Macular hole – surgical treatment, epidemiology, and risk of bilateral disease

Birger Lindtjørn

Thesis for the degree of Philosophiae Doctor (PhD)
University of Bergen, Norway
2022

UNIVERSITY OF BERGEN

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Date of defense: 08.12.2022

Year: 2022

Title: Macular hole – surgical treatment, epidemiology, and risk of bilateral disease

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Print: Skipnes Kommunikasjon / University of Bergen

Scientific environment

The doctoral education program was administered by the Department of Clinical Medicine, Faculty of Medicine, University of Bergen. The research described in Paper I and Paper II was performed at the Department of Ophthalmology, Stavanger University Hospital. For Paper III, we collaborated with the Departments of Ophthalmology at Haukeland University Hospital, Trondheim University Hospital, and the University Hospital of North Norway. For Paper IV the collaboration was extended to also include the Department of Ophthalmology at Oslo University Hospital.

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Contents

Acknowledgments

First, I would like to thank Vegard A. Forsaa for being an excellent supervisor and role model. Your medical and scientific knowledge has been invaluable during my Ph.D. work and training to become a vitreoretinal surgeon. Thank you for your patience and moral support. I am also very grateful to my co-supervisor, Jørgen Krohn. Thank you for your valuable input, moral support, and constructive discussions.

A special thanks to all the patients who participated in our studies. The research would not have been possible without your patience and willingness to undergo extra examinations.

I would also like to thank all my colleagues, nurses, and secretaries at the Department of Ophthalmology, Stavanger University Hospital, for your work and help in carrying out these studies. My gratitude goes to the Department of Ophthalmology, Stavanger University Hospital, for supporting me and providing me with time to conduct the research. Many thanks to the staff at the other Departments of Ophthalmology in Norway that participated in the multicentre studies.

I would also like to thank Prof. Jan Terje Kvaløy for your input and guidance regarding statistics and study planning. Thanks to Solveig Bjornes and Hamida Achour, who assisted in the data collection for Paper II.

I am blessed with a fantastic family. Thanks to my parents, Magnhild and Bernt, and my siblings Ommund, Eivind Johannes, Gerd Eli, and Anna Birgitte, who have played a significant role in my life. Thanks to my parents-in-law, Tove and Arild Vagle, for helping when needed. Finally, and most of all, I want to thank my wife and the love of my life, Ane. Thank you for your presence, support, and our children, Matilde, Samuel, and Ludvig.

Abbreviations

CI	Confidence interval
ERM	Epiretinal membrane
ETDRS	Early Treatment of Diabetic Retinopathy Study
FDP	Face-down positioning
ILM	Internal limiting membrane
ITT	Intention to treat
IVTS	International Vitreomacular Traction Study
logMAR	logarithm of the Minimum Angle of Resolution
MH	Macular hole
NSP	Nonsupine positioning
OCT	Optical coherence tomography
PP	Per protocol
PPV	Pars plana vitrectomy
PVD	Posterior vitreous detachment
RPE	Retinal pigment epithelium
SD	Standard deviation
SF_6	Sulphur hexafluoride
TBT	Tennis ball technique
VA	Visual acuity
VMT	Vitreomacular traction

Abstract

Introduction:

Macular hole (MH) reduces the visual acuity and impairs the quality of life. Individuals with MH in one eye have an increased risk of developing MH in the fellow eye compared to the general population. Surgical treatment has been available for the last 30 years, but has often been strenuous and uncomfortable.

Aims:

This thesis aimed to investigate the epidemiology of MH and reduce the disadvantages that are associated with MH surgery. Paper I investigates the incidence of MH in Southern Rogaland. Paper II studies the risk of bilateral MH disease and aims to identify optical coherence tomography (OCT) features associated with an increased risk of MH formation in the fellow eye. In Paper III, the purpose is to investigate the correlation between postoperative positioning compliance and closure rate. Paper IV explores whether air is non-inferior to sulphur hexafluoride (SF_6) gas for MH ≤400 μm in diameter.

Methods:

Paper I and II are retrospective studies of patients operated for MH or identified with MH at the Department of Ophthalmology, Stavanger University Hospital. Only patients living in Southern Rogaland County were included. The inclusion period of Paper I was from January 2008 to December 2014. For Paper II, the inclusion period was extended by four years to include December 2018. Optical coherence tomography images were reviewed, and the MHs were classified according to the International Vitreomacular Traction Study (IVTS) classification. Paper II focused on the OCT analysis of the fellow eye to determine the presence or absence of intraretinal abnormalities, which may be associated with an increased risk of MH formation. Paper III is a prospective multicentre study. Patients who underwent surgery for MH were equipped with a positioning measuring device the first 24 hours after surgery. The accumulated time spent in supine position was recorded. Paper IV is a prospective, randomised noninferiority multicentre study. Patients with MH ≤400

μm were randomised to receive air or SF_6 gas as intraocular tamponade. After surgery, the patients followed a nonsupine positioning regimen for three days. The noninferiority margin was set to a 10 percentage points difference in closure rate.

