Table 1). The K⁺ ratio did not differ significantly between SO patients and controls (p = 0.096). The Mg²⁺ ratio was lower (0.75 versus 1.0) and the LDH ratio higher (0.15 versus 0.08) in SO patients compared with controls. The difference in Cl⁻ ratio between the groups was moderate (1.15 versus 1.21) but statistically significant (p < 0.0001).

Patients with SORVL

The electrolyte concentrations in retro-oil fluid of a patient suffering from SORVL during SO tamponade (patient 1) and a patient that developed SORVL after SO removal (patient 2) are presented in Table 2. The K^+ level in retro-oil fluid of patient 1 was similar to SO patients without SORVL. Patient 2 had a high K^+ level in retro-oil fluid (7.92 mmol/l), but no loss of visual acuity or a central scotoma at the time of sampling during SO removal (Table 2).

	Ocular fluid		Serum		Ocular fluid-to-serum ratio	
	SO-patients	Controls	SO-patients	Controls	SO-patients	Controls
	(n=16)	(n=27)	(n=16)	(n=27)	(n=16)	(n=27)
Potassium	4.49 (3.95-7.92)	4.72 (4.17-8.34)	4.36 (3.24-5.66)	4.31 (3.75-4.93)	1.04 (0.81-2.34)	1.13 (0.89-1.71)
Magnesium	0.64 (0.50-1.17)	0.82 (0.70-1.03)***	0.84 (0.58-1.00)	0.82 (0.72-1.06)	0.75 (0.69-1.82)	1.00 (0.77-1.24)***
Chloride	120.0 (109.3-133.5)	124.3 (119.6-149.8)**	103.8 (97.6-111.6)	103.9 (97.8-109.6)	1.15 (1.10-1.30)	1.21 (1.15-1.40)***
Sodium	144.5 (135.2-157.4)	147.2 (140.7-173.4)	139.1 (133.3-148.3)	138.2 (131.7-147.3)	1.04 (0.99-1.15)	1.06 (1.03-1.26)
Calcium	1.56 (1.43-2.46)	1.61 (1.42-2.68)	2.32 (1.66-2.45)	2.28 (2.09-2.50)	0.65 (0.59-1.48)	0.71 (0.59-1.12)
Glucose	3.93 (0.76-8.64)	3.60 (2.71-4.88)	5.22 (4.24-8.48)	5.52 (4.59-7.08)	0.77 (0.11-1.03)	0.65 (0.51-0.75)
LDH	29.1 (19.9-62.4)	15.8 (7.0-23.0)***	189.4 (147.0-547.6)	172.6 (139.8-379.7)	0.15 (0.06-0.36)	0.08 (0.04-0.15)**

Table 1 - Electrolytes, glucose and lactate dehydrogenase in ocular fluid and serum and ocular fluid-to-serum ratios

SO-patients, patients treated by intraocular silicone oil tamponade including both patients with silicone oil-related visual loss; LDH, Lactate dehydrogenase measured in U/L. All electrolytes and glucose are measured in mmol/L.

*, p < 0.01; **, p < 0.001; *** for Mann-Whitney U tests with Bonferroni-Holm correction for differences in ocular fluid, serum and ratios between the SO-patients and the controls. Median values and ranges are shown.

Table 2 - The individual electrolyte, glucose and lactate dehydrogenase values of the two silicone oil patients with silicone oil-related visual loss

	Ocular fluid		Ocular-fluid-to-serum r	atio
	Patient 1	Patient 2	Patient 1	Patient 2
Potassium	4.53	7.92	1.09	1.84
Magnesium	0.67	1.17	0.81	1.50
Chloride	124.2	124.1	1.18	1.19
Sodium	148.5	150.4	1.06	1.08
Calcium	1.49		0.64	
Glucose	3.22	0.76	0.61	0.11
LDH	25.5		0.15	

Patient 1, Silicone oil related visual loss (SORVL) during silicone (SO) tamponade; patient 2, SORVL after SO removal. LDH, Lactate dehydrogenase measured in U/I. All electrolytes and glucose are measured in mmol/I. Calcium and LDH could not be measured in patient 2 due to limited sample volume.

Discussion

The underlying mechanism of SORVL, a dramatic complication of SO tamponade, is not elucidated yet, but retinal toxicity is thought to be fundamental to this visual loss^{9,11–13,19,34,72} This study investigated the vitreous concentration of K⁺ during SO endotamponade and its potential association with the development of SORVL. Winter et al. demonstrated that porcine eyes filled with perfluorocarbon liquid display toxic K⁺ levels in retro-oil fluid and suggested that this may induce cell death of Müller cells.¹⁹ Given the central role of Müller cells in cone cell homeostasis and in the cone visual cycle, loss of these cells could affect central visual function.⁷⁵ Also, Müller cell degeneration is characterized by atrophy of the inner retinal layers, similar to OCT findings in eyes after SO tamponade in general but especially in cases with SORVL.^{10,27,34,76,77}

To test this 'K⁺ accumulation hypothesis' we compared the electrolyte composition of retro-oil fluid to normal vitreous humour. K⁺ levels in retro-oil fluid were relatively higher in the patient that developed SORVL after SO removal (patient 2). However, this patient also revealed atypical magnesium and glucose concentrations compared with the other patients (Table 2). In general, intra-ocular SO tamponade was not associated with increased K⁺ levels in retro-oil fluid. In addition, the patient with SORVL at the time of electrolyte sampling (patient 1) showed K⁺ levels in the retro-oil fluid within the normal range. Therefore, we consider SORVL not to be the result of potassium siphoning failure per se. However, we cannot exclude that peaks in K⁺ levels may contribute to the development of SORVL.

