Diplomarbeit

Effect of intravitreal C3F8 gas in patients with vitreomacular traction – a retrospective case series

eingereicht von

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zur Erlangung des akademischen Grades

Doktorin der gesamten Heilkunde

(Dr. med. univ.)

an der

Medizinischen Universität Graz

ausgeführt an der

Universitätsklinik für Augenheilkunde

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Graz, 12.02.2017

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Graz, am 12.02.2017 *Anna-Maria Haas eh*

Acknowledgment

I would like to thank Priv.-Doz. Dr. Werner Wackernagel and Dr. Christoph Mayer, who have given me the possibility to conduct this paper. Whenever I needed support, you took the time to guide me through the writing process and helped me with new ideas and inputs.

I want to express my sincere gratitude to my parents Gabriele and Anton, who have not just guided me throughout my life with unconditional love but without whom I would have never managed to accomplish my medical education. Thank you for your continual encouragement, relentless support, helpful advice, great generosity and for being my greatest role models. Papa, your ophthalmological expertise has essentially helped me in accomplishing this paper. Mama, our hourly talks have always cheered me up and helped me to endure harder times.

Additionally I want to thank David, who is always there for me and helps me to continuously improve, both academically and personally.

Last but not least, I want to express my deepest thanks to my family and friends, especially my wonderful siblings Johannes and Clara and my incredible grandparents. Without you I would not be who I am today.

Zusammenfassung

Ziel: Diese Fallserie versuchte die Wirksamkeit einer einmaligen intravitrealen Applikation von Perfluoropropangas (C3F8) für die Behandlung von vitreomakulären Traktion mit oder ohne Makulaloch zu beurteilen.

Methoden: In dieser retrospektiven Fallserie bekamen sieben Augen von sechs PatientInnen mit einer symptomatischen vitreomakulären Traktion in der optischen Kohärenztomographie, eine davon mit zusätzlich einem Makulaloch, eine einmalige intravitreale C_3F_8 Gasinjektion von bis zu 0.3mL. Der primäre Endpunkt war die Lösung der vitreomakulären Traktion einen Monat nach der Injektion. Die sekundären Endpunkte beinhalteten die Lösung der vitreomakulären Traktion innerhalb sechs Monate, die Verschließung eines Makularlochs ohne einer weiteren vitreoretinalen Intervention, Veränderungen in der zentralen fovealen Dicke und der Sehschärfe.

Ergebnisse: Insgesamt hatten drei von sieben Augen (42.86%) eine mit optischer Kohärenztomographie dokumentierte Lösung der vitreomakulären Traktion innerhalb eines Monats und 3 weitere Augen (85.71%) zeigten eine Loslösung innerhalb eines halben Jahres. Von den letzteren wiesen 2 der 3 Augen gleichzeitig eine epiretinale Membran auf und eines eine simultane diabetischen Retino- und Makulopathie. Der Patient mit einem Makulaloch hatte innerhalb eines Monats eine vitreomakuläre Traktionslösung musste sich jedoch wegen Persistenz des Makulalochs einer Vitrektromie unterziehen. Assoziierte unerwünschte Ereignisse waren ein Makulaödem mit einem Schichtloch nach der Injektion bei einem Patienten und ein anderer Patient entwickelte eine Netzhautablösung.

Schlussfolgerung: Die intravitreale Gasinjektion mit C3F8 Gas in eine kostengünstige und vielversprechende minimalinvasive Option für die Behandlung von symptomatischer vitreomakulärer Traktion mit oder ohne Makulaloch. Weitere größere Studien, die vor allem die C_3F_8 Gasinjektion mit anderen Therapieoptionen vergleicht, sind erforderlich.

Abstract

Purpose: This case series tried to assess the efficacy of a single intravitreal perfluoropropane gas injection for the treatment of vitreomacular traction with or without a macular hole.

Method: In this retrospective case series, 7 eyes of 6 patients with symptomatic vitreomacular traction documented on optical coherence tomography, one with a macular hole additionally, received a single intravitreal C_3F_8 gas injection of up to 0.3mL. The primary end point was vitreomacular traction release at one month after injection. Secondary end points included resolution of vitreomacular adhesion within six months, nonsurgical closure of macular holes and change in central foveal thickness and best-corrected visual acuity.

Results: Overall, three of seven eyes (42.86%) had release of vitreomacular traction at 1 month after injection, with three further eyes (85.71%) releasing within six months documented on optical coherence tomography. Out of the latter two of the three eyes showed a concurrent epiretinal membrane and one a concurrent diabetic retino- and maculopathy. The patient with a macular hole had resolution of vitreomacular traction within one month but had to undergo vitrectomy because of nonclosure of the macular hole.
Associated adverse events were a macular edema with a consequent lamellar hole after injection in one patient and another patient developed a retinal detachment.

Conclusion: Intravitreal perfluoropropane gas injection is an inexpensive and promising minimally invasive option for the treatment of symptomatic and persistent vitreomacular traction with or without showing a macular hole. Further larger studies, especially contrasting C_3F_8 gas injection with other treatment options, are needed.

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Abbreviations

BCVA	best-corrected visual acuity
C_3F_8	perfluoropropane gas
CME	cystoid macular edema
DM	diabetes mellitus
ERM	epiretinal membrane
FTMH	full thickness macular hole
ILM	inner limiting membrane
IOP	intraocular pressure
LE	left eye
LMH	lamellar macular holes
MIVI-TRUST	microplasmin for intravitreal injection-traction release without surgical treatment
MH	macular hole
OASIS	ocriplasmin for treatment of vitreomacular treatment
OCT	Optical Coherence Tomography
PPV	pars plana vitrectomy
PVD	posterior vitreous detachment
RE	right eye
RPE	retinal pigment epithelium
SD-OCT	Spectral Domain Optical Coherence Tomography
SF_6	sulfur hexafluoride gas
VA	visual acuity
VMA	vitreomacular adhesion
VMT	vitreomacular traction
VMTS	vitreomacular traction syndrome

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PART I – General Part

1 Anatomy

The human eye is an asymmetrical sphere, with a diameter of approximately 24mm and a volume of 6.5ml. One can additionally subdivide the eye into two spheres, the cornea and the sclera, a smaller one in the front with a greater curvature and a bigger one posteriorly, respectively. The eye has a three-layered coat, the utmost corneoscleral coat, the uvea and the inmost retina, which comprise the structures within. The transparent cornea borders on the Limbus corneae the relative avascular sclera forming a tough protective fibrous envelope together. (1)

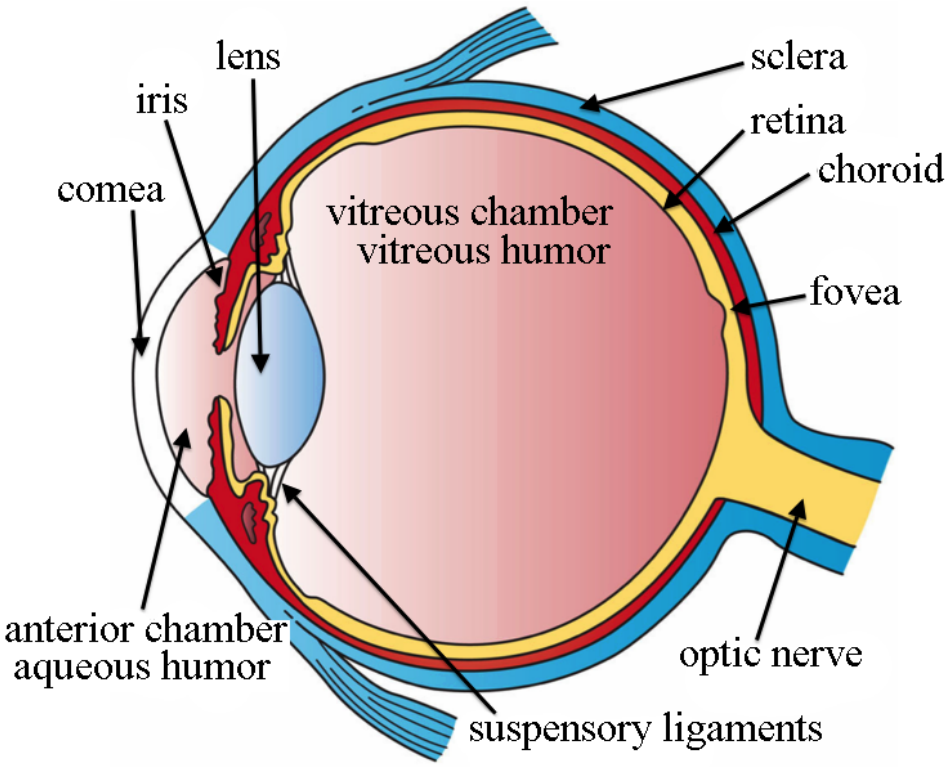

Figure 1 Anatomy of the eye

The uvea consists from anterior to posterior of three components the iris, ciliary body and choroid. The latter is a highly vascularised and pigmented, 0.2mm thin membrane located between the sclera and the retina. (2)(1) Predominantly its function is to provide oxygen and nourishment to the outer third of the retina. (3) Histologically the human choroid has five layers from internal to external the membrane of Bruch, the choriocapillaris, the Haller's layer, the Sattler's layer and the suprachoroid.(1) The innermost of the three coats is called

retina, consisting of an inner neurosensory retina and a retinal pigment epithelium, which derive from the inner and outer layer of the invaginated optic cup, respectively. (4)

Two-thirds of the volume of the eye is taken up by the vitreous cavity containing the vitreous body, which extends from the lens and ciliary body to the retina. The vitreous, 4ml in volume, is a transparent viscoelastic gel, which contains no cells except occasionally at the vitreous base. It is comprised of 98% water and 2% collagen fibres, mainly type II, and hyaluronic acid. A cortical zone with a higher occurrence of collagen fibrils is distinguished from a more liquid central vitreous. The central part is traversed from the optic nerve disc to the lens by the Cloquet's canal, being a remnant of the course of the hyaloid artery of the fetal eye.

Due to the fluid flow from the vitreous towards the choroid the inner neurosensory retina stays attached to the retinal pigment epithelium. Strong adherence of the cortical vitreous occur where the ILM is thinnest, at the vitreous base, the optic disk and the inner limiting membrane of the retina, especially near retinal vessels. (1)(5)(6)

Humans have a dual blood supply of the retina, with the central retinal vessel nourishing the inner two-thirds of the retina and the outer-third deriving its nutrition from the choriocapillaris, which derives from the posterior and anterior ciliary arteries. The central retinal artery arises from the ophthalmic artery in the optic canal and as it enters the retina divides into four main branches. The capillary network density is the highest in the macula, decreases towards the periphery and is absent from the fovea itself, therefore being dependent on the choroidal circulation. (4)(5)

The retina is divided into a photosensitive part known as the Pars optica retinae and a non-photosensitive part the Pars caeca retinae. The latter containing only pigmented epithelium is present on the posterior surface of the ciliary body and iris. The transition zone between these two parts is formed by the Ora serrata. (2)(7)

The retina has ten layers, which are beginning with the outmost layer and proceeding towards the innermost layer as follows:

1. The pigment epithelium
2. The rod and cone layer
3. The outer limiting membrane
4. The outer nuclear layer
5. The outer plexiform layer
6. The inner nuclear layer
7. The inner plexiform layer
8. The ganglion cells layer
9. The nerve fiber layer
10. The inner limiting membrane

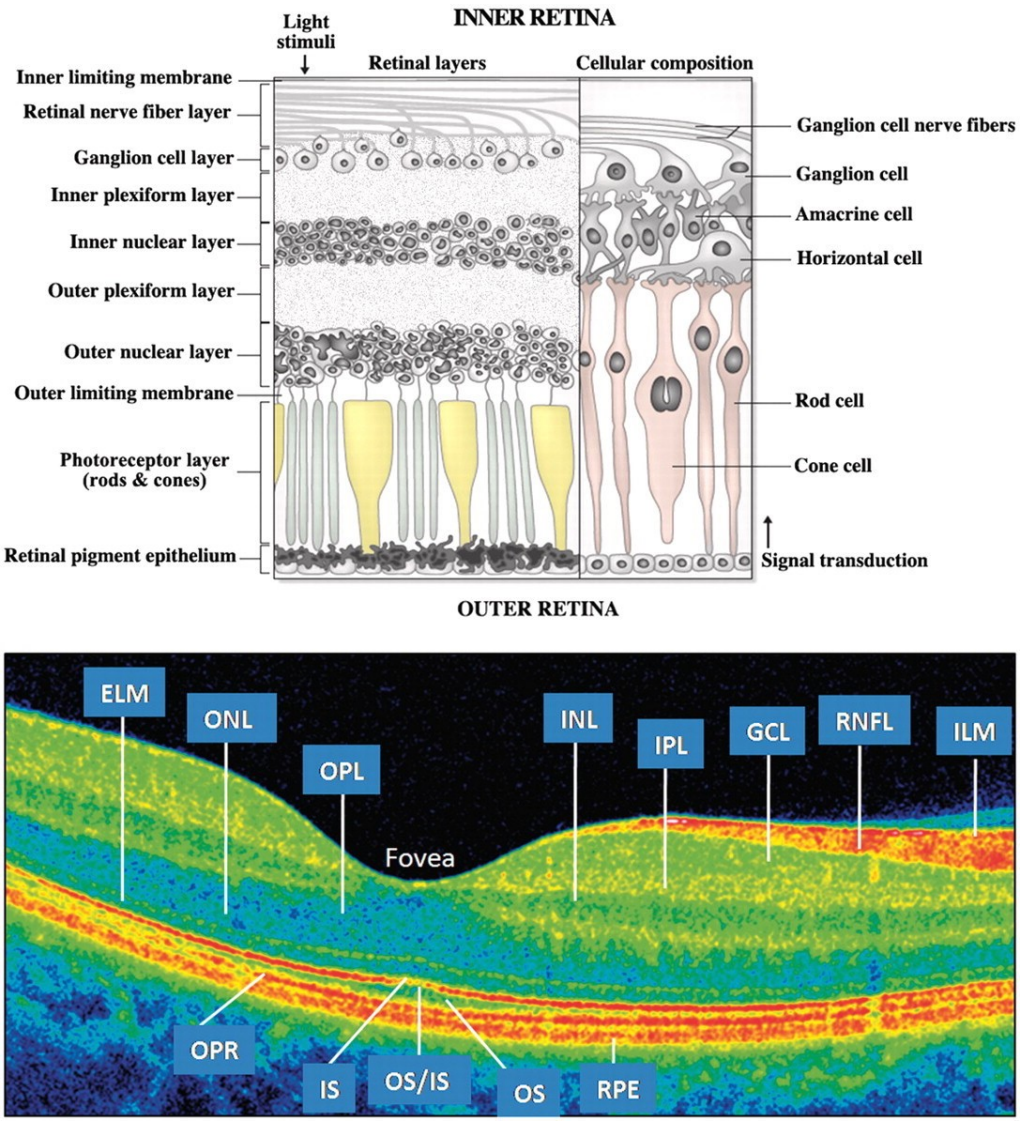

Figure 2 The ten layers of the retina schematic and on OCT

For descriptive purposes, one can divide the retina into two halves, nasal and temporal, dragging a vertical line through the fovea and four quadrants, supero- and inferonasal and supero- and inferotemporal, by adding a horizontal line through the optic nerve. (1)