Results:

The sex and age-adjusted incidence of MH was 7.9 eyes per 100 000 inhabitants per year. The male-to-female ratio was 1:2.2. Thirteen percent of the MH were classified as small, 31% as medium-sized, and 55% were classified as large MH. In Paper II, we found an overall risk of bilateral MH disease of 8.8% (95% CI, 5.8–13.2%). Outer retinal defects were present in 42% of the fellow eyes which subsequently developed an MH, compared to 7% of the fellow eyes which did not develop an MH in the study period (P=0.001). A total of 205 patients were included in Paper III, two of them were lost to follow-up. The MH closed after single surgery in 202 out of 203 cases, giving a closure rate of 99.5% (95% CI, 93.3–99.9%). Due to the very high closure rate, correlation analyses between positioning compliance and closure rate were not possible. One hundred and fifty participants were included in Paper IV, 75 in each group. In 10 patients who received air as tamponade, the MH did not close after the first surgery. All MH in the SF_6 group closed after a single surgery. Six patients were excluded from the per-protocol (PP) analysis. The closure rates for the air and gas group in the PP analysis were 90% (95% CI, 79.9–95.5%) and 100% (95% CI, 93.9–100%), respectively.

Conclusion:

The incidence of MH in Norway is comparable to that of a study from the USA with a similar population. Women are more likely to develop an MH than men, and individuals with MH in one eye, have an increased risk of MH development in their fellow eye. It is possible to achieve excellent closure rates when applying a nonsupine postoperative positioning regimen. Air was inferior compared to SF_6 gas for MH ≤400 μm in diameter in regard to closure rate.

Sammendrag (abstract in Norwegian)

Bakgrunn:
Makulahull er en tilstand som hemmer sentralsynet og gir redusert livskvalitet. Personer som har fått et makulahull i et øye, har økt risiko for å utvikle makulahull også i det andre øyet. De siste 30 årene har det vært mulig å behandle tilstanden kirurgisk, men behandlingen har ofte vært en påkjenning for pasientene.

Formål:
Formålet med dette ph.d.-arbeidet var å kartlegge epidemiologien av makulahull og å redusere ulempene forbundet med makulahulkirurgi. Artikkel I tilstreber å kartlegge insidensen av makulahull i Rogaland fylke, mens Artikkel II har som formål å identifisere optisk koherens tomografi (OCT) funn forbundet med økt risiko for makulahull i det andre øyet. I Artikkel III er hensikten å undersøke sammenhengen mellom lukningsrate og pasientenes etterlevelse av postoperativ posisjoneringsinstruks. Artikkel IV undersøker om luft er ikke-underlegen sammenlignet med svovelheksafluorid (SF_6) gass for makulhull med diameter ≤400 μm.

Metode:
Artikkel I og II er retrospektive studier av pasienter som ble operert for makulahull eller identifisert med makulahull ved Stavanger universitetssykehus. Kun pasienter som var bosatt i Sør-Rogaland ble inkludert. Artikkel I inkluderte pasienter som ble diagnostisert i perioden januar 2008 t.o.m. desember 2014, og artikkel II inkluderte pasienter fra perioden januar 2008 t.o.m desember 2018. Bilder av makulahullene tatt med OCT ble gransket og klassifisert. Artikkel II fokuserte på granskning av OCT bilder av det ledsagende øyet hvor man så etter intraretinale abnormaliteter og tilhørende risiko for utvikling av makulahull. Artikkel III er en prospektiv multisenter studie. Pasienter som ble operert for makulahull ble monitorert i ett døgn med et instrument som registrerte hodets posisjon. Artikkel IV er en prospektiv randomisert

ikke-underlegenhet multisenterstudie. Pasienter med makulahull ≤400 μm i diameter ble randomisert til enten å få luft eller SF_6 gass som intraokulær tamponade, og ble instruert i å unngå ryggleie og unngå å se opp de første 3 døgn etter operasjonen. Grensen for non-inferioritet ble satt til 10 prosentpoeng forskjell i lukningsrate.