Strikingly, the levels of Mg²⁺ were significantly lower in retro-oil fluid compared with vitreous humour, indicating a potential influence of SO on magnesium homeostasis. Magnesium is a pleotropic mineral involved in the majority of biochemical processes in the human body. Curiously, magnesium deficiency is linked to N-methyl-D-aspartate (NMDA) receptor mediated retinal toxicity (excitotoxicity). In the healthy eye, NMDA-receptors are blocked by magnesium and lower magnesium levels may induce overstimulation of the NMDA-receptors. Moreover, decreased thickness of the ganglion cell layer and the inner plexiform layer on OCT, which is found in eyes after SO tamponade, is also seen after experimental excitotoxicity in animal retinas.⁷⁸ However, magnesium is also essential for maintaining retinal adhesiveness.⁷⁹ Thus, lower magnesium concentrations in retro-oil fluid may reflect preexisting concentrations related to retinal detachment, independently of SO. Still, the role of magnesium in SORVL warrants further investigation.

Statistically significant differences were also found in sodium and chloride absolute values and ratios. However, these differences were so small that we think that the clinical consequences would be negligible.

Intra-ocular SO tamponade is complicated by its propensity to emulsify and by subsequent sequestration of SO in varying ocular tissues and the optic nerve.^{66–69} Wickham et al. suggested that migration of SO into the optic nerve may be responsible for cases of unexplained visual loss before and after SO removal (e.g. SORVL).⁶⁹ Curiously, histopathological

studies of eyes treated by SO tamponade for various vitreoretinal disorders revealed that emulsified SO was present in the optic nerve in 13-24%, a frequency that is in the same range as previously reported for SORVL.^{10,34,66,68,69} Interestingly, SO globules in the retina or the optic nerve are frequently engulfed or in close proximity to macrophages and accompanied by low-grade chronic inflammation.^{68,69} After removal of SO, the emulsified SO remains mostly trapped in the ocular tissues and could explain the irreversible nature of SORVL. In addition to the toxic potential of emulsified SO, the role of magnesium in optic nerve tissue homeostasis also requires consideration. Magnesium is critical to optic nerve tissue maintenance and a strong decline in magnesium concentrations can lead to optic nerve damage or neural degeneration.⁸⁰ Also, low magnesium concentrations induce an inflammatory response with activation of macrophages contributing to oxidative stress of affected tissue.⁸¹ The underlying mechanisms of emulsified SO and low magnesium concentrations in the concentrations in the context of decreased macular function in SORVL patients are currently unclear and warrant further investigation.

Another proposed hypothesis of SORVL is phototoxicity. Dogramaci et al. calculated that foveal light exposure is increased at the time of SO removal as a result of optical vignetting effect of different oil bubble sizes.²¹ The occurrence of SORVL during tamponade, however, cannot be explained by light toxicity during SO removal. In summary, K⁺ levels are not increased in retro-oil fluid, which makes the hypothesis of potassium siphoning failure as a general feature of SO tamponade and an underlying mechanism of SORVL unlikely.

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CHAPTER 4

Discussion

DISCUSSION

The aim of this thesis was to evaluate functional recovery following vitreoretinal surgery for two retinal disorders. We focussed on visual prognosis of idiopathic epiretinal membrane (iERM) surgery and visual loss after silicone oil tamponade for rhegmatogenous retinal detachment (RRD). In this chapter, the main findings of the thesis will be reviewed. Methodological considerations will be addressed in more depth and clinical implications and future perspectives will be discussed. These issues will be discussed separately for iERM (**chapter 2**) and RRD (**chapter 3**).

IDIOPATHIC EPIRETINAL MEMBRANE

An iERM is a common ophthalmological disorder with a prevalence of 19.5-31% which increases with age.¹⁻³ Pars plana vitrectomy is considered to be the standard treatment and visual outcome is favourable in most cases.⁴⁻⁸ As this concerns elective surgery, a careful consideration of the trade-off between the risks and benefits of surgical intervention is required. However, individual outcome is hard to predict.⁵⁻⁸ Prognostic models for individual visual outcome are important to improve patient counselling and to specify the indications for iERM surgery.

Main findings

Systematic review

Chapter 2.1 provides a systematic review of the current literature on potential predictors for visual acuity following surgery for iERM. Factors that were most extensively studied were preoperative visual acuity, central foveal thickness (CFT) and inner segment/outer segment (IS/OS) integrity on optical coherence tomography (OCT). We concluded that preoperative visual acuity was the only variable consistently associated with postoperative visual acuity. The integrity of the IS/OS junction on OCT was probably, and CFT was not associated with postoperative visual acuity. The severity of metamorphopsia, the integrity of cone outer segment tips on OCT, and fundus autofluorescence are potential promising predictive factors, but further studies are needed to draw firm conclusions.