The posterior pole or area centralis is a cone-dominated region and located a few millimetres temporal of the optic disc. In the area of the posterior pole is the macula lutea. The term macula, anatomically fovea, refers to its colour being partly yellow as a result of the deposition of carotenoid pigments protecting the macula against impairment of UV irradiation. The fovea centralis, anatomically foveola, lies centrally in the macula with a diameter of 0.35mm. In this purely of cone receptor filled region of the retina, the receptors are slimmer, more densely packed (150000/mm^2) and are exposed directly to the light without any dispersion. Within the foveola each cell is interconnected in a 1:1 ratio with a single bipolar cell and a single ganglion cell, thereby guaranteeing a maximal transmission of the

stimulus. Beyond the posterior pole the peripheral retina is stretching to the ora serrata. It is rich in rods and has only a single layer of ganglion cell bodies. (1)(4)(5)

The internal part of the retina borders with the vitreous body and its external part is in weak attachment with the retinal pigment epithelium, leaving a potential space. The only two points where the retina is tightly attached to the retinal pigment epithelium is posteriorly at the optic disc and anteriorly at the ora serrata. On the inner side of the retina the internal limiting membrane adjoins to the vitreous. (4)

2 Definition

2.1 Posterior vitreous detachment

The cortical vitreous and ILM of the retina are connected at their interface by a glue-like matrix, composed of proteogylcans, including laminin and fibronectin. (8)(9)

Physiological with aging, the vitreous gel progressively liquefies (synchysis), thereby creating lacunae or fluid-filled pockets in the vitreous. Gradually these pockets consolidate and enlarge, subsequently collapse (syneresis). This weakens the adhesion between the posterior hyaloid membrane (PHM) and ILM, leading to separation, or PVD. (10) (11) This process evolves and progresses in the course of years, usually beginning in the perifoveal macula and subsequently separating at multiple sites throughout the peripheral fundus as well. (8) (12) Typically its onset is spontaneous, but sometimes induced by trauma, cataract surgery, uveitis and panretinal photocoagulation. (13) Even though PVD is asymptomatic in most of the cases, patients may present with acute symptoms such as floaters or photopsia when the vitreous detaches from the nerve head. These patients often show the presence of a Weiss ring, confirming vitreopapillary separation and the end of a years-long process. (12)(8)

An uncomplicated PVD occurs when the process of vitreous liquefaction and vitreoretinal adhesion proceed concurrently and to a similar extend. (14)(15) But a PVD can be complicated by retinal tear followed by retinal detachment due to mobility of the vitreous causing traction on the retina at the vitreous base.

Nevertheless, the PVD does not always result in a complete and clean separation. When liquefaction outpaces the degree of weakening of vitreoretinal adhesion or abnormal adhesion of the vitreous cortex to the ILM occurs, one refers to a condition called anomalous PVD. (15)(16) High myopia, vitreous haemorrhage, inflammation, hereditary vitreoretinal

syndromes, trauma, retinal vascular diseases and aphakia may accelerate premature vitreous liquefaction. Complications following PVD, such as VMA, VMT, ERM, FTMH and lamellar holes and pseudoholes, occur in up to 27%. (13) (16) (17)

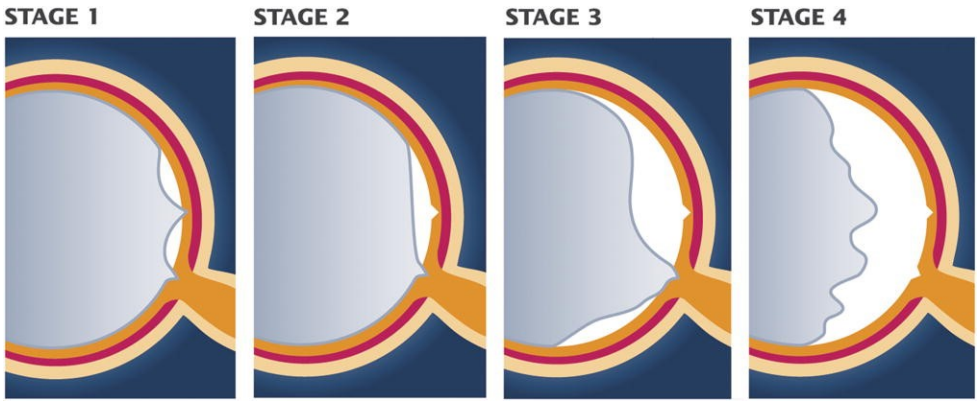

Figure 3 Development of posterior vitreous detachment

2.2 Vitreomacular Adhesion

Having an incomplete separation of the PVD, wherein a part of the vitreous body is persistently attached to the macula area without retinal abnormalities, is diagnosed as VMA. The cortical vitreous raises above the retina remaining yet partly connected to it. Patients with VMA usually don't experience any visual impairment. In case minimal symptoms are however present non-interventional management is favoured. VMA is now considered as a normal stage in the process of PVD. (16)(8)(18)

A group of retina specialists, the International Vitreomacular Traction Study (IVTS) Group, has developed an OCT-based classification scheme for several disorders of the VMI. On OCT, VMA was defined as a perifoveal vitreous cortex separation with partial residual vitreomacular attachment and no detectable changes in foveal morphology or in underlying retinal tissues. The macular remains attached to the cortical vitreous within a 3 mm radius of the fovea.

VMA may be subclassified by size of attachment area as either focal (≤ 1500µm) or broad (> 1500µm). The 1500µm cut off has been chosen, because this diameter is known to be an area of increased vitreous adhesion to the fovea. Furthermore the value has been used in former published literature and by OCT reading centers for the distinction of focal and broad. It is important to note, that small regions of dehiscence (< 1 mm) in broad attachment zones should be disregarded. If differentiation has a prognostic impact remains uncertain up to now. By the presence of associated retinal abnormalities, such as age-related macular degeneration, retinal vein occlusion, or diabetic macular edema, the term to describe VMA should be "concurrent". For cases with absent ocular diseases the term "isolated" should be reserved. (8)

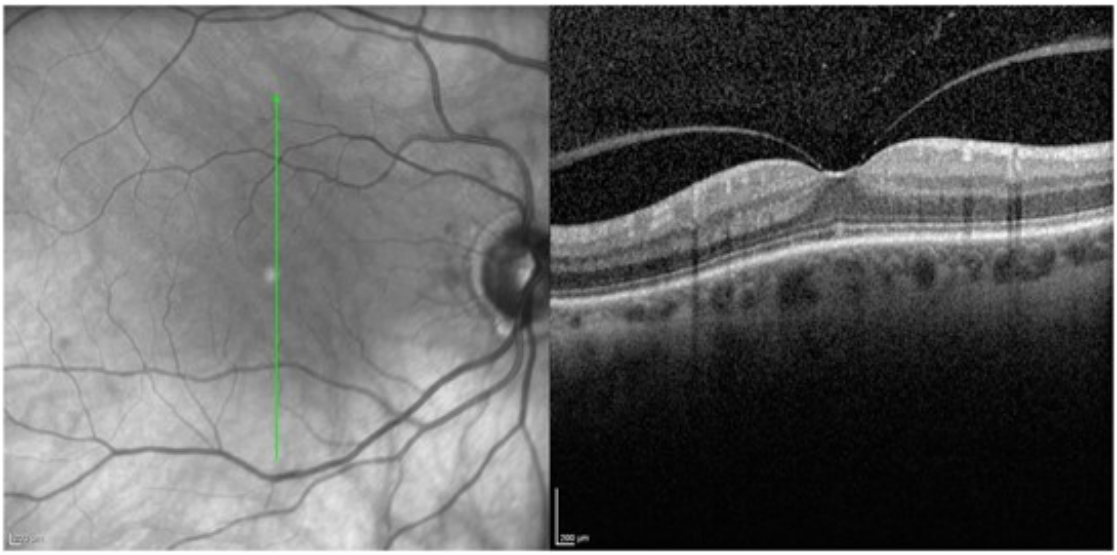

Figure 4 OCT shows focal VMA with normal foveal contour and retina morphology

2.3 Vitreomacular Traction

If VMA has not sufficiently weakened, these adherences can cause excessive traction forces on the macular. The combination of detectable retinal anatomic changes on OCT with concurrent perifoveolar PVD is known as VMT. With PVD progressing and traction increasing, the anteroposterior forces may promote intraretinal pseudocyst formation, elevation of the fovea from the RPE, or a combination that typically has a negative impact on ones vision. Symptoms typically include decreased central vision with some degree of metamorphopsia. (8) (9)

In 1970 Reese et al. were the first to describe VMTS, both clinically and histopathologically, as a condition in which an incomplete PVD caused a macular traction and decreased visual acuity. (19) (20) (21)

VMT has a spontaneous release rate of 32% over an average time of 23 months, concluding that an initial observation period is a reasonable option for patients with VMT. (16) (22) Nevertheless it tends to progress over time. (23)

In former times, VMT syndrome was thought to be an isolated pathology. Currently, it is considered to be an important etiological factor in the development for a wide spectrum of macular diseases, including CME, MH, and ERM. (24) (25)

A variant of the VMTS is the vitreofoveal traction syndrome, where the adhesion of the vitreous persists only at the fovea, causing problems in the centre of vision. (19)

When PVD progresses, thereby exerting exorbitant traction force on the macula, detectable changes in the foveal anatomy can occur. Signs of perifoveolar PVD in combination of anatomical changes on OCT allow the clinician to diagnose VMT. All of the succeeding three

aspects must be present on at least one B-mode OCT scan: (1) evidence of perifoveal PVD from the retinal surface; (2) macular attachment of the vitreous cortex within a 3-mm radius of the fovea; (3) association of attachment with distortion of the foveal surface, intraretinal structural changes, and/or elevation of the retina at the fovea above the RPE, but without interruption of retinal layers in its full-thickness.

VMT was subclassified in the same ways as VMA as broad or focal, depending on the diameter of vitreous attachment to the macular surface, and as isolated or concurrent, according to whether or not other ocular diseases are present. While broad traction areas of attachment can lead to thickening of the macula, vascular leakage on fluorescein angiography, macular schisis, and cystoid macular edema, focal ones can cause an elevation of the foveal floor and/or the formation of pseudocysts in the central macula area. (8)

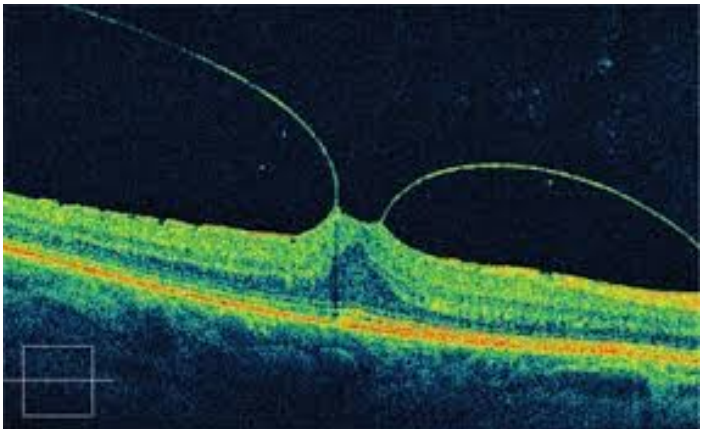

Figure 5 Vitreomacular traction with minor distortion of the foveal contour

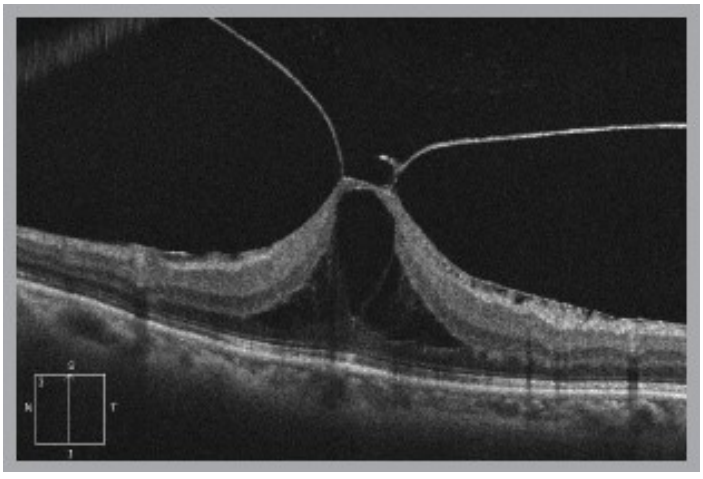

Figure 6 Vitreomacular traction with distorted foveal contour and with schisis-like separation of the retinal layers

2.4 Epiretinal Membrane

The ERM, also known as macular pucker or cellophane maculopathy, is a pathologic, avascular fibrocellular membrane that proliferates on the surface of the inner retina. (19)(26) PVD is believed to play a central role in the pathogenesis of idiopathic ERM. On the one hand it is suspected, that during the process of PVD a break in the ILM may develop, enabling glial cells to migrate and proliferate on this thin and translucent acellular membrane on the surface of the retina. On the other hand, and perhaps more likely, it is proposed that residual vitreous tissue is left on the retinal surface after PVD. This condition is called vitreoschisis and is found in almost half of all autopsied eyes with PVD. The vitreous cortical remnants may proliferate to form an ERM, whose exact cell composition has not yet been identified. Hyalocytes have the ability to transdifferentiate, impeding the etiological progression. (8)(27)

Not only PVD associated pathogenic mechanisms can explain ERM, but also retinal vascular disease, diabetes, trauma, inflammatory conditions, tumors and retinal dystrophies are associated causes. (16)(26)

In clinical practice, ERM are often classified as cellophane macular reflex or preretinal macular fibrosis, the early and the late form, respectively. The latter, showing superficial retinal folds or traction lines, is the more severe stage than the cellophane macular reflex, which does not produce distortion of the inner retinal surface. As a result, preretinal macular fibrosis causes significant contraction of the membrane, full-thickness distortion and folding of the macula resulting in visual impairment in about 80% of cases. (26) (28) (19) In general, symptoms vary greatly from patients having normal or near-normal visual acuity to complaining from a plethora of visual disturbances, such as blurred vision, decreases visual acuity, metamorphosia, monocular diplopia and macro- or micropsia. (29) Complications, such as retinal hemorrhages, exudates, vascular abnormalities, edema, macular pseudoholes, and macular holes have been described leading to further visual impairment. (26)

Diagnosing an eye with suspected ERM is primarily clinical with slit lamp biomicroscopy. OCT has emerged as an important clinical assessment, not only enabling to detect ERM, but also assisting in topographic localization and identification of vitreoretinal relationships.