Resultater:

Den alders- og kjønnsjusterte insidensen i Sør-Rogaland av makulahull var 7.9 øyne per 100 000 innbygger per år. Kvinner utviklet makulahull 2.2 ganger oftere enn menn. Tretten prosent av makulahullene ble klassifisert som små, 31% som medium og 55% som store makulahull. I Artikkel II fant vi at risikoen for bilateral sykdom var 8.8% (95% konfidensintervall (KI), 5.8%–13.2%). Ytre retinale defekter var tilstede i 42% av øyne i gruppen som utviklet hull i det ledsagende øyet sammenlignet 7% i gruppen som ikke utviklet hull i det andre øyet (p=0.001). I Artikkel III ble 205 pasienter inkludert, 2 pasienter gikk ut av studien og lukningsresultater var ikke tilgjengelige for analyse. Hos 202 av 203 pasienter lukket makulahullet seg etter første operasjon, derav en beregnet lukningsrate på 99.5% (95% KI, 93.3%–99.9%). Pga. den høye lukningsraten var det ikke mulig å gjøre en korrelasjonsanalyse mellom lukningsrate og postoperativ posisjonering. I Artikkel IV ble 150 pasienter inkludert, 75 i hver gruppe. Hos 10 pasienter i luftgruppen lukket ikke makulahullet seg, mens alle makulahull i gassgruppen lukket seg etter første operasjon. Seks pasienter ble utelukket fra per protokoll (PP) analysen. Lukningsraten for luft og gass i PP analysen var henholdsvis 90% (95% KI, 79.9–95.5%) og 100% (95% KI, 93.9–100%).

Konklusjon

Insidensen av makulahull i Norge er sammenlignbart med studier med en lignende populasjon i USA. Kvinner blir oftere rammet og individer som har utviklet makulahull i et øye, har økt risiko for å utvikle makulahull i sitt andre øye. Det er mulig å oppnå gode lukningsrater også uten at pasienter må følge et strengt posisjoneringsregime med ansiktet vendt ned etter operasjon. Luft viste seg å være underlegen SF_6 gass.

List of Publications

Paper I

Forsaa VA, Lindtjørn B, Kvaløy JT, Frøystein T & Krohn J. (2018). Epidemiology and morphology of full-thickness macular holes.
***Acta Ophthalmologica*, *96*(4), 397–404.**

Paper II

Lindtjørn B, Krohn J & Forsaa VA. (2021). Optical coherence tomography features and risk of macular hole formation in the fellow eye.
***BMC Ophthalmology*, *21*(1), 1–7.**

Paper III

Lindtjørn B, Krohn J, Austeng D, Fossen K, Varhaug P, Basit S, Helgesen OH, Eide GE & Forsaa VA. (2019). Nonsupine positioning after macular hole surgery: a prospective multicenter study.
***Ophthalmology Retina*, *3*(5), 388–392.**

Paper IV

Lindtjørn B, Krohn J, Haugstad M, Stene-Johansen I, Austeng D, Basit S, Fossen K, Varhaug P, Kvaløy JT, & Forsaa VA.
Air versus Sulfur Hexafluoride Gas Tamponade for Small and Medium Sized Macular Holes: a Randomized Noninferiority Trial.
Ophthalmology Retina*, *published online April 07, 2022

1. Introduction

The retina is a thin light-sensitive layer of tissue that covers the inner wall of the posterior part of the eyeball. Its role is to sense the light and convert it into nerve signals. The eye optics creates an image of the visual world on the retina, which is converted to electrical nerve impulses and transmitted through the optic nerve and optic tract to the visual cortex. The macula, the central part of the retina, is defined as the retinal area between the major temporal vascular arcades (Figure 1).[1]

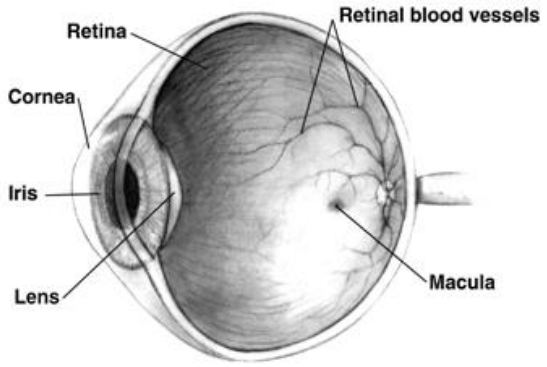

Figure 1. A cross-sectional view of the human right eye. © Public domain

A macular hole (MH) is a full-thickness hole including all the retinal layers from the internal limiting membrane (ILM) to the photoreceptor cells.[2] It typically occurs in the most central part of the macula, called the foveola.