Cohort studies

In a retrospective cohort study, described in **chapter 2.2**, we investigated the predictive value of the OCT parameters derived from the systematic review for visual acuity 3 months following iERM surgery. Preoperative clinical and OCT characteristics, and preoperative and postoperative data on visual acuity were collected for 66 eyes with an iERM. Preoperative visual acuity was positively correlated with visual acuity 3 months after iERM surgery. Baseline characteristics and a broad range of OCT parameters were not independently associated with postoperative visual acuity.

In a prospective cohort study of 39 eyes we developed a prediction model for change in visual acuity 6 months after surgery for iERM (**chapter 2.3**). Preoperative visual acuity, the presence of an iERM or vitreomacular traction in the fellow eye and hyperfluorescence on fundus autofluorescence could explain 71.8% of the change in visual acuity.

Methodological considerations

Systematic review

Limitations in prognostic research in general include publication bias, selective reporting, poor statistical analysis and inadequate replication or validation of initial findings.^{9,10} The main strengths of our systematic review, were the structured search in the literature and the assessment of the risk of bias based on predefined criteria (**chapter 2.1**). Out of the 35 eligible studies, 19 were considered to be of adequate quality. The assessment of the methodological quality, as we performed in our systematic review (**chapter 2.1**), allows for inclusion of studies with low potential on bias and subsequently more reliable conclusions.

Cohort studies

Many studies, such as included in the systematic review, focused on one or a few potential predictive factors and performed univariable analyses. However, preoperative visual acuity is strongly correlated with postoperative visual acuity and multivariable analyses including preoperative visual acuity are essential for studying the additional predictive value of preoperative variables. Accordingly, we performed multivariable analyses in our retrospective and prospective cohort studies (**chapters 2.2** and **2.3**).

In clinical practice, the duration of follow up tends to be longer for patients with worse outcome or slow recovery. Retrospective studies that included patients with a minimum time of follow-up, usually 6 or 12 months, would probably sample patients with less favourable outcome. In our retrospective cohort study (**chapter 2.2**), we included all eligible patients that underwent surgery between June 1, 2011 and May 31, 2013. In order to limit attrition bias, or selective loss to follow-up, we used visual acuity three months following surgery. These data were available for 80% of the patients. Limiting inclusion to patients that had a longer follow-up period had reduced the size of the cohort. Although visual acuity can improve up to 1 year after surgery, a 3-month follow-up has been reported appropriate for the identification of predictors.^{5,11-13} We think that the strengths of the associations will differ with a longer follow-up time, but not the direction of the association. A disadvantage of such a short postoperative period is that the variation in outcome may be too small to detect all potential predictive factors.

The potential for selection bias is reduced in a prospective cohort study like the one we described in **chapter 2.3**. Such a design makes it possible to include all eligible patients and to standardize the duration of follow up.

The literature on prognostic factors for ERM surgery is not based on large data sets.^{5,14–21} The sample size of prospective cohort studies ranges from 20 to 80 eyes.^{19–21} These numbers do not allow for the identification of many predictors and are associated with a high potential of chance findings.^{9,22} Prediction models and their estimates tend to be too optimistic, particularly when fitted on small data sets.²³ There are statistical methods available that can be used for variable selection and regularization in order to enhance the accuracy and interpretability of prediction models, e.g. least absolute shrinkage and selection operator (LASSO), or ridge and elastic net regression.^{24,25} Our prospective cohort, described in **chapter 2.3**, consisted of 39 eyes. We used LASSO regression for variable selection and to adjust for overfitting, of the estimates of the predictors. By using LASSO regression in our prospective cohort study we developed a more robust model with reliable regression coefficients.

An issue that needs consideration is cataract formation during follow-up. Cataract, or lens opacification, can rapidly progress following vitrectomy, and will negatively affect visual outcome after surgery.^{4,26} There are several options to methodologically deal with this issue. The most common solutions are either inclusion of pseudophakic patients only and no phakic patients, or performing combined vitrectomy and cataract extraction on all phakic patients. Some studies perform a sensitivity analysis for the effect of lens status or combined surgery.^{8,11,15} Cataract progression can lower visual acuity but since it is presumably not related to the prognostic determinants, we do not expect that cataract formation would lead to bias. Still, one should be aware that the improvement in visual acuity in patients who underwent a combined procedure is not only attributable to the removal of the iERM. Clinically significant cataract was present in 8 of the 82 eyes (12.1%) of our retrospective cohort (**chapter 2.2**). A subgroup analysis excluding 21 phakic eyes (26%) did not yield different results. In our prospective cohort (**chapter 2.3**), patients with clinically significant cataract were excluded.

The indication for iERM surgery arises from the discussion between patient and surgeon. This decision making process is influenced by the surgeons' own experiences with parameters affecting visual outcome. In other words, the selection of patients with an indication for surgery is not random. This may be relevant for the generalizability and the applicability of our prognostic model.