The highest incidence of ERM is found in people over the age of 50, with several clinical studies noting, that it affects between 7-11.8% of the population. (29) Females are insignificantly more frequently affected than males and 20% occur bilaterally. (30) The management options of ERM are either observation or surgical intervention. The former is

accomplished in the vast majority of patients, due to no respectively slow progression of the ERM. However, retinal pathologies can origin or progress, such as progressive membrane thickening, retinal detachment, lamellar hole formation, or macula edema, causing visual impairment to proceed. These patients benefit from pars plana vitrectomy with peeling the membrane from the surface of the macula. (26)(19)(29)

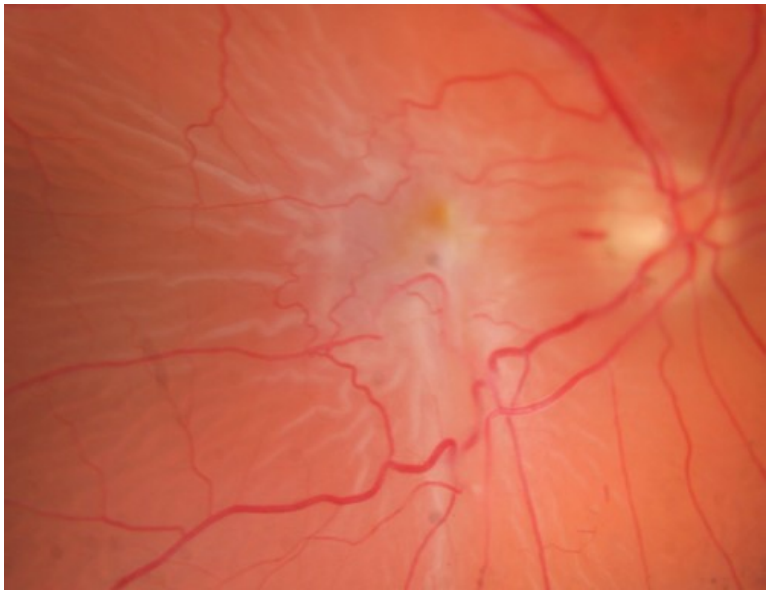

Figure 7 This fundus photo shows a thick white membrane over the macula with retinal folds and contraction of the macula

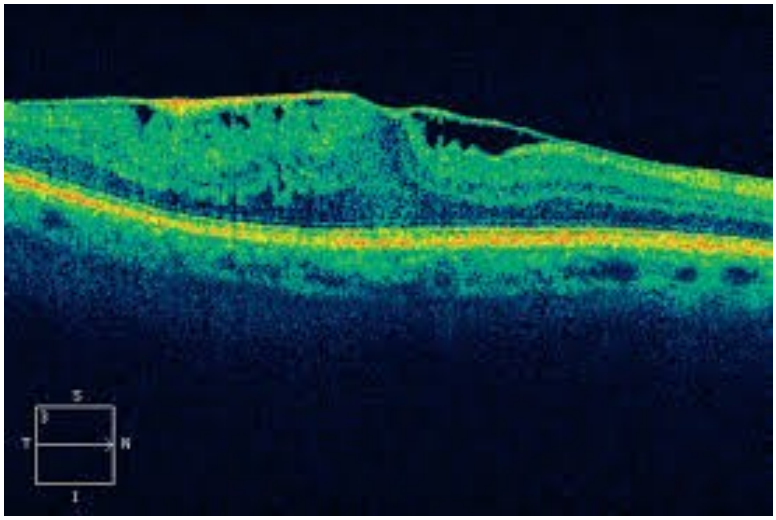

Figure 8 Epiretinal membrane on the surface of the retina with retinal thickening. Several nonreflective pockets were formed between the ERM and internal limiting membrane due to retinal contraction

2.5 Macular Hole

A macular hole is a full-thickness defect of the neurosensory retina within the center of the macula. The lesion includes all neural retinal layers except the RPE. (4)(31)(16) Even though Knapp made the first case description of a macular hole as early as 1869, little attention was paid to it until the 1990s by most ophthalmologists, since pathogenesis was poorly understood and cure impossible. (19) Although the pathogenesis remains dubious, interest in this disease has extremely increased since Kelly & Wendel reported on vitrectomy being an effective treatment. (32)(37)

Three possible theories are being discussed: the traumatic theory, the cystic degeneration and vascular theory, and the vitreous theory. Even though it was at first presumed that approximately 50% of macular holes are due to blunt trauma, it is now known that the majority of macular holes is idiopathic in aetiology, thereby placing special emphasis on the vitreous theory.(4) (34) (35) It has been postulated that idiopathic macular holes are due to focal shrinkage of the prefoveolar vitreous cortex and tangential retinal traction forces of the vitreous on the macula, a so called primary FTMH. (4) The advent of high-definition OCT has brought back the long-time assumed theory of anteroposterior vitreous traction. (24) While some opine that PVD is not essential to macular hole formation, others emphasize its role in the pathogenesis. (35) (33) A secondary FTMH is associated with other ocular pathologies including high myopia, macular schisis, lightning strike and ocular trauma. (8)

The hallmark complaint of a FTMH is loss of central vision and metamorphopsia. (33) While early stages of FTMH are often asymptomatic, especially patients with a unilateral macular hole, progressed late-stage macular holes lead to severe visual impairment seriously affecting the vision related quality of life. (31)

Women are affected three times more often than men with an average onset of 65 years. Reasons for this female dominance remain speculative, since the only significant risk factor examined was increased plasma fibrinogen (>2.95 g/liter).

Macular holes usually occur unilaterally and patients can be pacified, because the risk of fellow eye involvement is low and ranges from 3 to 22%. (4)(31)(33)(36) However a patient, diagnosed with FTMH unilaterally, already showing VMA or VMT on OCT in the fellow eye, is at higher risk for developing a FTMH bilaterally. This special circumstance is referred to as impending macular hole, but the possibility of spontaneous resolution maintains. (8)

The most valuable tool for diagnosing macular holes is a contact lens biomicroscopic evaluation of the lesion and OCT. Further helpful tests are ancillary testing, the slit-beam test,

referred to as Watzke test, where the light beam is interrupted due to the FTMH and last but not least clinically most useful OCT. (19) (35)

Besides observation and pharmacologic vitreolysis, the management of macular holes is a pars plana vitrectomy. The procedure comprises a complete posterior vitreous separation, peeling of ILM, gas tamponade and as a consequence strict face-down posturing for at least three days postoperatively. (4)(16)(31)(33)

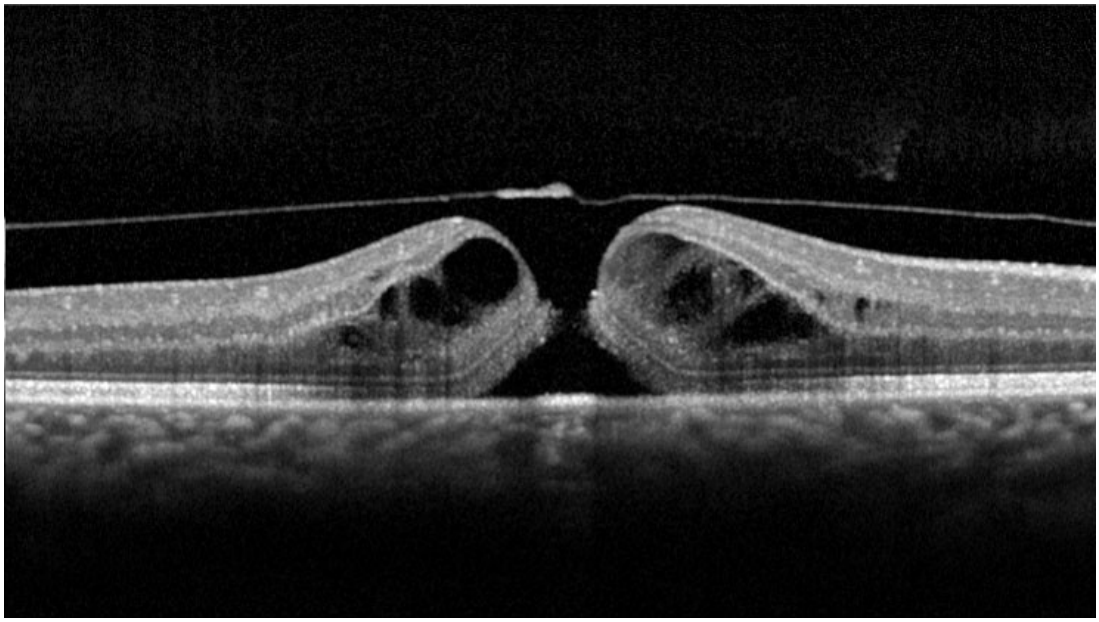

Figure 9 shows a full-thickness macular hole with a detached vitreous and an operculum and with intraretinal cysts

Even though only one OCT B-scan is required for definition, it is recommended to analyze a series of closely spaced scans, especially when in doubt. Tractional foveal cystoid space, breakdown and elevation of central photoreceptors as well as traction on the inner retina can all be causative for the actual opening of the foveal center and may appear with a retinal tissue floating anterior to the retinal break, known as an operculum. (37)

The widely used and quoted classification scheme for idiopathic macular holes by Gass, dividing macular holes into four stages (Stage 0 to Stage 4), has long been standard for classifying macular holes. This still widely used and quoted classification can be set in contrast with the newer and more up to date classification proposed by the IVTS Group, which should nowadays be used and is confronted on table 2.

The OCT-based criteria for FTMHs are classified by size, by status of the vitreous and by cause. Aperture size is measured across the hole at the narrowest point in the mid-retina, using the caliper function on spectral-domain OCT. MHs showing less than 250µm aperture size are determined to be small, holes between 250-400µm are classified as medium and holes bigger than 400µm are defined as being large. Distinguishing between these sizes is

important, because it correlates with the anatomic closure rate and recommends treatment with both medication and surgery. While small FTMH rarely close spontaneously, have a nearly 100% closure rate performing vitrectomy, and respond best to pharmacologic vitreolysis, large FTMH have a 90-95% closure rate accomplishing vitrectromy with ILM peel and no anatomic success with pharmacologic vitreolysis.

Whether VMT is present or absent has also been included in the classification system for macular holes. The etiology of FTMH is the third component of the IVTS classification, dividing them in primary, when being idiopathic, and secondary, if caused by other ocular pathologies not related to previous VMT. (8)

Table 1 Classification of the International Vitreomacular Traction Study Group

VMA	VMT	Full-thickness macular hole
Size		
Focal (≤1,500μm) or broad (>1,500μm)	Focal (≤1,500μm) or broad (>1,500μm)	Small (≤250μm) Medium (>250-≤400μm) Large (>400μm)
Characteristic		
Isolated or concurrent	Isolated or concurrent	Status of vitreous: with or without VMT Cause: primary or secondary

VMA = Vitreomacular Adhesion; VMT = Vitreomacular Traction

Table 2 Correlation between the Macular Hole Stages in Common Use and the International Vitreomacular Traction Study Classification System for Vitreomacular Adhesion, Traction, and Macular Hole

Full-thickness Macular Hole Stages in Common Use	International Vitreomacular Traction Study Classification System
Stage 0	VMA
Stage 1: impending macular hole	VMT
Stage 2: small hole	Small or medium FTMH with VMT
Stage 3: large hole	Medium or large FTMH with VMT
Stage 4: FTMH with PVD	Small, medium, or large FTMH without VMT

VMA = Vitreomacular Adhesion; VMT = Vitreomacular Traction; MH = Macular Hole; FTMH = Full-Thickness Macular Hole; PVD = Posterior Vitreous Detachment

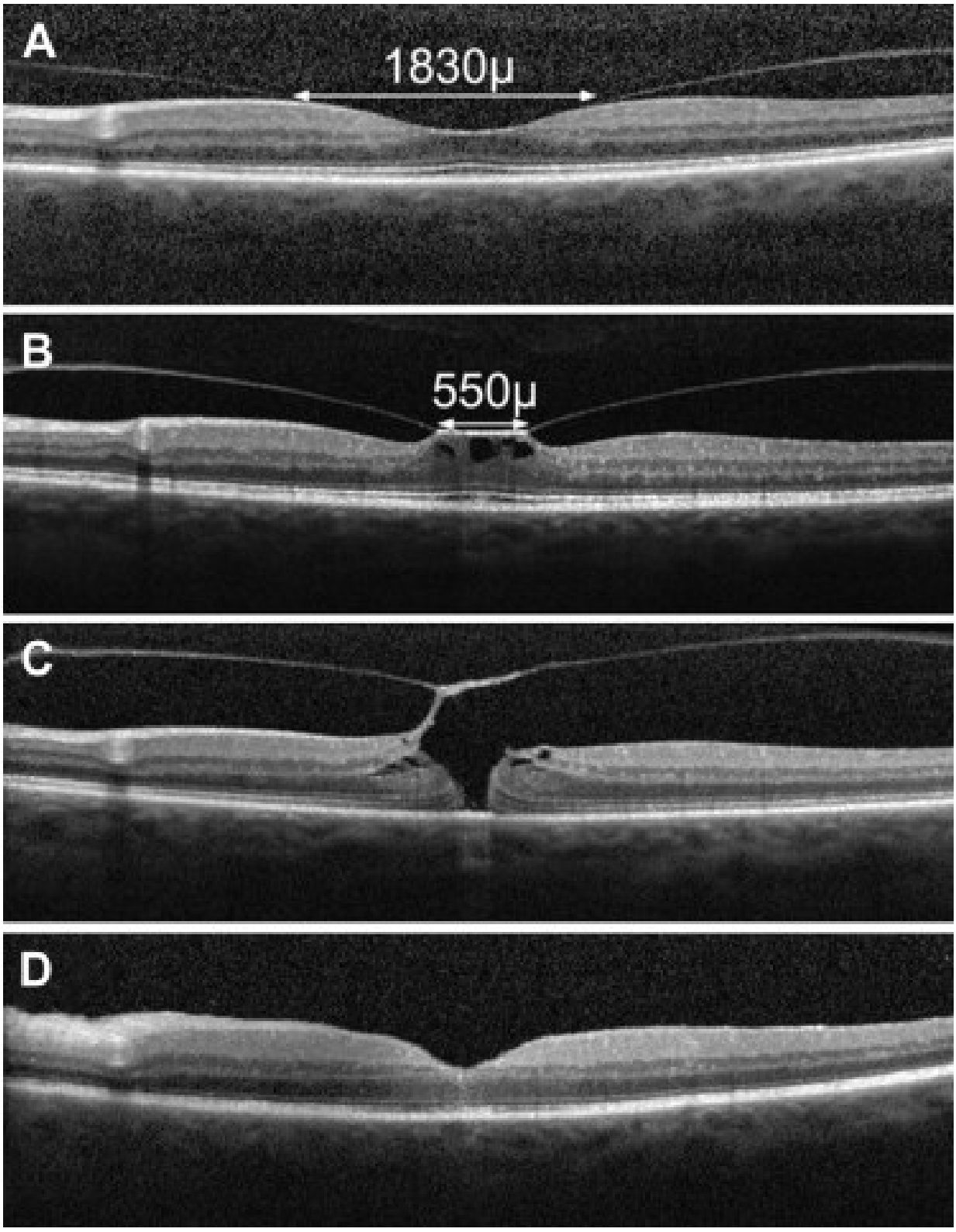

Figure 10 The progression of a vitreomacular traction (B) to a macular hole (C). Following vitrectomy, macular hole closure was achieved (D)