In 1869, Knapp was the first to describe an MH in a case with a history of ocular trauma.[3] Initially, ocular trauma was thought to be the most common cause of MH. [4] However, in an article by Lister in 1924, MHs were classified as traumatic and non-traumatic.[5] Until Kelly & Wendel published their results of a pilot study on idiopathic MH in 1991, there was no known treatment for MH.[6] If left untreated, most MH will progress over time, and a majority of the affected eyes will end up with visual acuity (VA) of 20/200 or worse.[7-10] Kelly & Wendel did not only prove that it was possible to close an MH, but they also demonstrated VA improvement. In 52 patients, 30 (58%) of the MH closed. In 22 of these 30 patients, the VA improved two lines or more. In 1993 their series of 52 patients was extended to 170 eyes, and closure was achieved in 73% of the cases, and in 55%, the VA improved by at least two lines.[11] Since then, the surgical treatment for MH has become a standard procedure and the results have greatly improved. Today, one can expect closure rates above 90%.[12-17]

1.1 Epidemiology

The Beaver Dam Eye Study (1994) examined 4926 individuals older than 42 years with fundus photography, and estimated the prevalence of MH to be 0.3%.[18] At about the same time, the Baltimore Eye Survey (1996) investigated the prevalence and causes of visual impairment (VA worse than 20/40, but better than 20/200) among 5308 inhabitants older than 40 years and reported a prevalence of 0.1%. The data from these studies were collected a few years before surgical MH treatment was available, and thus, the prevalence provided a good indication of the disease burden.[19] Later epidemiological studies have found similar prevalence estimates.[20-22]

The prevalence is the proportion of people who have a specific disease at a given point, whereas the incidence is the number of new cases during a defined time period.[23] As treatment for MH has become widely available in the developed world, incidence data gives a better indication of the disease burden. McCannel et al. conducted a retrospective study on the MH incidence in Minnesota, USA, and reported an incidence of 7.8 persons and 8.7 eyes per 100 000 inhabitants per year. [24]

Macular hole predominately affects women with a female to male ratio of 2–3:1 and typically occurs in the seventh and eighth decade of life.[24, 25] Persons with MH in one eye have an increased risk of MH formation in their fellow eye. According to studies on fellow eye involvement, this risk is 7–16.7%.[8, 24, 26-32] Contrary to the earlier understanding of MH, Aaberg et al. in 1970 reported that the majority of MH were idiopathic and both McCannel et al. and Darian-Smith et al. reported 90% idiopathic MH.[7, 24, 26] Idiopathic MH are now called primary MH and is caused mainly by vitreomacular traction (VMT). This thesis focuses on primary MH, and the term macular hole refers to a full-thickness retinal defect.

1.2 Symptoms

Patients with MH typically report reduced VA and distorted central vision, so-called metamorphopsia.[33-35] One might expect that patients with an MH report a central

scotoma. Even though a small central scotoma may be found with specific testing, scotoma is seldom a presenting symptom.[33, 34]

In a prospective study by Saito et al. in 2000, 51 patients with MH were examined for metamorphopsia.[33] All patients had some degree of metamorphopsia with the central pincushion type (61%), where the lines bow toward the centre, as the most common form (Figure 2). An unspecific distortion of the central visual field was found in the remaining 39% of the patients.