We investigated the potential of fundus autofluorescence (FAF) to predict visual outcome following iERM surgery in a prospective cohort study (**chapter 2.3**). We hypothesized that

hyper- or hypofluorescensce on FAF could indicate irreversible damage or that hyperfluorescence could indicate potential recovery. Hyperfluorescence on FAF was associated with less change in visual acuity and may be a sign of impending damage (**chapter 2.3**).

Clinical implications

The strong correlation between visual acuity before and after surgical treatment for iERM described in our systematic review (chapter 2.1) was confirmed in our cohort studies described in **chapter 2.2** and **2.3**. Better preoperative visual acuity is correlated with better postoperative visual acuity (**chapter 2.2**) and with less change in visual acuity (**chapter 2.3**). These findings indicate that maintenance of good visual acuity can be achieved with surgical treatment. On the other hand, patients with low preoperative visual acuity show more change in visual acuity (**chapter 2.3**). This implicates that those patients can benefit from surgery as well. If left untreated, 28.6% of the iERMs will show progression within 5 years.²

A recent randomized clinical trial allocated patients with an iERM to immediate surgical intervention or to a watchful waiting approach for 1 year.²⁷ The authors defined the maximal acceptable visual loss to be less than 5 letters on the early treatment diabetic retinopathy study (ETDRS) charts.²⁷ Patients that exceed this limit during monitoring would cross over and undergo surgery.²⁷ These authors advocate that deferral of surgery and regular monitoring is a safe approach.²⁷

Although excellent vision can be preserved with early surgical treatment, visual improvement can also be achieved in eyes with lower visual acuity. In order to prevent surgery in patients with stable visual acuity, a watchful waiting approach to observe the individual natural course could be applied. Only in case of objective visual deterioration, surgery would be indicated.

Future perspectives

In our prospective cohort study (**chapter 2.3**), we identified two new predictors for changes in visual acuity: the presence of an iERM or vitreomacular traction in the fellow eye, and increased fundus autofluorescence. Further studies are needed to either confirm the predictive value of these factors or to refute our results.

Distance visual acuity is most commonly used as outcome measure and is considered to represent treatment success. However, visual function comprises more than distance visual acuity and includes, among others, reading ability, metamorphopsia and contrast sensitivity. These visual functions are important for the performance of daily tasks and have a great impact on vision-related quality of life.^{28,29} Therefore, they probably better reflect the treatment effect of iERM surgery.^{28,29} Studies investigating the impact on the presence of an iERM on reading ability, metamorphopsia, and contrast sensitivity provide additional information on the impact of an

iERM on visual function in daily life. Additionally, studies investigating the effect of surgical treatment for iERM on these aspects of vision would be helpful in patient counselling.

In **chapter 2.3**, we report that patients with an iERM in their dominant eye presented with better preoperative visual acuity. However, they also experienced more restrictions in daily life than patients in whom the non-dominant eye was affected. Ocular dominance may not only play a role in the impact of iERM symptoms on daily life but also in patient's perception of treatment success. It would be interesting to investigate the influence of ocular dominance on change in vision-related quality of life after iERM surgery. Moreover, one might consider including ocular dominance in the decision-making process of surgical treatment of patients with an iERM.

Although extensively studied, the pathophysiology of iERM formation is still not elucidated.³⁰ A variety of cell types was identified in iERM and epiretinal membranes also develop secondary to other retinal disorders, such as diabetic retinopathy, vascular occlusions and retinal detachments.³⁰⁻³³ Epiretinal fibrosis can be triggered by various stimuli and the epiretinal membranes that are considered to be idiopathic may be more heterogeneous than presumed. Idiopathic ERMs might be the result of several disorders that led to membrane formation, each via different pathways and triggered by different stimuli. Our finding that patients with an iERM in both eyes tend to show less improvement may be an indication of such a separate entity. Studies on the identification of different underlying mechanisms could be helpful in the understanding of the clinical spectrum and of the differences in functional outcome following surgery. Moreover, further differentiation of iERMs based on pathophysiology could perhaps allow for a better prediction of the course of iERM.

RHEGMATOGENOUS RETINAL DETACHMENT

In general, the visual prognosis of surgery for RRD is favourable if the macula remains attached. However, a number of patients with profound and unexplained visual loss following silicone oil (SO) tamponade for a macula-on RRD triggered the studies that constitute **chapter 3**. This severe visual loss can occur during SO tamponade or shortly after SO removal and seems to be irreversible. Up till now, little is known about the frequency, the risk factors and the pathophysiology of this disorder.

Main findings

Clinical findings

In **chapter 3.1** we describe a retrospective cohort of patients with a macula-on RRD treated by either SO or gas tamponade. An unexplained visual loss was found in 30% of the eyes treated by SO and the duration of tamponade was identified as the only risk factor. The ganglion cell layer (GCL) together with the inner plexiform layer (IPL) on OCT was thinner in eyes with SO-related visual loss (SORVL). Microperimetry revealed a deep and small central scotoma in eyes suffering from SORVL. This central scotoma was different from the microperimetry pattern seen in eyes after a macula-off RRD with similar visual acuity that had not had SO tamponade. Accordingly, microperimetry could be valuable in the diagnostic work-up of low visual acuity following the use of SO.