2.6 Lamellar Holes

Lamellar macular holes are characterized by a partial loss of neurosensory retina and separation of the outer and inner foveal retinal layers. It typically appears on biomicroscopy as a well circumscribed, round or petal-shaped reddish lesion in the inner retinal surface. (4)(8) (38)

The introduction of OCT, being the gold standard for diagnosis, has further described the morphology of LMH including (1) the presence of irregular foveal contour; (2) a defect in the inner fovea; (3) schisis (typically being between the outer plexiform and outer nuclear layers); and (4) maintenance of an intact photoreceptor layer. The latter is also the best way for differentiation from FTMH. (8)(38)

There are various theories on the pathogenesis of lamellar macular hole formation, comprising being secondary to a chronic cystoid macular edema, an abortive process of FTMH formation and centrifugal traction of epiretinal membranes, leaving the issue unresolved up to now. (38)(39)(40)

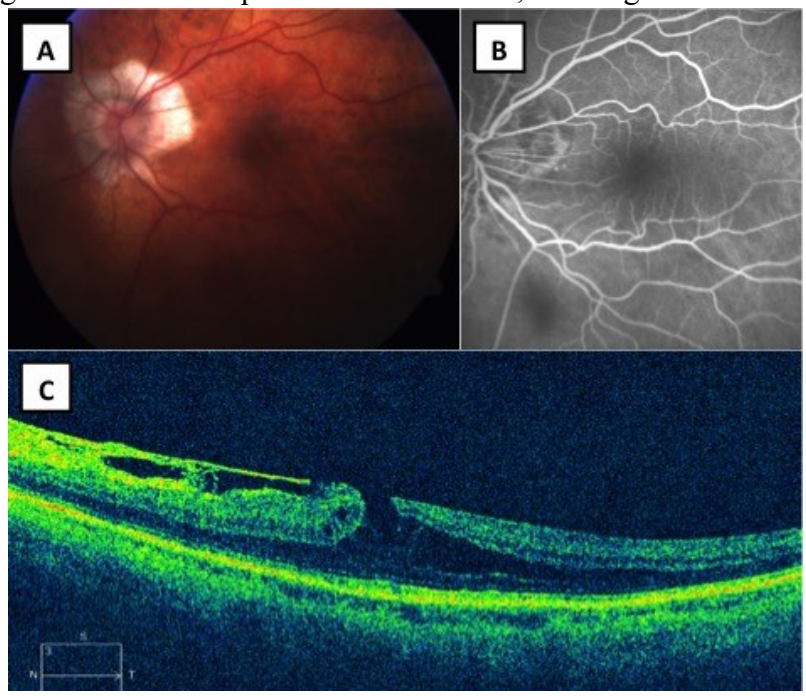

Figure 11 On the colour fundus photograph a slight distortion of the retinal vessels in the macula is seen (A), but more precisely on fluorescence angiography (B). The OCT reveals an ERM with formation of a lamellar hole and a schisis-like elevation of the retina

Govetto et al. recently demanded to redefine the current concept of lamellar macular hole and suggested to introduce two distinct subtypes: tractional and degenerative. The former is characterized on OCT by a "moustache" like appearance with a sharp-edged schisis-like intraretinal split, an intact ellipsoid layer and an inner/outer diameter ratio being less than 1:2. Tractional epiretinal membranes and/or vitreomacular traction are assumed to be causal of tractional lamellar holes.

The latter looks like a "top hat" with a disrupted ellipsoid zone, round-edged cavitation, a foveal bump, the presence of epiretinal proliferation and an inner/outer diameter ratio being more than 1:2. The degenerative pathophysiological pathway remains incompletely understood. (38)

Patients complain about mild metamorphopsia, stable visual acuity and no significant decrease in visual loss. The Beaver Dam Eye Study has found the prevalence of LMH being 3.6% and equally present in male and female. (41) Even though lamellar holes seem to be stable over time it has been reported that 5.8% develop to FTMH. Whether vitrectomy is beneficial in patients diagnosed with LMH remains controversial. While some believe surgical treatment to be beneficial, others remain sceptical. (42) (43)

2.7 Macular Pseudohole

Macular pseudohole is a clinical diagnosis, appearing as a discrete, reddish, round or oval lesion in the fovea. To distinguish a macular pseudohole from a FTMH and LMH, it is of most importance to know, that there is no loss of foveal tissue. With OCT four characteristics have been added: (1) invaginated or heaped foveal edges, (2) concomitant ERM with central opening, (3) steep macular contour to the central fovea with near-normal central foveal thickness, and (4) no loss of retinal tissue. (8)

The pathogenesis of macular pseudohole is due to centripetal contraction of an ERM, as proposed by Allen and Gass. Its contraction moves the underlying retinal tissue toward the center of the fovea, creating a steep foveal pit and increased parafoveal retinal thickness, that mimics a hole. Hence the term pseudohole. If traction is persistent, retinal tissue progressively gets thinner, with the possibility of worsening and developing a FTMH. (44) (45)

Macular pseudoholes are typically observed, except when showing significant deterioration in vision. Hence pars plana vitrectomy with membrane peeling is a possible surgical treatment. (16)

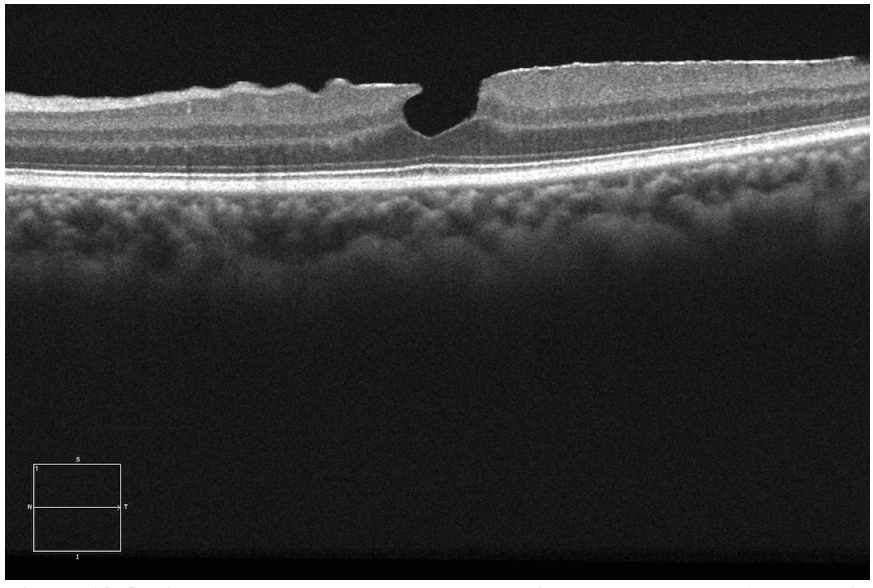

Figure 12 Optical coherence tomography showing a pseudohole. An ERM is present with a central opening over the fovea. The fovea contour is slightly raised and the retina is broken, but with intact photoreceptor inner segment–outer segment boundary

3 Epidemiology

Only little information about the epidemiology of idiopathic VMT exists, probably due to its overlap with many other ophthalmologic diseases. (46) (47)

The Beijing Eye Study reported the prevalence to be 2.4%, while Liu and colleagues describe it with 4.11% among the Urban Community Population in China. In the latter, VMT was found in males and females in 4.41% and 3.87%, respectively. (47)(48)

The Beaver Dam Eye Study found VMT to be present in 1.6% with 16.7% occurring bilaterally, using SD-OCT. (41) In all three studies the prevalence for VMT increased with age, with the mean age being around 65-75 years. In the Beaver Dam Eye Study and Beijing Eye Study postmenopausal women were affected more often than men, prompting speculations that a decreased estrogen level has an impact on the connective tissue in the vitreous gel. (41) (47) (48)

Data on the prevalence of FTMH are available from the Blue Mountains Eye Study, the Beijing Eye Study, a Study in Southern India, and a Study in China reporting it to be 0.02%, 0.09%, 0.17% and 0.38% respectively. (36) (49) (50) (48) With SD-OCT technology the Beaver Dam Eye Study reported a prevalence of FTMHs of 0.4%. (41)

4 Diagnosis

It is very difficult to diagnose VMT syndrome and MH by thorough ophthalmological history and clinical examination with slit lamp biomicroscopy alone. (20) (31) The use of dynamic B-scan ultrasound, auxiliary especially for visualizing partial PVD, and fundus fluorescein angiography, providing important information about potential retinal capillary leakage, are useful complement investigations in the assessment of VMT. (51) (52) However, OCT has become the principal ancillary test in the diagnosis of VMT and MH with great importance on clinical practice.

4.1 Optical Coherence Tomography

OCT is a noninvasive, non-contact, highly sensitive imaging system that permits to diagnose various abnormalities of the vitreoretinal interface. Since its introduction in 1991 it has become widely available for clinicians and has set new standards for diagnosis and management. This is mainly due to the fact that it is easy to handle and that it provides high-

resolution cross-sectional images of biological tissues, giving valuable information of the retina and its surrounding structures. Another principal advantage is the noninvasive nature of the test, signifying minimal to no discomfort for the patient.

OCT works similar to B-scan ultrasonography but uses near-infrared light instead of sound to generate images. For posterior segment imaging, light with a wavelength of 800-820nm generated from a superluminescent-diode based light source, is used. A partially reflective mirror is used to split the light source into two beams, namely a reference beam and a measurement beam. The latter is directed into the patient's retina and is backscattered from its different layers. Depending on the optical features, the light can either be absorbed, reflected or refracted. The reference beam, on the other hand, is directly reflected back towards the beam splitter from a mirror being at a known distance. The two light waves combine and interfere at the beam splitter, causing an interaction, laying the basis on which OCT produces images. When the path traversed by the reference beam and the measurement beam is equal it results in a constructive interference. On the contrary, a destructive interference occurs with the measurement beam traversing a larger distance than the reference beam. Hence, the light waves either intensify or diminish each other, depending on the tissue they interact with. The interference patterns of the two beams are processed into a single depth profile, a so-called A-scan (axial-scan). Multiple A-scan signals of the structure are aligned to produce a two-dimensional in vivo cross-sectional image of the retina. This is referred to as B-scan (brightness-scan). In order to distinguish between the different layers of the retina, a false colour coding system can be used, depending on the intensity of the reflected light. Structures with high, medium and low reflectivity correspond to red, yellow/green and blue, respectively. A non-reflective area, like the vitreous, is represented by black. (53) (19) (29) (13) In clinical practice, the introduction of Spectral or Fourier Domain OCT has largely eclipsed the use of conventional OCT, because of the significantly improved scanning speed, detection sensitivity and axial resolution of the former. Another great advantage of SD-OCT is that it allows high-resolution three-dimensional images. (54)

Vitreomacular Traction

OCT has led to a higher recognition of the VMT syndrome. Typically, one sees hyperreflective bands, representing the posterior hyaloid inserting onto the inner retinal surface attended by hyporeflective retinal cysts, diffuse retinal thickening, and/or subretinal fluid. Even though OCT cannot measure the tractional force exerted from the vitreous on the fovea, the concept of Spaide et al., postulating that the diameter of VMA is inversely related

to foveal deformation is widely shared. (20) (55) (13)

Macular Holes

OCT is also very helpful to identify macular holes. When on OCT an interruption of all neural retinal layers in the fovea is seen in several scans, it is an unequivocal sign. Often retinal thickening in the hole margins with hyporeflective cystic spaces is seen as well. OCT can further detect FTMH at their earliest stage and help the examiner with distinction of FTMH, pseudohole and lamellar hole. (56) (55)

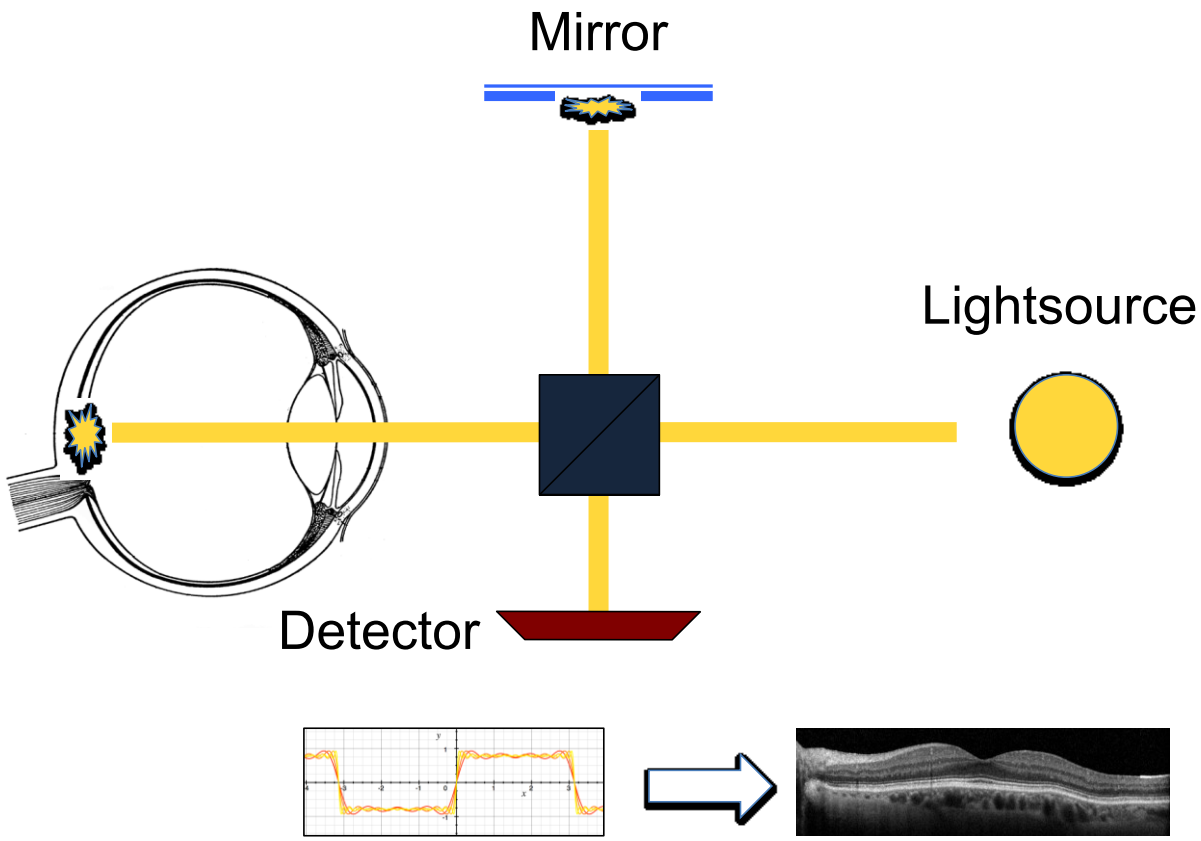

Figure 13 Working principle of an OCT

OCT has proven to be more sensitive than clinical examination for the detection of pathologies of the VMI, including VMT and MH. With ophthalmoscopy alone, VMT was diagnosed in only 8% of patients, as opposed to 30% of the same patients performed with OCT. (11)

Furthermore, OCT is an excellent tool for the management and documentation of the clinical course of the pathologies of the VMI. Last but not least, it is a great benefit in patient education, in order that they better understand their disorder and management. (13)

5 Treatment

There are different options for the treatment of VMT and MH, including watchful waiting, medical therapy and vitrectomy.