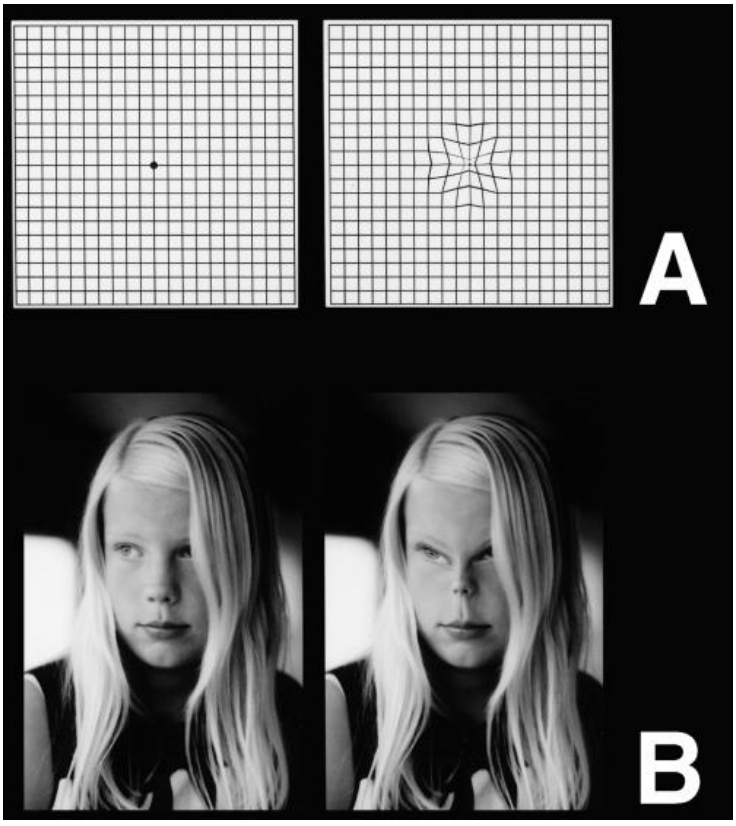

Figure 2. The pincushion metamorphopsia. Reproduced with permission from Acta Ophthalmologica (2002;80:579–87), Copyright John Wiley and Sons. The images on the right illustrate the pincushion effect with the central lines curving toward the centre.[36]

In a large register study from the UK with 1483 primary macular hole operations, the median preoperative VA was logMAR 0.78 (equivalent ≈ Snellen 0.2).[14] Nine percent

had a VA of counting fingers or worse. In 50% of the cases, the duration of symptoms was not known. In the remaining 50% with known duration, the median duration was 3 months (range, 0–60 months).

1.3 Pathophysiology

The current understanding of primary MH development is closely associated with posterior vitreous detachment (PVD). In 1924, Lister wrote about the shrinking vitreous, but cystic retinal degeneration was thought to be the cause of "non-traumatic holes".[5] In 1970, Aaberg et al. considered vitreoretinal adhesion and VMT as important components in MH formation. They reported a premacular operculum in 26% of MH patients that was thought to represent an avulsion of the inner retinal layers. It was a common belief that the MH was a substance defect of the retinal layers resembling a punched-out lesion. An important and highly cited paper is that of Gass from 1988, where the theory of tangential vitreofoveal traction was introduced.[37] According to Gass, MH formation was initiated by a prefoveal vitreous shrinkage, which causes anteroposterior traction at the vitreofoveal interface and elevation of the foveal area. Soon thereafter, tangential traction caused the MH formation. Four stages of MH were introduced. Little hope was left to eyes with the presence of an MH, but advice for potential trials on preventing MH formations was given. As Kelly & Wendel demonstrated good VA improvement after successful MH surgery, Gass revised his theory in 1995.[38] A MH was no longer understood as a punched-out lesion in the central macula. According to Gass' revised theory, VMT led to central retinal dehiscence followed by centrifugal displacement of surrounding retinal tissue. Jensen & Larsen demonstrated with binocular kinetic perimetry the radial centrifugal displacement of the photoreceptors in MHs.[39]

The revised four stages of MH by Gass were as follows:

> Stage 1 A: Impending MH. Elevated fovea and absent foveal depression. MH formation is often prevented by vitreofoveal separation
>
> Stage 2: Small full thickness MH, <400 μm in diameter. Often without vitreofoveal separation.
>
> Stage 3: Full thickness MH, ≥400 μm in diameter without complete PVD.
>
> Stage 4: Full thickness MH with complete PVD.

The vitreous body is important to maintain structural integrity and optical clarity of the eye.[40, 41] It is also thought to play an important role in ocular and refractive development and the prevention of oxidative stress.[42] The vitreous consists mainly of water (98%), collagen and hyaluronan.[43] Starting only a few years after birth, the vitreous gel gradually liquefies. In individuals older than 70 years, more than 50% of the vitreous is liquefied.[44] The vitreous gel is surrounded by the vitreous cortex, which at birth is attached to the retina. As the vitreoretinal adhesion weakens with age, small holes in the premacular vitreous cortex occur. Liquefied vitreous enter the potential space between the vitreous cortex and ILM, and vitreous currents, due to eye and head movements, cause further dissection of the vitreous cortex.[45] The vitreous cortex is most firmly attached to the pars plana region, peripheral retina, optic disc, and fovea. Optical coherence tomography studies have demonstrated that the PVD typically starts in the perifoveal region, followed by separation of vitreous from the foveal region and finally from the optic disc.[46] Figure 3 illustrates the typical stages of PVD development.