Subsequently, we performed a prospective cohort study in which we included patients with a macula-on and macula-off RRD treated by vitrectomy and gas or SO tamponade (**chapter 3.2**). We confirmed our previous findings regarding the typical central scotoma in eyes with SORVL following SO tamponade for a macula-on RRD. Moreover, we demonstrated that this central scotoma could also be observed in eyes following SO tamponade for a macula-off RRD. Furthermore, subtle abnormalities on microperimetry were observed in some eyes following SO tamponade for macula-on RRD. The GCL plus the IPL on OCT were thinner in all patients following SO tamponade compared to gas tamponade.

Electrophysiology

The aim of the study described in **chapter 3.3** was to localize the functional deficit of SORVL by means of electrophysiology. Multifocal electroretinogram (mfERG), pattern electroretinogram (pERG) and visual evoked potential (VEP) were performed in 9 eyes with SORVL. Counterintuitively, it was found that implicit times of the first positive peak on mfERG were consistently prolonged in all eyes, indicative of retinal damage, but with preserved response density.

Pathophysiology

In **chapter 3.4**, we describe the results of our study in which we tested one of the hypotheses on the pathophysiology of SORVL. It is suggested that potassium accumulates in the fluid around the SO bubble (retro-oil fluid). We measured potassium, and other electrolyte, levels in retro-oil fluid and in vitreous fluid of patients who underwent vitrectomy for floaters or a macular hole. Potassium was not increased in retro-oil fluid, which makes the 'potassium accumulation' hypothesis unlikely. Magnesium concentrations were significantly lower in eyes with SO tamponade.

Methodological considerations

Clinical findings

An important methodological issue when comparing gas and SO tamponade is that the decision for gas or SO tamponade is based on the estimated risk of redetachment. Inherent differences in prognosis between patients treated by gas and SO tamponade will lead to so called 'confounding by indication'.³⁴ Two important indications for SO in primary RRD surgery are giant retinal tears and proliferative vitreoretinopathy (PVR) grade C and D. PVR is estimated to occur in 5-10% of the eyes with retinal detachments and it is the major cause of treatment failure.^{35,36} Patients can present with PVR, but in the majority of cases it develops following surgery.^{35,36} It is characterized by the growth of membranes on the retinal surface or the posterior hyaloid.^{35,36} Posterior contraction of these membranes can prevent reattachment or can induce redetachment of the retina.^{35,36} The advantage of SO over gas is its potential to restrict further extension of a retinal redetachment because it provides prolonged tamponade. Gas dissolves spontaneously while SO requires a second vitrectomy to remove it. The decision for the type of tamponade is made by the surgeon at the time of surgery and is based on the estimated risk of redetachment considering multiple factors. In general, the more severe or complex cases receive SO tamponade. Thus, the indication for SO use, instead of SO itself, may be related to the occurrence of SORVL. This is an example of confounding by indication. Only a randomized clinical trial (RCT) with proper randomisation is appropriate to exclude confounding by indication. In 1992, the Silicone Study Group performed a RCT and randomized eyes with RRD and PVR grade C3 or more to vitrectomy and either C₃F₈ gas or SO (1000 centistokes) tamponade.³⁷ Macular attachment was achieved in about 80%, regardless of tamponade. Subgroup analysis indicated that eyes with anterior PVR may benefit from SO tamponade.³⁸ Another RCT in eyes with giant retinal tears randomized eyes to C₃F₈ gas or SO tamponade and reported similar anatomical and functional outcomes.³⁹ Considering the reported incidence of SORVL of 30-53% one might wonder whether eyes actually benefit from SO tamponade.⁴⁰⁻⁴³ A RCT comparing anatomical and functional outcomes following gas and SO tamponade may be ethically justified in patients with overlapping risk estimates for redetachment if treated by gas tamponade, and the occurrence of SORVL if treated by SO tamponade. However, this category

of patients is hard to define and proper randomisation would be difficult to achieve in clinical practice. Furthermore, both tamponades have their own pros and cons and no alternatives are yet available. The optical clarity of SO enables appropriate assessment of the retina in contrast to gas which causes disturbing reflections. Signs of proliferative vitreoretinopathy preceding a potential redetachment are usually visible within 4-12 weeks.³⁶ In case of a redetachment, SO tamponade is indicated because it requires surgical treatment including a retinectomy.^{44,45} Considering the pros and cons of both tamponades, the use of SO tamponade can be favourable in eyes with a high risk on or with a redetachment, if used with caution. This means strict indications and removal as early as possible to reduce the risk on SORVL.

In our cohort studies (**chapters 3.1 and 3.2**), we compared eyes with SO tamponade to eyes with gas tamponade. Compared to a RCT, this observational study design is a second best option in current clinical practice in our opinion. With this design, the association between visual outcome, including visual acuity and retinal sensitivity measured by microperimetry, and SO tamponade can be investigated and compared to gas tamponade. However, adjustment for unknown variables is not possible, which should be taken into account when the results are interpreted.