5.1 Observation

Some patients with VMT maintain good VA and mild metamorphopsia and hence require no treatment, because the adhesion resolves spontaneously. Investigations of spontaneous clinical courses differ greatly with Weinand et al, John et al. Dimopoulos et al. and Charalampidou et al. observing a spontaneous release of traction in 10-11%, 32%, 43%, and 53% respectively with a mean follow-up of 1 to 2 years. (20) (47) (57) (46) (10)

Theodissiadis et al., Almeida et al. and Condenotti et al. tried to find factors, which help to predict the spontaneous VMT release. The following 5 factors were noted:

(1) Adhesion diameter less than 400µm
(2) Wide angle between the vitreous surface and nasal and temporal macula
(3) Isolated inner retinal layer distortion
(4) Treatment of concurrent retinal diseases with intravitreal injections
(5) 'Vitreomacular interface area' value less than 101 002µm^2 as calculated by OCT

The amount of patients in these retrospective studies was humble and there is a given possibility of selection bias. Therefore it is advisable to do further, larger and prospective investigations for confirmation of these reported predictive factors. (46)

Since resolution is hard to predict, observation is a feasible option for those patients with mild symptoms. After 3 months a reexamination of these patients with OCT is advisable, in order to decide whether medical therapy or vitrectomy is indicated. (47)

While VMT with mild symptoms can release spontaneously in some cases, the incidence of spontaneously closing MH is reported to be as low as 2.7% to 8.6%. Furthermore MH usually progress to larger holes, with studies showing an increase in hole size of 21.7%-77% over a 6 years follow-up. As a result, a generous indication for surgery should be given. (58)

5.2 Vitrectomy

At the moment, PPV is seen as the standard intervention for the treatment of VMT when observation and/or medical therapy are either ineffective or not indicated. When patients with persistent VMT continue to complain about symptoms, such as metamorphopsia, blurred vision and reduced visual acuity, a generous indication for a PPV should be made. (46) (59)
The main purpose of this surgery is the separation of the posterior hyaloid from the retinal surface, in order to restore normal central retinal anatomy and close a MH if present. Surgical removal of anteroposterior and tangential traction are usually carried out with 23-, 25-, or 27-gauge systems in local, monitored anesthesia. The use of vital dyes is an effective and helpful tool to highlight the ILM, ERM and vitreous remnants, thereby guaranteeing the complete removal of this very thin and transparent membrane. Various vital dyes are in use, such as triamcinolone acetonide, indocyanine green, brilliant blue and trypan blue with brilliant blue.
The vitreous is separated from the retina and then completely removed.

In order to release all tractional forces in cases with MH presence, a broad ILM peeling reaching the vascular arcades is carried out, leading to an approximation of the hole edges and in this way facilitating closure. If large MH (>400μm) are present, also an alternative technique is described, called the inverted ILM flap technique. (59) (10) (60) After having examined the retina for peripheral breaks a retinal tamponade is performed with either air, SF_6, C_3F_8 or silicon oil to conclude MH surgery. (61) (31)

Even though vitrectomy is a very well tolerated and safe surgery, a remaining risk for complications is left. The most common postoperative complication of PPV is the formation or progression of cataract, developing in more than 80% of phakic eyes within the first few years. Other less frequent reported adverse effects are retinal tears, retinal detachment, visual field loss and endopthalmitis. (46) (60) (61) (31)

Clinical outcomes after vitrectomy for VMT are very variable. Performing a systematic review, Jackson et al. reported, that 32.9% of eyes gained ≥2 Snellen lines. Some patients have unchanged or worse vision after surgery. Although visual gain is not achieved in all patients, some of them appreciate the relief or reduction from metamorphopsia and distortion. (60) (62)

Regarding the efficacy of vitrectomy for MH, success rates are in general high. In the last years, studies reported closure rates of 91 to 98% with improvement also in visual acuity. (61)

5.3 Intravitreal medical therapy

5.3.1 Ocriplasmin

Until recently, observation and pars plana vitrectomy were the only treatment options for VMT and MH. Since the approval of Ocriplasmin in 2012 by the US Food and Drug Administration and in 2013 for the use in the European Union, the first nonsurgical treatment option for VMT, including when associated with MH, is available. (47) (63) It has to be said, that the use of Ocriplasmin in patients showing MH without VMT would be deemed off-label. (61)

Ocriplasmin is a recombinant 27 kilodalton human serine protease with proteolytic activity targeting collagen, fibronectin and laminin, main components of the vitreomacular interphase. Consequently, it can induce vitreous liquefaction and separation of the vitreous cortex from the retinal surface. (64)

The efficacy and safety of a single intravitreal injection of 125μg ocriplasmin in patients showing VMT with or without MH was evaluated in two multicentered, randomized, double-masked, placebo-controlled, phase 3 clinical trials, referred to as the MIVI-TRUST studies. The combined results of the two studies showed that in the ocriplasmin group 26.5% of the patients had total resolution of VMA after 28 days compared to 10.1% in the placebo group. Additionally, secondary endpoints such as total PVD, closure of MH and visual gain ≥ 3 lines, were achieved in 13.4%, 40.6% and 12.3% of patients receiving ocriplasmin and 3.7%, 10.6% and 6.4% of eyes receiving placebo, respectively. These results were all statistically significant. (9)

Further data was provided by the OASIS study, with a longer follow-up of 24 months. This study had similar results as the MIVI-TRUST trials, with statistically significant nonsurgical release of VMT at day 28 in 41.7% of patients treated with a 125μg ocriplasmin injection compared to 6.2% receiving a vehicle injection. The ocriplasmin group did show a high closing rate of FTMH too, however did not reach statistical significance (30% versus 15.4%, p=0.163). (65)

Various clinical trials have been realised since the commercialisation of ocriplasmin, in order to further maximize VMT release rates, improve patient selection and, last but not least, assess its safety and efficacy in 'real-world' clinical practice. (66) (46)

Haller et al. tried to identify positive predictive factors, which can be associated with successful pharmacologic VMT resolution in a post hoc subgroup analysis of the MIVI-TRUST data. They ascertained, that age <65 years, a small adhesion diameter (≤1500μm),

presence of FTMH and absence of epiretinal membrane have a positive effect on resolution of VMT. Additionally they reported MH closing more likely when its size amounted to smaller than 250µm. (67) Warrow et al. added three predictive factors: transient outer layer abnormalities on OCT, shorter adhesion duration and absence of retinal layer comorbidities. (68) For now, regarding MH closure, Steel et al. completed these factors saying, that MH 'width factor' of less than 60µm was heavily associated with hole closure. (69) (65) All reported predictive factors are summarized in the table 3. (65)

Also the incidence and type of ocular adverse events was targeted of various authors. In the MIVI-TRUST study the most frequent one was vitreous floaters with 16.8% in the ocriplasmin group compared to 7.5% in the placebo group. Other adverse events in this study, such as photopsia, conjunctival haemorrhage, injection-related eye pain, blurred vision and visual impairment, were also reported. Most of these events were temporary, minor and improving with time. (9) Furthermore the American Society of Retinal Specialists identified categories of related adverse events after an ocriplasmin injection: acute reduction in visual acuity, electroretinogram changes, dyschromatopsia, retinal tear or detachment, lens subluxation or phacodonesis, abnormal pupillary reflex, retinal vascular changes, and OCT ellipsoid zone alterations.

Table 3 Reported positive predictive factors for successful vitreomacular traction release with 0.125mg injection of ocriplasmin

Phakic status
Age < 65 years
Small adhesion diameter (≤ 1500 µm)
Presence of full thickness macular hole
Absence of epiretinal membrane
Absence of concurrent retinal disease
Shorter duration of VMT
Transient outer retinal layer abnormalities on OCT
Macular hole size <250µm
Macular hole 'width factor' (basal diameter-minimum linear diameter) <60µm

5.3.2 Perfluorpropane Gas

In 2013 Rodrigues et al. published the results of a retrospective conducted study investigating the efficacy of a single intravitreal injection of 0.3ml of 100% perfluoropropane (C_3F_8) gas as

an alternative treatment option for patients with symptomatic and persistent VMT (> 3 months' duration). Fifteen eyes of fourteen patients were included in this study. The primary outcome, complete VMT release on OCT at 1 month after gas injection, was accomplished in 40% (6 of 15 eyes). Within six months, three more eyes had resolution of VMT, which raised the success rate to 60% (9 of 15 eyes). Additionally the authors identified factors such as maximal pretreatment foveal thickness less than 500μm, extension of VMA less than 750μm and low vitreous face reflectivity as being predictive for pneumatic release of VMT. Mean VA, being a secondary outcome measure, did not improve but on the contrary decreased by 0.03 logMAR units from baseline even though foveal contour restored in 77% of eyes with successful VMT resolution. Very relevant is the fact that they didn't find any serious adverse events, associated with the intravitreal gas injection, in particular retinal tears, detachments or IOP increase. (70)

Recently, Steinle et al. assessed the efficacy of pneumatic vitreolysis to achieve VMT resolution following an intravitreal 100% perfluoropropane injection of up to 0.3ml as well. Up to now, this trial represents the largest series using C_3F_8 gas, including 30 eyes of 29 patients, among whom some had previous unsuccessful ocriplasmin treatment, concurrent DM, or coexisting ERM. The primary measurement of interest, being the same as in the study mentioned above, was achieved in 73% (22 of 30 eyes) after one month and increased to 83% (25 of 30 eyes) by final follow-up. In detail, VMT released in 90% (9 of 10 eyes), 83% (5 of 6 eyes) and 83% (5 of 6 eyes) of eyes diagnosed with DM, concurrent ERM and unsuccessful previous ocriplasmin treatment, respectively. On average release of VMT was seen on SD-OCT 13 days past the gas injection. There was no significant difference between release rates of phakic versus pseudophakic eyes. This clinical trial showed an improvement of mean Snellen VA from 20/50 before to 20/40+ after gas injection. No side effects, such as formation of cataract, retinal tears, detachment, endophthalmitis or hemorrhages of the vitreous body, were noted, except for the considerable increase of IOP in one patient. (71)

In 1995 Chan et al. were the first to investigate whether an intravitreal gas bubble can treat MH. In this trial, ten of the 11 stage 1, three of the six stage 2 and none of the stage 3 MH closed. (72) Rodrigues and associates reported the successful resolution of VMT in one patient showing an impending MH, however progressing to a FTMH and therefore requiring a PPV with ILM peeling and nonexpansile perfluoropropane tamponade. (70) Steinle and colleagues also demonstrated successful VMT release in all three patients with FTMH being smaller than 200μm in width. However, only two FTMH closed with the third undergoing a vitrectomy for closure. (71)

5.3.3 Sulfur Hexafluoride Gas

Day et al. recently published the results of a 0.3ml intravitreal expansile 100% sulfur hexafluoride (SF_6) injection for the treatment of patients with symptomatic VMT syndrome. This small retrospective clinical trial including nine eyes of nine patients showed a release of VMT of 55.6% (five of nine eyes) on SD-OCT at one month, with significant reduction in mean central subfield thickness but absent statistical significance in mean VA. One patient developed a peripheral retinal hole, requiring laser retinopexy. Otherwise no side effects were observed. Two patients in this trial showed an impending MH with VMT, whereas the traction could be released and the holes could be closed following the SF_6 injection. (73)

PART II- Study Part

6 Introduction

Posterior vitreous detachment, typically occurring between the ages 45 and 65, is defined as the separation of the vitreous body from the internal limiting membrane of the retina and is a physiological age-related process. (74) When the vitreous fails to detach completely, vitreomacular adhesion, showing no retinal abnormalities, or vitreomacular traction, with detectable retinal changes on optical coherence tomography, are the consequences. Typical symptoms of vitreomacular tractions are decreased vision and metamorphopsia. (21)

Current treatment options include observation, when patients are either asymptomatic or when symptoms do not aggrevate, medical therapy with ocriplasmin and pars plana vitrectomy, remaining the mainstay when the former have no indication or failed to succeed. Data from the microplasmin for intravitreal injection – traction release without surgical treatment, short MIVI-TRUST, showed nonsurgical success of vitreomacular traction release within 28 days in 41.7%, which was statistically significant, and closure of macular hole in 30%.(46)

Two studies, conducted by Rodrigues et al. and Steinle et al., investigating the release rate of vitreomacular traction and the closure of macular hole using intravitreal perfluoropropane gas, showed very promising results as well. (70) (71) The purpose of this case series, was to further examine the effect of a single intravitreal perfluoropropane gas injection with patients showing a symptomatic vitreomacular traction with or without macular hole.

7 Materials and Methods

A retroprospective case series of patients who elected to undergo an intravitreal C3F8 injection for the treatment of symptomatic VMT syndrome, including when associated with MH, between March 2013 and September 2015 was performed at the Department of Ophthalmology at the Medical University of Graz. In total seven eyes of six patients, with a mean age of 60,4 years (range, 43-75 years) were treated with a perfluoropropane gas injection. All patients underwent baseline testing of Snellen visual acuity**,** biomicroscopy of the anterior and posterior segment and SD-OCT. This case series is in accordance with the declaration of Helsinki and the approval of the ethics committee of the Medical University of Graz was obtained.

All intravitreal injections of expansile gas were accomplished in an operating room and were in all cases performed by the same surgeon. Following the use of topical 1% Tetracaine anesthetic, an eyelid speculum, drape and the lavage of the conjunctival sac with povidone-iod, up to 0.3ml of 100% perfluoropropane gas was injected. Three eyes received 0.2ml and 4 eyes 0.3ml of 100% C_3F_8 gas. Using a 30-gauge needle on a 1-ml tuberculin-syringe the gas was injected through the pars plana at a 3.5mm distance of the limbus.

Regarding the positioning after surgery the patients were told to avoid supine positioning because of the risk of cataract formation. Postoperatively the patients had to use ofloxacin eye drops three times daily for four days. Follow-up appointments were variable and depended on the decision of the surgeon.

The primary outcome measure was release rate of VMT validated using SD-OCT at 1 month. Secondary measurements of interests included release of VMT within six months, change in central foveal thickness and in best-corrected VA and closure of MH. Only a change of BCVA of two or more Snellen lines was regarded as significant. For statistical analysis, snellen acuity was converted into logMAR units.