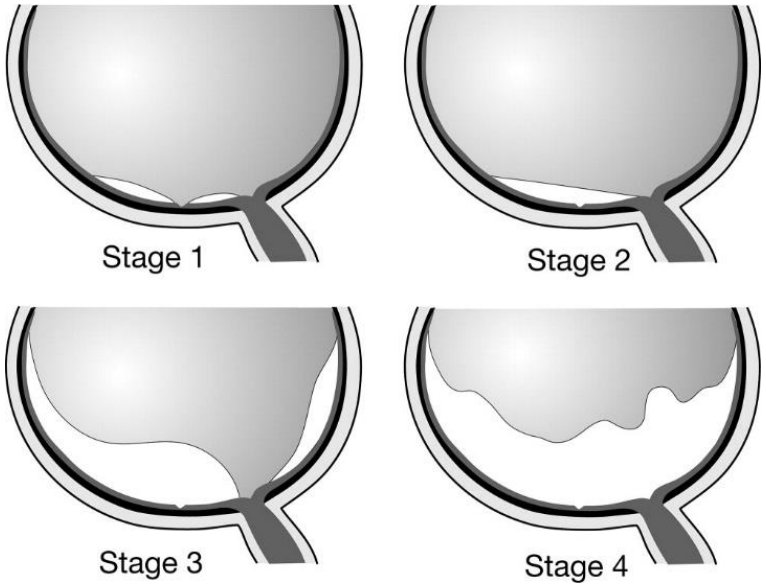

Figure 3. Stages of posterior vitreous detachment (PVD). Stage 1, perifoveal PVD with vitreofoveal adhesion. Stage 2, macular PVD with no vitreofoveal adhesion. Stage 3, extended PVD with only vitreopapillary adhesion remaining. Stage 4, complete PVD. Reproduced with permission from *Am J Ophthalmol* (2010;149:371–82.e1.), Copyright Elsevier.[44]

The VMT causes the primary event in MH formation, a tear or some mechanical damage to the Müller cell cone which causes foveal dehiscence or instability. But what causes the hole to enlarge? After observing 46 eyes with stage 2–4 MH with OCT for eight months, Tornambe announced his hydration theory in 2003.[47] After foveal structural damage, vitreous fluid accumulates in the retinal tissue surrounding the foveal dehiscence and causes tissue swelling. The swelling retina can only expand in the direction of the vitreous cavity, and as the ILM is stiffer than the deeper retinal tissue, the ILM draws the MH edges aside and the MH opens analogous to a drawbridge (Figure 4).[47]

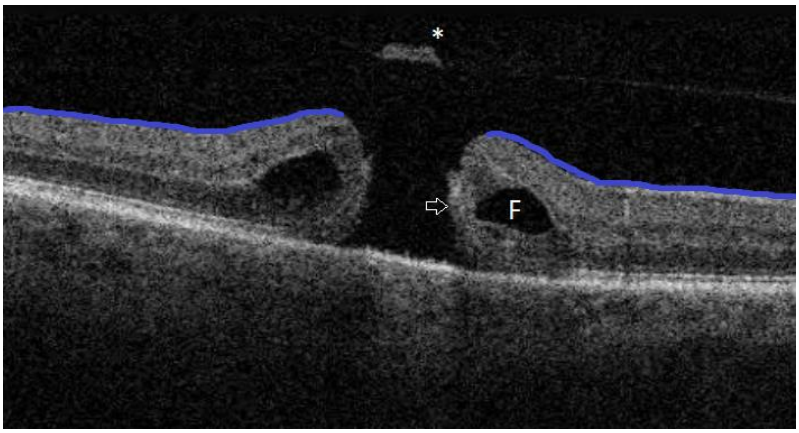

Figure 4. A macular hole with intraretinal fluid (F) in the adjacent thickened retina. The thin blue line resembles the internal limiting membrane (ILM).
*Pseudooperculum. The arrow points at detached photoreceptors. © Birger Lindtjørn.

The type of initial structural foveal change caused by VMT and the path to a fully developed MH may differ.[48] An eye with complete PVD, is unlikely to develop MH.[49, 50] However, MH occasionally occurs in eyes with documented PVD. In these cases, the vitreous detachment process has probably caused some damage to the foveal structure. Subsequently, development of an epiretinal membrane (ERM) may cause further tangential traction and foveal dehiscence.[48] The reported spontaneous closure rate of MH varies from 4% to 11.5%.[51] Small MH, <250 µm in diameter, with only a few months of symptom duration, are more likely to close spontaneously.[51]

1.4 Diagnosis and current classification

Macular pathology is suspected in patients with decreased VA and visual distortions. An MH can be seen during ophthalmoscopy, but may be confounded with a macular pseudohole or lamellar hole. A small central scotoma on an Amsler grid test or a positive Watzke Allen test may indicate an MH, but OCT is the concluding examination. Optical coherence tomography of MH was first reported by Puliafito et al. in 1995 and allows minute imaging of retinal pathologies, which has boosted the understanding of macular diseases.[52] The OCT images resemble a histological picture and enable accurate detection of the macular vitreoretinal interface. The International Vitreomacular Traction Study (IVTS) Group published in 2013 a new consensus regarding the classification of vitreomacular interface diseases based on OCT findings.[2]

Macular holes are now classified as follows:

Small MH:	≤250 µm in diameter
Medium MH :	>250 – ≤400 µm in diameter
Large MH:	>400 µm in diameter
Status of vitreous:	With or without VMT
Cause:	Primary or secondary

The MH diameter is measured using the calliper function embedded in the OCT software and measured at the narrowest point in the mid retina, roughly parallel to the retinal pigment epithelium (RPE).