In the study described in **chapter 3.1**, SORVL was defined as an unexplained loss in visual acuity of 2 or more Snellen lines. In case of visual loss of 2 or more Snellen lines, medical records were reviewed for potential causes. In the absence of an explanation and if visual had not improved within 6 months after SO removal, visual loss was considered to be unexplained. In these patients, a microperimetry was performed and a central scotoma was present in all eyes with unexplained visual loss. However, microperimetry was not performed in patients with visual loss in combination with other abnormalities and where SORVL could not be excluded. Accordingly, in some patients visual loss may have been attributed to any complication of the RRD or its treatment, while it should have been attributed to undetected SORVL. If so, we would have missed some patients with SORVL. This misclassification would have led to an underestimation of the incidence of SORVL.

In **chapters 3.1** and **3.2**, the time of follow-up was longer for patients with SO tamponade compared to patients with gas tamponade, as it included the duration of SO tamponade. Time since last vitrectomy however, was around 2 months in all groups. Since patients with SO tamponade had more time to recover from RRD, any effects of this difference in the duration of follow up would have resulted in better visual outcomes. We observed poorer visual outcomes, which may therefore be an underestimation of the real effect.

SORVL is characterized by visual loss and a central scotoma, which could lead to unstable fixation. Imaging of the macula or assessment of its function can be challenging in eyes with fixation difficulties. For the interpretation of OCT scans, it should be taken into account that several scans are averaged to constitute a single image in order to improve image quality. Unstable fixation increases the potential that minor abnormalities disappear when several OCT-scans are averaged. Subtle retinal abnormalities, e.g. slight cystic macular oedema, might be overlooked. In **chapters 3.1** and **3.2**, single scans were also evaluated separately to ensure that no visible anatomical abnormalities have been missed.

The assessment of macular function can be corrupted by fixation difficulties.^{46,47} The Optos OCT device (Optos OCT/SLO; Optos Plc., Dunfermline, UK) combines microperimetry with SLO and OCT. The SLO allows for tracking of the eye movements and enables real-time observation of the fundus while testing retinal sensitivity.^{48,47,49} SLO also secures reliable reassessment of a previously tested area for clinical follow-up.⁴⁶ In the prospective cohort study comparing visual outcome following SO and gas tamponade (**chapter 3.2**), we used this feature by testing patients during SO tamponade and prior to the potential occurrence of a central scotoma. Furthermore, the combination of SLO with microperimetry and OCT enables us not only to correlate functional deficits to structural abnormalities, but also to check whether the centre of area tested by microperimetry corresponds to the fovea on topography.^{48,47,49} All these functions together are helpful for accurate assessment of macular function in patients with fixation difficulties.^{46,48,47,49}

Electrophysiology

The aim of our study that reports on the electrophysiological findings in eyes with SORVL was to determine whether SORVL is a maculopathy or an optic neuropathy (**chapter 3.3**). For that purpose, mfERG, pERG and VEP was performed in 9 patients with SORVL. In case of monocular SORVL, fixation problems that result from the central scotoma affect electrophysiological examinations less than the previously OCT imaging or microperimetry because they can be recorded binocularly. Sufficient vision of the fellow eye enables good fixation.^{50–52} We improved the reliability of the mfERG responses by the use of a protocol including 4 short recording periods instead of 2 longer recording periods. Furthermore, the thorough data analysis of our mfERG, pERG and VEP data yielded more accurate results.

Factors affecting stimulus luminance can influence electrophysiological investigations. For that reason, we corrected for differences in pupil size, which can occur after vitrectomy, by full dilation of both pupils in our study of the electrophysiology of SORVL (**chapter 3.3**). Lens and media opacities can cause scattering of light and therefore also of the light stimulus.^{53,54} As a consequence, response densities on multifocal electroretinogram can be reduced in eyes with

opacities.^{53,54} However, it has no effect on implicit times.^{53,54} Any interocular differences in media opacities could have affected response density ratios but could not have induced prolonged implicit times as measured in eyes with SORVL.

Clinical implications

Clinical findings

Although incidence rates for SORVL among macula-on RRD are found between 30% and 53%, the absolute number of reported cases is still low.⁴⁰⁻⁴³ We identified 11 patients with SORVL after a macula-on RRD in the UMC Utrecht in 2011 and 2012 (**chapter 3.1**). However, it concerns a serious complication of an otherwise successful treatment.^{44,55,56} Our prospective cohort study described in **chapter 3.2** demonstrates that SORVL may also occur in patients with a macula-off RRD. The number of patients with SO tamponade for a macula-off RRD is much higher than of patients with SO tamponade for a macula-off RRD is much higher than of patients with SO tamponade for a macula-off RRD probably go unnoticed because their visual loss is explained by a detached macula. This indicates that SORVL may affect many more people than previously assumed. Microperimetry in these patients may detect the typical central scotoma of SORVL. For this reason, we suggest to do microperimetry in patients with a lower than expected visual acuity following SO tamponade, also in cases with a macula-off RRD.

Another important finding in our study is the presence of more subtle functional changes after SO use, as demonstrated by microscotomas on microperimetry. Although not always accompanied by reduced distance visual acuity, patients may experience difficulties in reading or other visual functions in daily life.