7.1 Inclusion and exclusion criteria

To be included in this case series, the patients had to show a SD-OCT confirmed vitreomacular traction with an adherence diameter of less than 1500μm.

Exclusion criteria were patients who had undergone a vitrectomy or intravitreal injection before, show an active ocular infection, an age-related macular degeneration or a glaucoma, had an operative ocular intervention less than three months ago or presented a retinal detachment in the other eye.

8 Results

Seven eyes of six patients underwent an intravitreal 100% C_3F_8 gas injection for the treatment of VMT and MH. Three of the patients were male and three female, whereas both eyes of one woman were assessed. The patient demographics, as well as the pre- and posttreatment characteristics are listed in table 3.

Three of the seven eyes (42.86%) had concurrend ERMs, among whom one (14.26%) presented with concurrent diabetic retino- and maculopathy. Mean time from diagnosis to operation were 63 days (range, 6-223 days and SD 75.86) and mean adhesion diameter was 328.57μm (range, 63-803μm and SD 235.66). The patient having an extent of adhesion of 803μm did not have release of VMT. Traction release by 1 month after injection was observed in 3 of the 7 eyes (42.86%), while further 3 eyes detached within 6 months (85.71% final release rate). Two of the three eyes with concurrent ERM released, however not within 1 month but after 5 and 10 weeks as well as 1 of 1 eye with concurrent diabetic retino- and maculopathy within 10 weeks. One of the six patients had a small MH (201μm) with VMT. Although the VMT released successfully after one week the MH did not close and hence underwent vitrectomy. Average days till VMT resolution were 54 (range, 7-173 days; median 28). Visual acuity improved by two or more Snellen lines in 42.86% and remained stable in 57.14%. But the median and range of Snellen visual acuity of 0.5 (range, 0.1-1.0) did not change after treatment. Overall, the mean central foveal thickness decreased in patients with release of VMT from 517.5μm (range, 335-780μm and SD 171,82) to 377.67μm (range, 200-816 and SD 257,93) before and after treatment, respectively.

One patient showed a macula edema with a consequent lamellar hole after the injection, whereas another patient developed a retinal tear with a retinal detachment with subsequent vitrectomy. No patient sustained complications during the intravitreal gas injection.

Table 4 Pretreatment and Posttreatment Characteristics

Case	Age	Sex	Eye	Diagnosis	ERM	DM	Before Treatment			After Treatment		PPV	Adverse Events	Outcome
							VA	CFT	EOA	VA	CFT			
1	66	M	OD	VMT	Yes	Yes	0.125	780	367	0.1	571	No	LH	QS
2	66	M	OS	VMT	Yes	No	0.25	590	803	0.4	816	Yes	Retinal Tear & Detachment	FAIL
3	43	F	OD	VMT	No	No	0.63	446	217	0.8	200	No	None	AS
4	72	M	OS	VMT with small MH	No	No	0.1	-	218	0.2	-	Yes	Non-closure of MH	AS
5	50	F	OS	VMT	No	No	1.0	335	397	1.0	205	No	None	AS
6	51	F	OD	VMT	No	No	0.5	351	229	1.0	204	No	None	QS
7	75	F	OD	VMT	Yes	No	0.5	603	69	0.5	270	No	None	QS

AS = absolute success (defined as VMT release within a month from treatment) CFT = central foveal thickness (in μm); DM = Diabetes Mellitus; EOA = extend of adhesion (in μm) ERM = epiretinal membrane; F= female; FAIL = failure (defined as no VMT release); LH = lamellar hole; M = male; MH = macular hole; OD = right eye; OS = left eye; PPV = Pars plana vitrectomy; QS = qualified success (defined as VMT release later than one month after injection) VA = visual acuity (in logMAR units); VMT= vitreomacular traction

8.1 Patient 1

Patient 1 was a male patient with an age of 66 years. He showed a SD-OCT confirmed VMT in the right eye in March 2013. Secondary ophthalmological findings were a diabetic maculopathy, a proliferative diabetic retinopathy, as well as a macula pucker. The preoperative BCVA was 0.125, the adhesion diameter 367µm and foveal thickness 780µm. The patient was observed for seven months (223 days), before he was treated with 0.3ml C_3F_8 gas. Three weeks after the intravitreal injection no release of traction was observed, but he had a decrease of vision due to a macular edema. Vitreomacular traction released ten weeks after the intervention, with the macular edema persisting. The foveal thickness was 571µm after treatment and BCVA after resolution of traction was 0.1. Gradually the macular edema decreased, but at the last check-up the patient showed a lamellar macular hole on OCT.

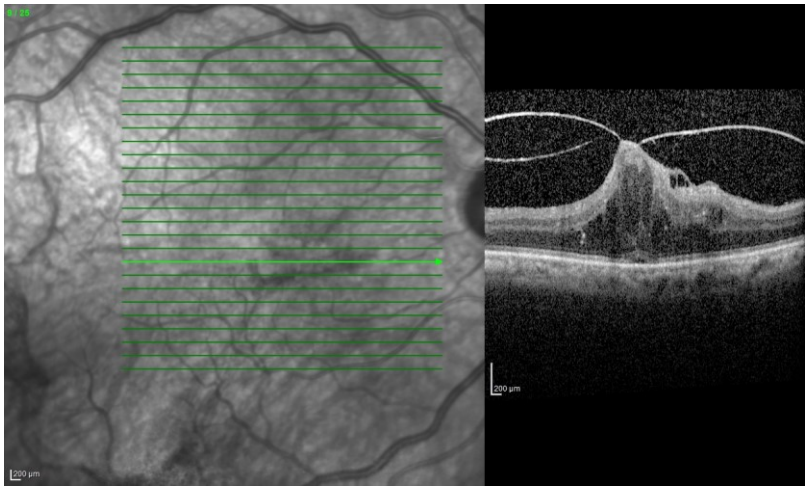

Figure 14 OCT of patient 1 obtained just before C3F8 intravitreal injection. The figure shows a vitreomacular traction with schisis-like splitting of the retina. The posterior vitreous is still attached at the optic disc

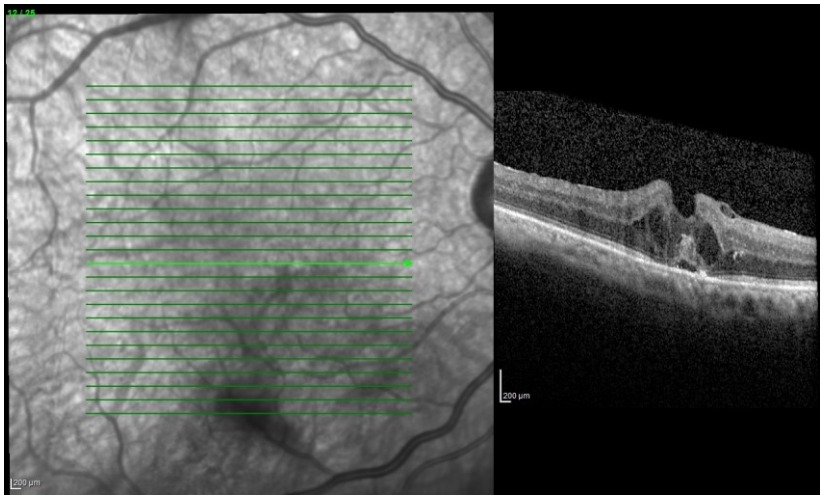

Figure 15 Ten weeks after injection the VTM was released, but a lamellar hole with intraretinal cysts has developed

8.2 Patient 2

The second patient was a 66 year old man, who presented himself in August 2013 with a VMT in the left eye diagnosed with SD-OCT. Additionally he showed an ERM on OCT. After two months (84 days) of watchful waiting the BCVA decreased to 0.25, foveal thickness was 580µm and the extent of adhesion was 803µm. The patient underwent an intravitreal injection of 0,3ml of 100% C_3F_8 gas. One week after the procedure there was no release of traction. At the follow-up three weeks after the procedure, the patient complained about a black shadow. While VA increased to 0.4 no release of traction was seen and the foveal thickness increased to 816µm. In the periphery at the 6 o'clock position he showed a retinal tear with retinal detachment, which implied a vitrectomy with gas.

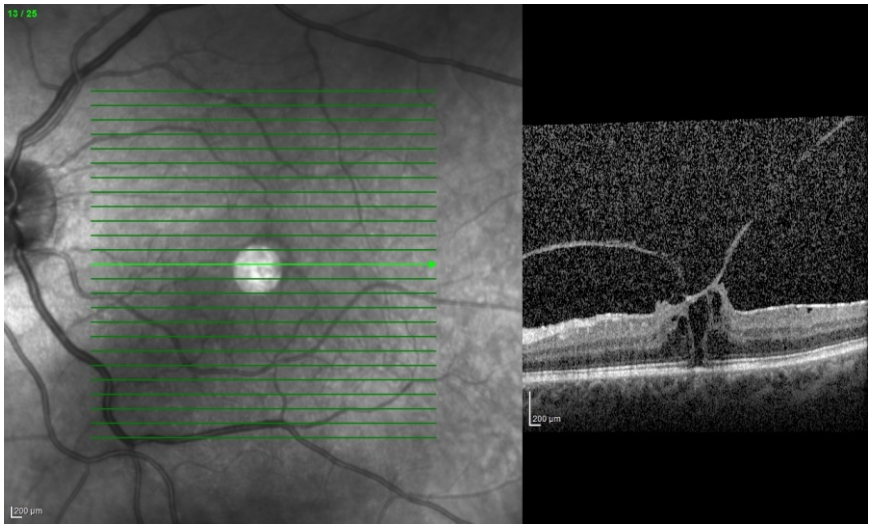

Figure 16 Baseline spectral domain optical coherence tomography of patient 2 with vitreomacular traction. OCT showed that the maximal diameter of the adhesion in horizontal scans was 803 µm. The retinal anatomy was disrupted under the adhesion zone

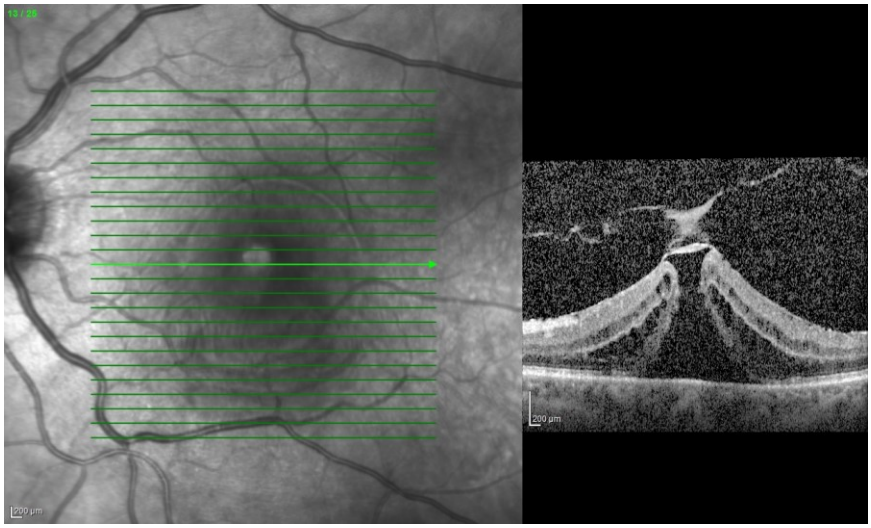

Figure 17 Three weeks after the injection no release of VMT was seen and the retinal thickness has increased by 236µm in patient 2

8.3 Patient 3

Patient 3 was a 43 year old woman, who presented herself with metamorphopsia and decrease of central vision in her right eye in October 2013. Focal VMT was diagnosed on OCT with an adhesion diameter of 217µm, a foveal thickness of 446µm and a BCVA of 0.63. Six days later she received an intravitreal injection of 0.2ml C_3F_8 gas. The vitreous released successfully 12 days after the injection with a postoperative foveal thickness of 200µm and an improvement of BCVA to 0.8.

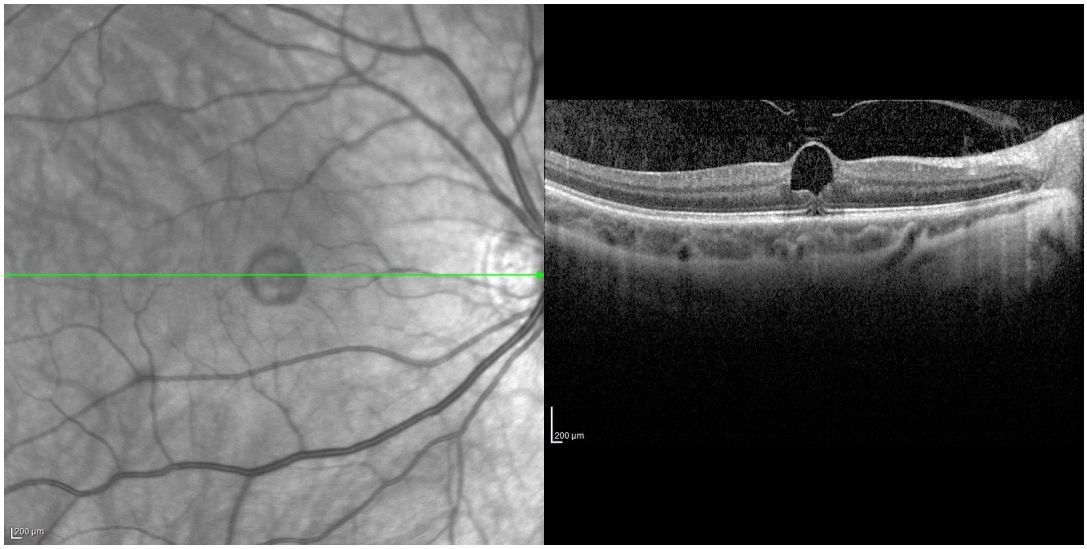

Figure 18 Preoperative OCT of Patient 3 with VMT and a huge cyst in the inner retinal layer. The ellipsoid zone underneath the VMT was disrupted

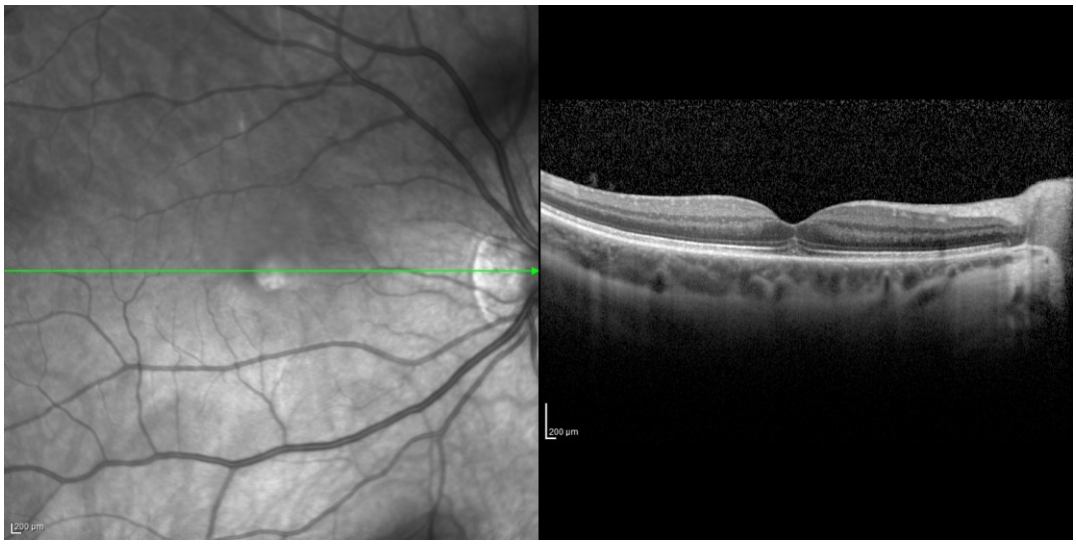

Figure 19 Figure shows vitreomacular traction release and restoration of the ellipsoid zone 12 days postoperatively in patient 3

8.4 Patient 4

The fourth patient, male and 72 years old, saw a blind spot in his central vision in his left eye in October 2013, which was diagnosed on SD-OCT as a small MH (201µm) with an adhesion expanse of 218µm. Initially he had a BCVA of 0.1. One week later 0.2ml C_3F_8 gas was injected into the vitreous. Again one week later there were no more signs of tractional forces seen on OCT however the whole remained open and increased to 475µm. Since the MH failed to close after one and a half months, a successful vitrectomy with gas was performed with an increase of BCVA to 0.2.