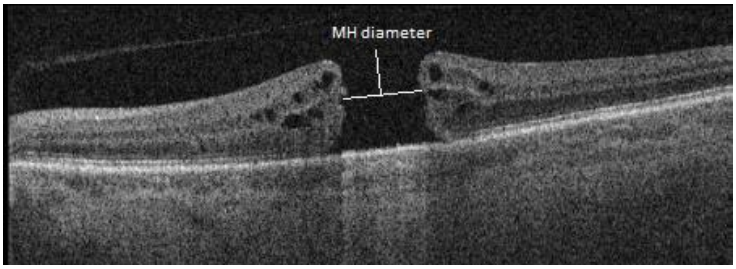

Figure 5. A large macular hole without vitreomacular traction (VMT). © Birger Lindtjørn

1.5 Treatment

1.5.1 Surgical treatment

The surgical method introduced by Kelly & Wendel consisted of pars plana vitrectomy (PPV), relief of any VMT, ERM removal, and fluid air exchange followed by an injection of a nonexpansive sulphur hexafluoride (SF_6) gas. After surgery, the patients followed a strict face-down positioning (FDP) regimen for at least seven days.[6] Kelly & Wendel stood on the shoulders of the work done on epiretinal membrane surgery and VMT in the 1980s. Kelly later wrote that the described peeling of ERM instead was peeling of the ILM.[53] Even today, PPV, relieving of any VMT, peeling the ILM, and installing a gas are the essential parts of the surgical procedure in MH surgery, but the surgical methods and instruments have been refined.

Vivian Kim reported in 1999 that the almost invisible ILM could be made visible by indocyanine green (ICG).[54] This made the ILM removal much more accessible, and Brooks reported in 2000 that routine ILM peeling significantly improved the closure rate in MH surgery.[55] A meta-analysis from 2014, comparing MH surgery with ILM peeling to MH surgery without ILM peeling, confirmed that ILM peeling significantly improves the closure rate and reduces the needs for additional surgery.[56] Soon after ICG was introduced as an ILM dye, concerns about retinal toxicity were raised.[57, 58] However, these were small retrospective studies with 20 and 22 patients. The ICG toxicity remains controversial; the American Academy of Ophthalmology still upholds ICG as an alternative for ILM staining in their Idiopathic Macular Hole Preferred Practice Pattern of 2020.[59, 60] Today, Brilliant Blue B (BBG) and Trypan Blue are effective and widely used ILM staining alternatives.[61]

Even though ILM peeling improves the closure rates, there are concerns about its side effects. The peeling manoeuvre alone may cause focal haemorrhages, oedema, nerve fibre layer damage by the surgical forceps, and eccentric MH formation.[62] As the basement membrane of Müller cells, the ILM serves as a structural interface between the vitreous and retina. During embryogenesis, the ILM is essential for retinal histogenesis.[63] Animal models show that the retinal ganglion

cells undergo apoptosis when the ILM is removed on embryonic day 5, but not on embryonic day seven or later.[63] Will ILM removal have any adverse effects other than those occurring during the surgery? In a prospective study of 105 patients who underwent MH surgery with ILM peeling, 56% of the patients developed small paracentral scotomas.[64] Ripandelli et al. performed a prospective, randomised trial comparing microperimetry performances in 60 patients with ERM. Both groups underwent PPV and peeling of ERM, but only 30 patients underwent ILM peeling. The ILM peeled group showed decreased sensitivity in the 4° central area and an increased number of absolute microscotomas.[65] Peeling or not peeling the ILM is no longer a contested topic. Internal limiting membrane peeling causes an increased closure rate in MH surgery, fewer reoperations, is cost-effective and the VA gain is at least as good as in MH surgery without ILM peeling.[56, 66] The current controversy is about the size and form of the peeled ILM area (Figure 6).[67]