The studies described in **chapter 3** have emphasized the risk of SO tamponade. This knowledge should be taken into account when considering the type of tamponade, and has resulted in even stricter indications for the use of SO in our department. Moreover, we identified the duration of SO tamponade as a risk factor for the development of SORVL (**chapter 3.1**). In our experience, the earliest presentation of SORVL was at 2.5 months after SO insertion. Based on this finding, the duration of SO tamponade is now strictly maximized to 3 months in the UMC Utrecht. If this critical period of SO tamponade is confirmed by others, than this should have consequences for the safety guidelines of commercially available SO.

Pathophysiology

In **chapter 3.4**, we provide reference values for potassium, sodium, chloride, magnesium, calcium, glucose and lactate dehydrogenase in the vitreous fluid of living human eyes. Up to now, only post-mortem or animal data were available for these substances.^{57,58}

Future perspectives

Clinical findings

Software that can discriminate separate retinal layers on OCT and measure their thickness is commercially available.^{43,59} These tools may be used to monitor retinal layer thickness during SO tamponade and to detect early retinal thinning that is described to occur in eyes with SO tamponade by others and by us (**chapters 3.1** and **3.2**).^{40,43,59} Accordingly, SO should be removed as soon as retinal thinning is detected, which might prevent the occurrence of SORVL. However, currently it is unknown whether thinning of the retinal layers is a good indicator for the occurrence of SORVL. More data are required to better understand the relation between retinal layer thickness and visual function in general and the occurrence of SORVL in particular. Eventually, it would be interesting to investigate the potential of OCT software measuring inner retinal layer thickness to monitor the risk on SORVL.

Electrophysiology

In our case series described in chapter 3.3, we performed electrophysiological examinations in patients with unilateral SORVL in order to locate the functional deficit. We found consistently prolonged implicit times on mfERG which advocates a retinopathy. We did not assess patients after SO tamponade without SORVL. A study comparing mfERG in patients treated by SO tamponade both with and without SORVL is required to ensure whether the prolonged implicit times on mfERG characterize SORVL, or whether they are side effects of SO tamponade.

Pathophysiology

In the healthy eye, vitreous fluid serves as an infinite buffer that is essential for regulation of homeostasis. Replacement of vitreous fluid by intraocular SO induces a dramatic change in environment; from aqueous to lipid. In general, hydrophilic substances cannot dissolve in oil and the infinite buffer function of the vitreous cavity is lost. One can imagine that this profound alteration in environment may disturb various homeostatic processes. Retro-oil fluid is a thin layer of aqueous fluid surrounding the SO bubble. Hydrophilic substances unable to dissolve in the SO can accumulate in this retro-oil fluid. On the other hand, lipophilic substances easily dissolve in SO and may be withdrawn from fundamental processes in the retina. Accumulation of harmful hydrophilic substances in the retro-oil fluid or withdrawal of essential lipophilic substances may induce retinal toxicity and subsequent retinal damage. The occurrence of SORVL could be explained by both mechanisms. However, some patients develop SORVL directly following SO removal. In those patients, accumulation of toxic substances seems less plausible as a cause of SORVL. Withdrawal of fundamental lipophilic substances could occur during SO tamponade and following SO removal. By removing the SO, one might remove a depot of essential components that had been built up in the SO bubble during tamponade. Disposal of this depot may induce direct damage to the retina and might explain the occurrence of SORVL

after SO removal. During SO tamponade, extraction of lipophilic substances from the retina or exchange of these substances between the retina and the SO bubble might depend on the degree of filling or on unknown patient characteristics, e.g. regarding lipid metabolism or dietary intake. On the other hand, the occurrence of SORVL during SO tamponade and the occurrence of SORVL shortly following SO removal could also reflect different entities causing similar symptoms. It is unknown whether SORVL results from cumulative damage representing a clinical spectrum of varying severity, or whether it is an on-off phenomenon that occurs after a certain threshold is reached. More data on macular function during SO tamponade and in eyes with SO without SORVL by means of microperimetry or multifocal electroretinogram could provide more a better insight in the clinical spectrum of SORVL.

Knowledge on the pathophysiology of SORVL could allow for the identification of risks factors and perhaps lead to preventive interventions. Several hypotheses have been put forward.

One theory refers to the accumulation of potassium levels in retro-oil fluid due to lost buffering capacity of the vitreous cavity.^{60–62} In **chapter 3.4**, we demonstrate that potassium levels are not raised in retro-oil fluid, which makes the hypothesis of potassium siphoning failure as a general feature of SO tamponade and an underlying mechanism of SORVL unlikely. However, magnesium levels were lowered in retro-oil fluid. Magnesium is a pleotropic mineral involved in the majority of biochemical processes.⁶³ Low magnesium levels are linked to *N*-methyl-D-aspartate overstimulation (excitotoxicity).⁶³ Thinning of the ganglion cell layers and inner plexiform layer on OCT, as seen in SORVL, is also shown after experimental excitotoxicity in animals.^{64,65} In addition, magnesium is essential for maintaining retinal adhesiveness and low magnesium levels might reflect pre-existing levels related to the retinal detachment.⁶⁶ The role of magnesium in SORVL requires further investigation.