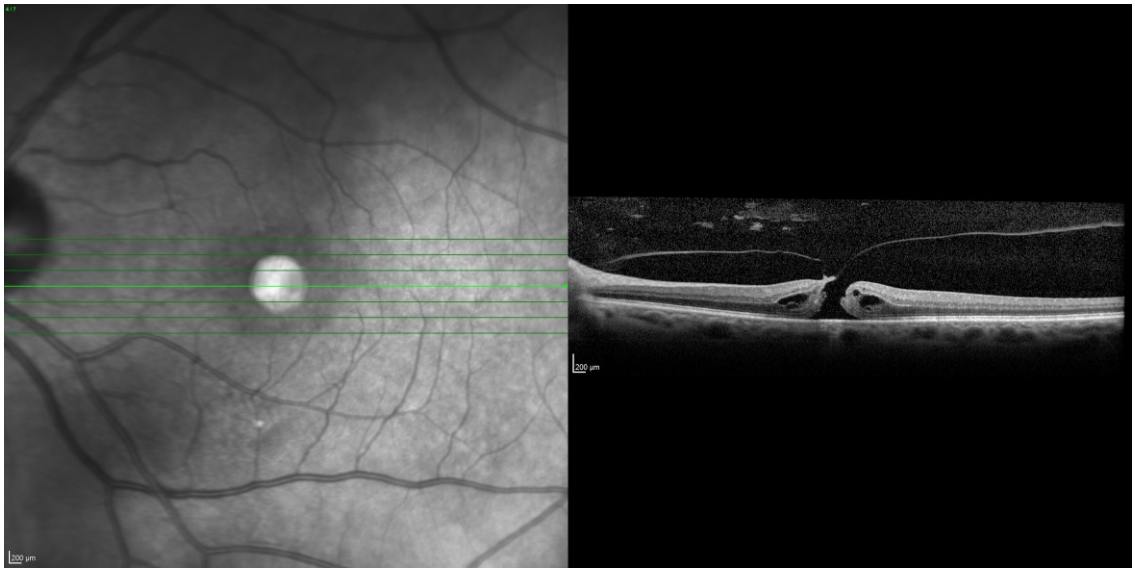

Figure 20 Baseline spectral domain optical coherence tomography of patient 4 with a macular hole with VMT

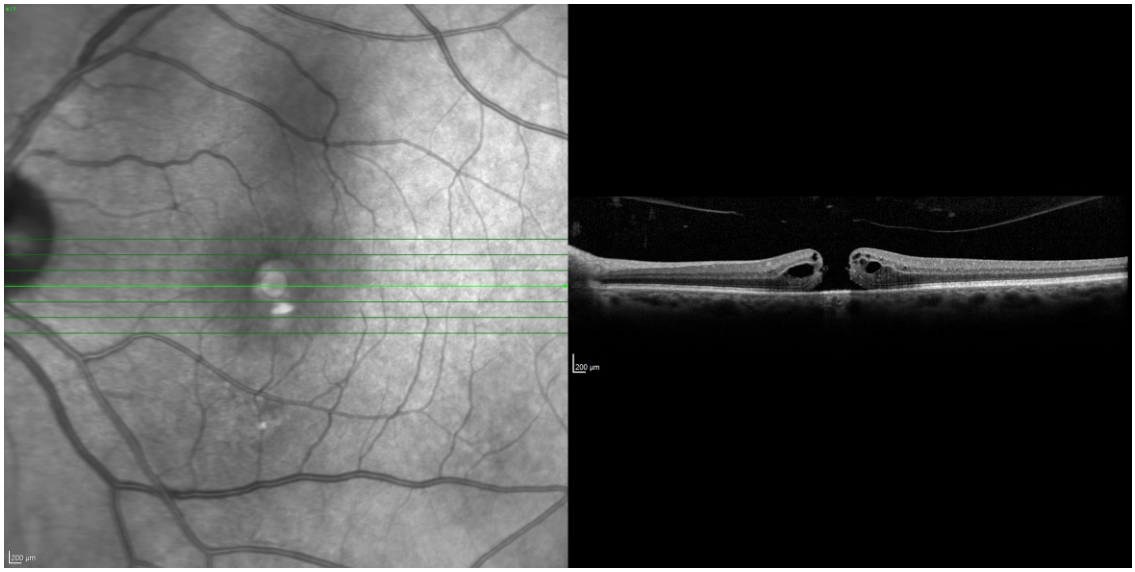

Figure 21 One week after injection of gas the vitreomacular traction has released but the macular hole did not close. So 5 weeks later while observing patient 4 underwent vitrectomy with gas

8.5 Patient 5

The fifth patient was a 50 year old woman, who presented herself with metamorphopsia in her left eye in September 2013. She was a myopic patient. On SD-OCT a VMT with an adhesion diameter of 397µm and a macula cyst were diagnosed in the left eye with the right eye not showing any pathology. She had an initial BCVA of 1.0 and the foveal thickness was 335µm. The intravitreal C_3F_8 gas injection with 0.3ml was completed three weeks after diagnosis. VMT released 173 days after injection with a foveal thickness of 205µm and a consistent BCVA. There was no macula cyst detectable on SD-OCT after resolution.

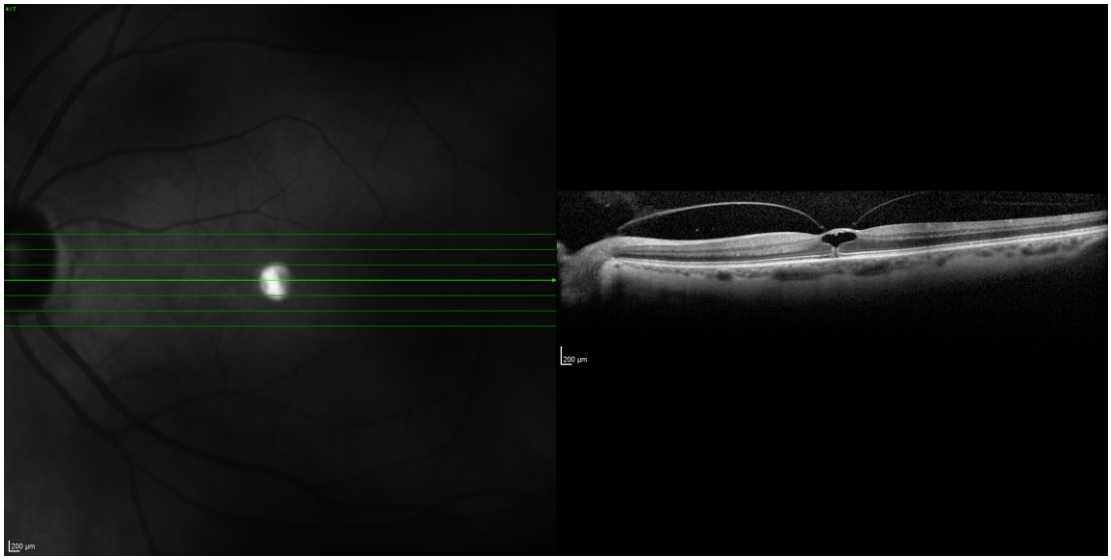

Figure 22 Baseline OCT of the left eye of patient 5 with VMT and with a huge cyst in the inner retinal layer and disruption of rhe ellipsoid zone

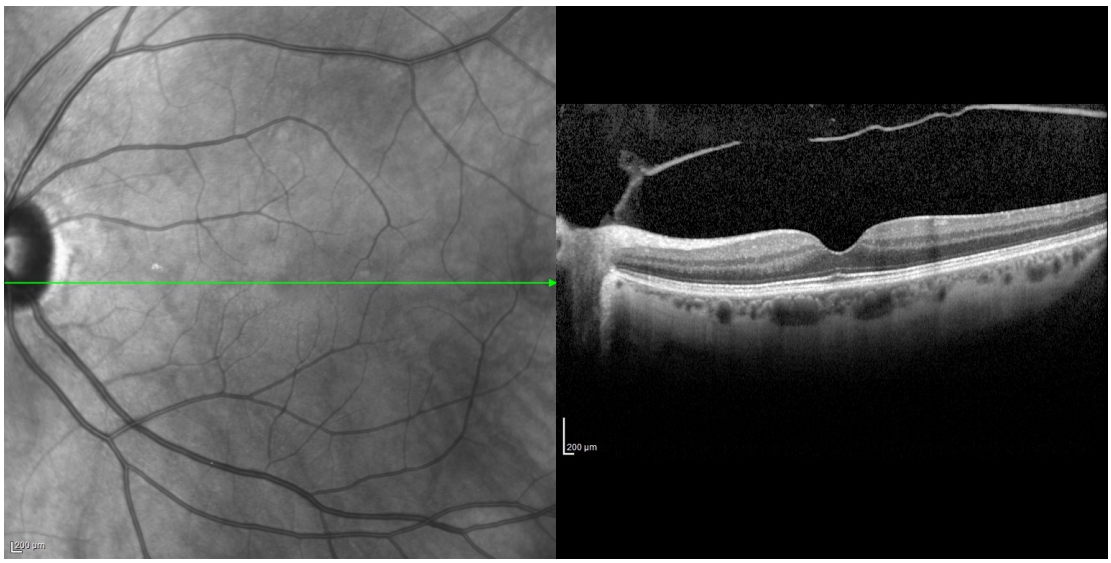

Figure 23 About five months postoperatively the OCT of the left eye of patient 5 shows vitreomacular traction release and restoration of the ellipsoid zone

In December 2014, with Patient 5 now aged 51, VMT with an adhesion diameter of 397µm was diagnosed with SD-OCT in her right eye. At presentation BCVA was 1.0 and foveal thickness was 351µm. After 54 days of observation with a VA decrease on the right eye to 0.5, the patient received a 0,3ml intravitreal C_3F_8 gas injection in her right eye. Three weeks later the vitreous body detached from the retina. After release BCVA amounted to 1.0 again and foveal thickness was 204µm.

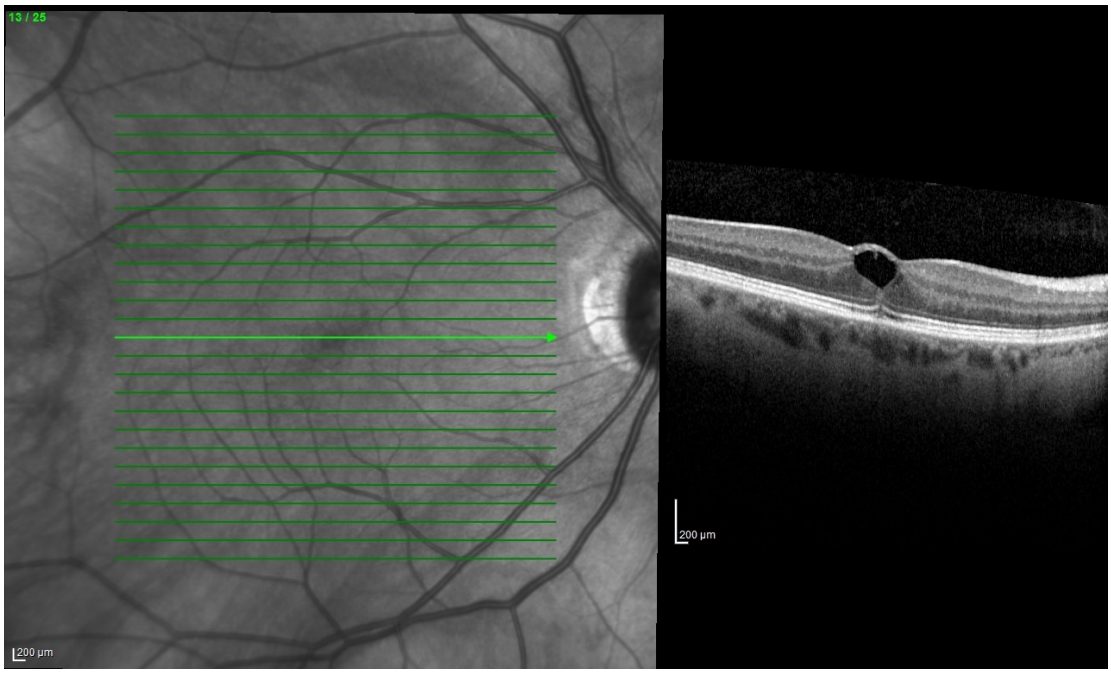

Figure 24 About one year later patient 5 presented with similar findings on OCT of the right eye

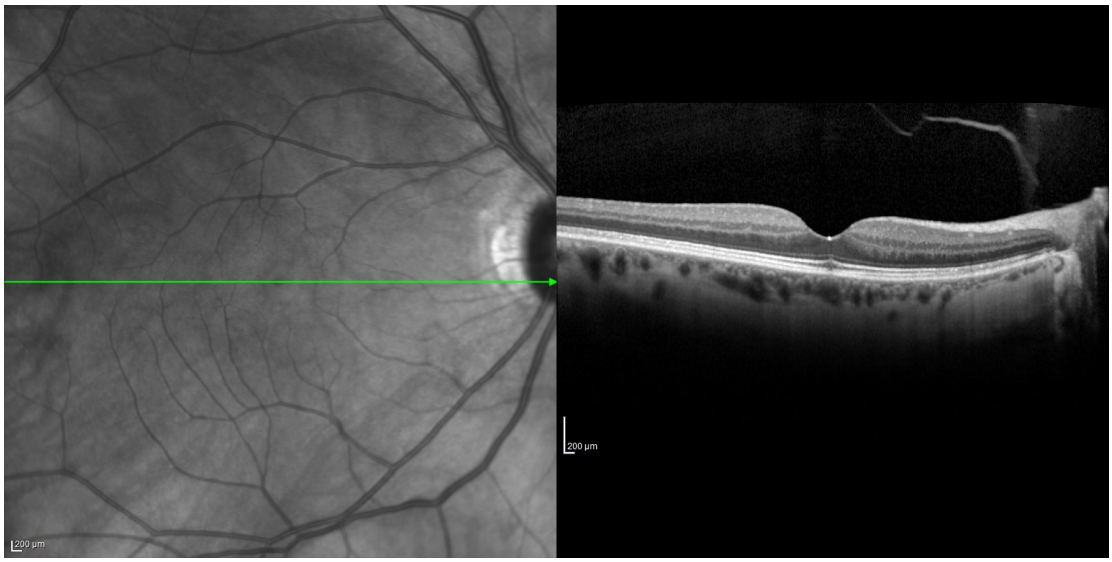

Figure 25 Three weeks after intravitreal injection OCT of patient 5's right eye shows vitreomacular traction release and restoration of the ellipsoid zone

8.6 Patient 6

Patient 6 was a 75 year old woman, who was diagnosed with VMT in her right eye with OCT in September 2015. At first presentation the BCVA was 0.5. Additionally the right eye showed a macula pucker. Foveal thickness and adhesion diameter measured 603µm and 69µm, respectively. Since after 47 days no spontaneous resolution occurred, the surgeon performed an intravitreal 0,2ml 100% C_3F_8 injection. After five weeks a separation of the vitreous from the macula could be seen on OCT. The BCVA of the patient did not change, but foveal thickness decreased to 270µm.