A second hypothesis is based on previous studies that detected lipophilic substances, e.g. retinol and cholesterol, in SO after removal.^{67–70} Macular pigments, lutein and zeaxanthin, are lipophilic and may be withdrawn from the retina and accumulate in the SO. Circumstantial evidence for this hypothesis came from a study by Herbert et al. who used confocal scanning laser ophthalmoscopy to show a reduction in macular pigment optical density (MPOD) in eyes with SO tamponade compared to fellow eyes without SO.⁶⁷ Lower macular pigment concentrations render the macula vulnerable to phototoxic damage and oxidative stress, which may subsequently affect visual function.^{71–73} An increase in MPOD by supplementation is found to increase visual acuity.^{74–76} The concentration of macular pigment peaks at the fovea and rapidly declines with increasing eccentricity.⁷⁷ In eyes with fixation problems, as in SORVL, it is difficult to ascertain that the obtained values correspond to foveal concentrations and not to eccentric concentrations. The use of methods that include SLO techniques improves the reliability of MPOD measurements. In addition, reliable MPOD measurements over time during

SO tamponade can provide important information about possible changes in MPOD in the presence of SO.

Migration of SO into the optic nerve has also been proposed as a cause of SORVL.⁷⁸ Some histopathological studies demonstrated the presence of emulsified SO in the optic nerve in 13-24% of the eyes treated by SO tamponade for various vitreoretinal disorders.⁷⁸⁻⁸¹ The duration of SO tamponade in these eyes ranged from 2 months to 12 years. Knecht et al. could not confirm these findings in post-mortem eyes that received SO tamponade for 50 days and proposed that other factors, e.g. high intraocular pressure during SO tamponade, should be involved in this migration process.⁸² Furthermore, it is unknown whether emulsified SO in the optic nerve could affect optic nerve function and, consequently, VEP recordings. We did not specifically investigate in our case series whether SO droplets were present in the optic nerve. Small hyperreflective areas are found on OCT-scans of the macula in eyes after 3 months of SO tamponade.^{83,84} It is suggested that they most likely indicate emulsified SO droplets.^{83,84} The presence of SO bubbles in the optic nerve or in the cerebral ventricles is demonstrated by magnetic resonance imaging in a few eyes with secondary glaucoma.⁸⁰ It seems unlikely that such variety in findings would cause such small and consistent abnormalities characteristic for SORVL.

Recently, a new hypothesis has been put forward, arguing that ganglion cell death exclusively underlies SORVL. The authors came to this conclusion based on the combination of physiological VEP recordings and response densities on mfERG together with reduced thickness of the nerve fiber layer, the GCL, and INL in 6 eyes with SORVL. However, thinning of these retinal layers is not only found in eyes with SORVL but also in eyes after SO tamponade without SORVL.^{40,42,59} It may therefore precede SORVL or it might be attributable to SO use in general and not be a sign of SORVL. As previously suggested, the relation between retinal layers thickness and visual function in general or the occurrence of SORVL requires further investigation.

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CHAPTER 5

Appendices

LIST OF PUBLICATIONS

Scheerlinck L, Kuiper J, Liem ATA, Schellekens P, van Leeuwen R. Electrolyte composition of retro-oil fluid and silicone oil-related visual loss. *Acta Ophthalmol.* 2016.

Scheerlinck LM, Schellekens PA, Liem AT, Steijns D, van Leeuwen R. Incidence, risk factors and clinical characteristics of unexplained visual loss after intraocular silicone oil for macula-on retinal detachment. *Retina*. 2016;36(2):342-350.

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Laban KG, **Scheerlinck LME**, van Leeuwen R. Prognostic factors sssociated with visual outcome after pars plana vitrectomy with internal limiting membrane peeling for idiopathic epiretinal membrane. *Ophthalmologica*. 2015;234(3):119-126.

Hettinga YM, **Scheerlinck LME**, Lilien MR, Rothova A, de Boer JH. The value of measuring urinary β 2-microglobulin and serum creatinine for detecting tubulointerstitial nephritis and uveitis syndrome in young patients with uveitis. *JAMA Ophthalmol.* 2015;133(2):140-145.

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Laura Scheerlinck was born on 27th of April 1987 in Sint-Truiden, Belgium, and moved in 1993 to Tilburg, the Netherlands. She attended the Theresialyceum in Tilburg and started in 2005 her study Medicine at the University of Utrecht. In 2008, she spent three months at the English Learning Centre in Bristol, the United Kingdom, where she obtained the Cambridge Advanced Certificate in English. After receiving her Medical Degree in 2012, she started the work described in this thesis under supervision of prof.dr. S.M. Imhof, dr. R. van Leeuwen, and dr. T.T.J.M. Berendschot at the Department of Ophthalmology of the University Medical Center in Utrecht. In September 2015, she obtained a Master in



Health Sciences in Clinical Epidemiology at the Julius Center in Utrecht. She was part of the organization committee of the Dutch Ophthalmology PhD Students (DOPS) meeting 2013. At the EURETINA Winter Meeting 2016, she received the first prize in the poster competition. She will start her residency in Ophthalmology in the same institute in October 2016.