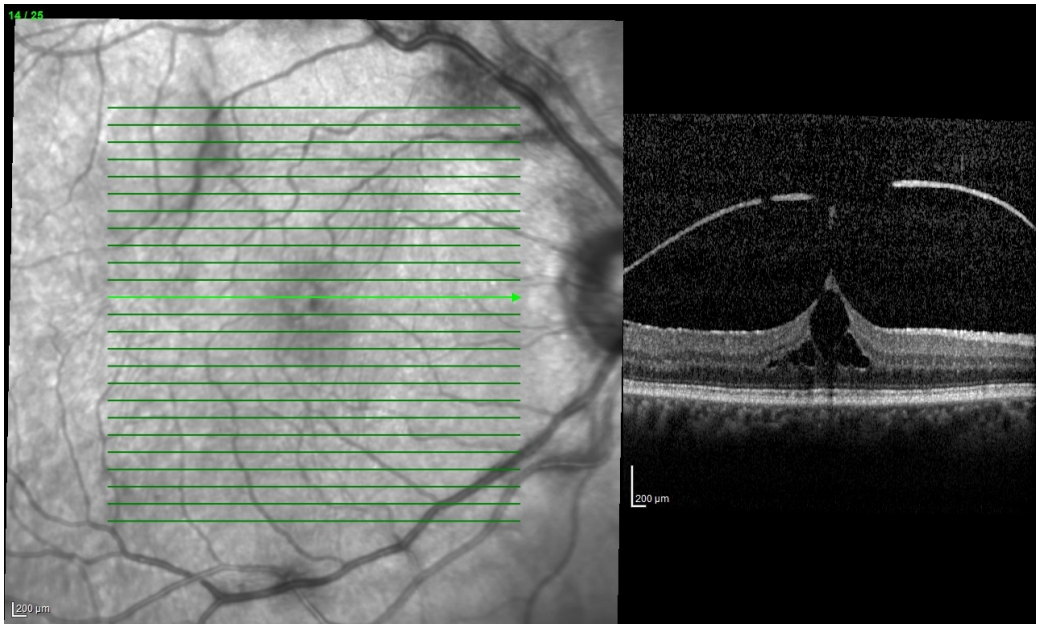

Figure 26 The OCT of patient 6 obtained just before C3F8 intravitreal injection shows a tent-like elevation of the retina with intraretinal cystoid spaces due to vitreomacular traction forces

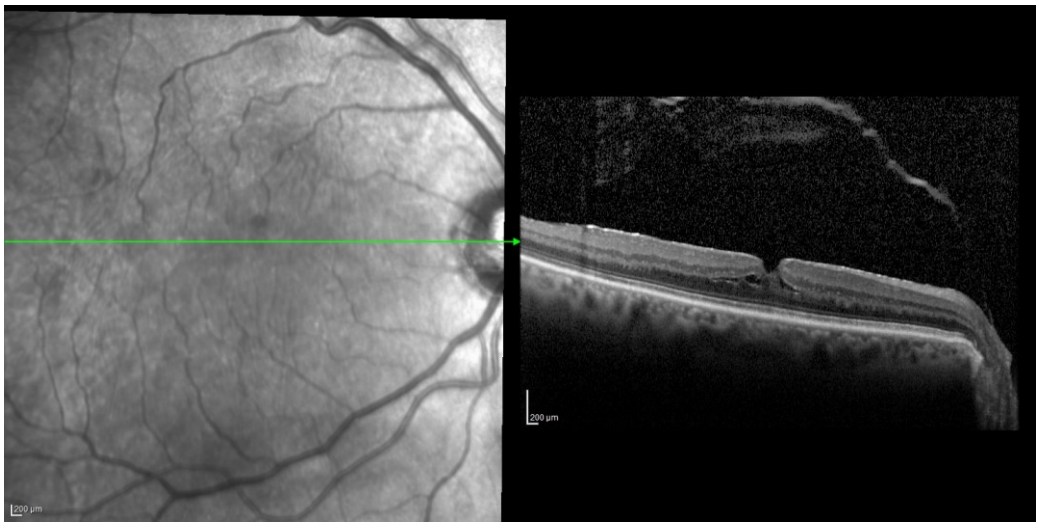

Figure 27 Five weeks after injection resolution of vitreomacular traction with some residual intraretinal cysts on OCT of patient 6 is seen

9 Discussion

This case series describes the use of a single intravitreal 100% C_3F_8 gas injection for the treatment of VMT with and without MH. This very small retrospective case series showed a successful release rate of VMT within the first month in 42.86%, within six months in 85.71%. Only one patient (14.29%) failed to respond and had to undergo vitrectomy shortly after injection because of a retinal tear and detachment. The patient (14.29%) presenting with a MH showed release of VMT, but had to undergo vitrectomy as a consequence of the nonclosure of the MH.

A very heterogenous patient selection was included, with patients showing concurrent ERMs (42.86%) and diabetic retino- and maculopathy (14.26%). Nevertheless successful release occurred with a very high frequency and one must say, that this patient population would not be considered ideal for best success rates. Two patients (28.59%) showed adverse events after the intravitreal gas injection, such as macular edema, retinal tear and retinal detachment.

In this case series individual visual acuity improvements were modest. Visual acuity improved by two or more Snellen lines in 42.86% and remained stable in 57.14%. It is disputable, if and to what extend the BCVA of the patient with a diabetic retino- and maculopathy had slightly decreased regarding the fact, that this diagnosis can cause severe vision loss with time. Additionally in one patient with a BCVA with 1.0 an increase in VA could not be expected.

The two MIVI TRUST studies, demonstrating the treatment efficacy of one single intravitreal 125µg injection of ocriplasmin, showed that at day 28 post injection 26.5% and 40.6% had resolution of adherence and nonsurgical macular hole closure, respectively. Both results were statistically significant. (9) Another study called OASIS, provided even higher numbers, with success rates in the ocriplasmin group of VMT release at day 28 of 41.7%. The closure of MH without any surgical intervention by month 3 was reported with 30%. (75) Sharma et al. found the resolution of VMT to be as high as 50% and a nonsurgical closure of MH in 27%. (22) All these studies only reported about the results of VMT resolution 28 days after the intravitreal injection and did not note release rates after six or twelve months, even though the OASIS study had a 24 months follow-up. With a longer observation interval it can be assumed that the results would as well have increased. Moreover a long-term follow-up is favourable in order to assess the final VA. Transient visual loss has been described in previous studies and a longer observation period can aid in definite judgment. In addition, further and larger ’real-world’ clinical series with heterogeneous patients collectives will give

more insight regarding collection of patients, adverse events and efficacy. There were a lot of ocular exclusion criteria in the MIVI-TRUST study, which can hence hardly be compared with the patient collective of everyday life. Ocriplasmin is a first-in class drug and it's safety profile is nowhere near completion. As the primary end point of the first and main studies were changes on OCT, these do not always go hand in hand with visual improvement or decline and more studies are needed that put the focus also on visual gain. (67) (9) (75)

Day et al. conducted a study with patients receiving an intravitreal sulfur hexafluoride injection for the treatment of VMT. A release rate of 55.6% as well as the closure of MH in two of two patients within the first month was documented with the results being even higher as with ocriplasmin. However the study involved only 9 patients compared to 464 treated with ocriplasmin in the MIVI-TRUST study, which makes these results hard to compare due to the fact that its harder to conclude about a population with less participants. (9) (73) Furthermore the study did not include patients with ERM or other concurrent retinal diseases, which are according to Haller et al. favourable factors for pharmacologic release and hence could have increased their release rate. (67) (73) Only one study has been published with injection of SF_6 gas so far and further study including patients with for example ERMs is required to confirm these results.

Vitrectomy still remains gold standard for symptomatic VMT, showing release rates of up to 98%, nonetheless entailing the risk of intra- and postoperative complications. (61) It is dependent on a very experienced surgeon and requires suitability for surgery, which is not always given in patients with advanced age. The main complication of cataract formation post operatively is also worth considering, since this requires another surgery, if not automatically done in the same intervention. Given the high success rate of vitrectomy, documented also after the completion of pharmacological therapy, it is also possible in the future to perform vitrectomy as a second-line therapy only in cases where medical therapy has failed. With pharmacologic vitreolysis previous to vitrectomy no additional side effects have been identified so far, on the contrary Lopez-Lopez et al. even considered if it could be coadjuvant by speeding up the surgery and minimising its complications. (46) (76) It would be of high interest to directly compare the use of an intravitreal injection of ocriplasmin, C_3F_8 and SF_6 gas, vitrectomy and placebo for patients with VMT in a single clinical trial.

Rodrigues et al. were the first to investigate the use of an intravitreal injection of expansile perfluoropropane gas in treating VMT in 2013. Release of VMT was successfully observed in 40% of patients within the first month and increased to 60% within half a year. (70)

In 2016 Steinle et al. assessed the posterior vitreous release rates after a single intravitreal injection of C_3F_8 for VMT treatment as well. At one month following injection initial VMT release was 73% and increased to 83% by the final follow-up visit, which was on average 160 days. (71)

These studies show similar results of VMT release as those found at the Medical University of Graz. Rodrigues et al. on the one hand included very few patients (15 eyes), while Steinle et al. on the other hand had 30 eyes investigated, up to now the largest collection of patients receiving a C_3F_8 gas injection. In all studies, including the case series performed in Graz, a very heterogeneous patient collective was included, with patients presenting with concurrent ERM, concurrent DM, exudative age-related macular degeneration and MH. In the study conducted by Steinle et al. 6 eyes (20%) in fact were included, where previous intravitreal ocriplasmin injection has failed to release traction and one eye (3%) which prior participated in another study receiving serial saline intravitreal injections. At final check-up five of these six eyes (83%) and the eye with three intravitreal saline injections (1 of 1 eyes) released. This brings up the question whether a single C_3F_8 gas injection works more efficient than ocriplasmin, whether previous intravitreal injections aid in releasing traction or whether these adhesions would have maybe released spontaneously.

Regarding ERM, Steinle et al. noted a success rate of 83% and suggested this therapy as a justifiable nonsurgical treatment in patients showing VMT and ERM. (71) In the case series of the Grazer Medical University, two out of three patients with concurrent ERM released traction, which was as well high but must be seen critically due to the small amount of patients. However these results are in contrast to Haller et al. proposing the absence of ERM as positive predictive factor, which was associated with successful VMT release. (67) Rodrigues et al. also identified predictive factors such as maximal foveal thickness before treatment less than 500µm and extension of VMA less than 750µm, that seem to have a positive impact on traction release rate. All patients participating in the case series of the Medical University of Graz, who had a maximal horizontal vitreomacular adhesion of lower than 750µm (85.71%), showed a successful vitreomacular traction release. These results strengthen the author's assumptions. At the only patient who failed to respond the extent of adhesion was 803µm. The question arises, whether a larger adhesion diameter and thus a stronger tractive force are favorable for retinal tear and detachment, as it was documented in this patient. However, the second postulated predictive feature of a maximal foveal thickness less than 500µm can not be seen in the case series of the Medical University of Graz. Three patients (42.86%) had a maximal foveal thickness of more than 500µm, among whom 2 had

vitreomacular traction release within six months. (70)
In none of the two studies (Rodriguez et al. and Steinle et al.) mean visual acuity improvement showed statistical significance, which might be due to the relative small amount of included patients.

Successful closure of early-stage MH with gas injection was described as early as 1995. (72) Rodrigues et al. included just one eye with an impeding MH at baseline, which progressed to a FTMH after C_3F_8 gas injection and eventually had to undergo vitrectomy for release of VMT. Steinle et al. had three eyes with FTMH of <200µm at baseline, whereof all three showed VMT release with gas and two had closure of their FTMH. The Grazer case series notes one patient with a MH, who had pneumatic release of VMT but required vitrectomy for the closing of the persistent MH. It has been previously described that MH with a diameter <200µm have a higher chance of closure after medical therapy, which can not be confirmed by the study done at the Medical University of Graz. The MH however did show a width of 201µm and a single case is of very low significance. (70) (71)

The main advantage of C_3F_8 gas is that it is easy to get, minimally-invasive and last but not least very cost-effective. Compared to a single injection of ocriplasmin, which costs about 3,950$, an intravitreal injection of perfluoropropane gas is by far cheaper. (77)

The main limitation of this study is the number of patients, making it almost impossible to get statistically relevant results. Furthermore the retrospective data collection and absence of a control group represented significant restrictions. The documentation of the patients was missing information like the intraocular pressure before and after injection. Consequently no statement can be made about these measures. In addition the time from diagnosis to intravitreal C_3F_8 gas injection was very variable and the advised three months of observation were rarely observed. Moreover the patient number is too small for evaluation of rare complications after intravitreal injection. Further studies addressing this very low-cost, minimally invasive and promising treatment of symptomatic VMT are warranted.

In conclusion, pneumatic vitreolysis with perfluoropropane gas is a promising nonsurgical option for treating VMT, with or without MH. The results of this case series suggest a further possibility to successfully release vitreomacular traction with a single intravitreal injection of C_3F_8 gas. Furthermore it gives clinicians another option, besides ocriplasmin and SF_6, to manage VMT in a less invasive manner. Additional studies with most notably a larger patient population are needed to further investigate into the risk/benefit profile of C_3F_8 gas and to directly compare perfluoropropane gas to other methods of medical and surgical vitreolysis.

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