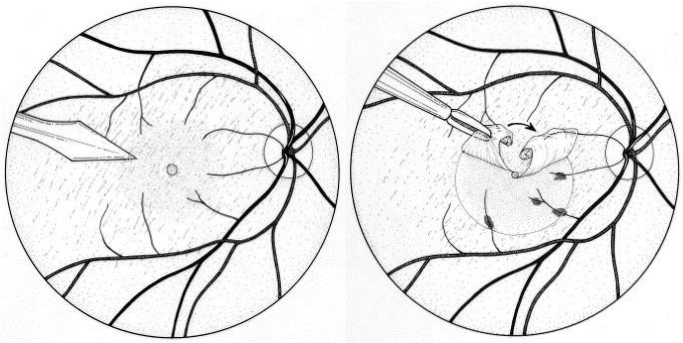

Figure 6. The initial ILM incision is made with a sharp blade or forceps, and a small flap is created. The ILM flap is grasped with an end-gripping forceps and extended 360° around the macular hole and removed. Reproduced with permission from *Ophthalmology* (2000;107:1939–48), Copyright Elsevier.[55]

Kelly & Wendel used SF_6 gas and recommended one week of a strict FDP regimen. The gas tamponade isolates the hole from the intraocular fluid and allows the intraretinal and subfoveal liquid to be absorbed. Face-down positioning was thought to be of paramount importance to ensure gas-foveal contact, and studies even suggested two weeks or more with FDP. However, FDP is troublesome for the patients, and there are reports of ulnar neuropathy and pulmonary emboli following FDP in MH surgery.[68, 69] Tornambe et al. demonstrated a primary closure rate of 79%

in a pilot study of 33 patients who underwent MH surgery without a postoperative FDP regimen.[70] Since then, there have been several studies investigating FDP versus nonsupine positioning (NSP) and different durations of FDP. [71] In 2019, two meta-analyses concluded that FDP is unnecessary for MH <400 μm in diameter.[13, 72] For large MH, FDP seems to facilitate better closure rates than NSP. Pasu et al. conducted a large, multicentre prospective trial comparing FDP to NSP for large MH.[73] The closure rate in the NSP group was 85.6% compared to 95.5% in the FDP group (*P*=0.08), and superiority of FDP could not be proved. Although the difference in closure rate was not statistically significant, the FDP group ended up with a significantly better VA (*P*=0.01).

The type of endotamponade also alters the bubble-fovea contact time. Table 1 lists the commonly used tamponades in vitreoretinal surgery, and their duration depends on the concentration used. As long as the tamponade is present within the eye, the patients are restricted from driving and cannot travel by plane or travel to altitudes 400–500 meters higher than the surgery site.

Gas tamponade	Commonly used concentration (%)	Mean duration (days)
Air	100	11
Sulphur hexafluoride (SF_6)	18–30	18
Hexafluorethane (C_2F_6)	12–22	35
Perfluorpropane (C_3F_8)	12–20	68

Table 1. Commonly used endotamponades and their duration within the eye.[74, 75]

Essex et al. published in 2016 an extensive register-based study comparing SF_6 gas to longer-acting gases.[12] A total of 2367 patients were included, and SF_6 was non-inferior to longer-acting gases in the surgical management of MH. The same study also investigated whether NSP is inferior to FDP. For the population as a whole, NSP was non-inferior to FDP. However, when only investigating patients with MH >400 μm, the results were inconclusive regarding the type of postoperative positioning regiment. A meta-analysis from 2022 investigating the effect of tamponade choice on closure outcome, found no difference between SF_6 and C_3F_8 or C_2F_6.[76] There is no longer a controversy about whether SF_6 is sufficient to achieve reasonable closure rates. Would it be possible to use even a shorter-acting tamponade such as air? Air

has a half-life of 1.3 days and remains in a pseudophakic eye for about 11 days.[75, 77] Several retrospective studies have reported using air as a tamponade in MH surgery.[75, 78-87] In these studies, the reported closure rates range from 75% to 100%. Forsaa & Krohn reported a closure rate of 95% for MH <400 µm in diameter in their prospective study with air as a tamponade in the setting of an NSP regimen.[75] However, the trial did not have a control group, and the closure rate was only 57% for large MH. We have addressed this knowledge gap in our study (Paper IV).

1.5.2 Expected outcome

Today, the closure rates are generally expected to be above 90%. Essex et al. reported in 2016 a closure rate of 95% in a large multicentre study conducted in Australia and New Zealand.[12] Steel et al. investigated the factors affecting the anatomical and visual outcome after MH surgery in a UK cohort of 1483 patients and found an overall closure rate of 95.7%.[14] As Figure 7 illustrates, the closure rate was negatively correlated with MH size. The Manchester Large Hole Study reported similar findings.[88]

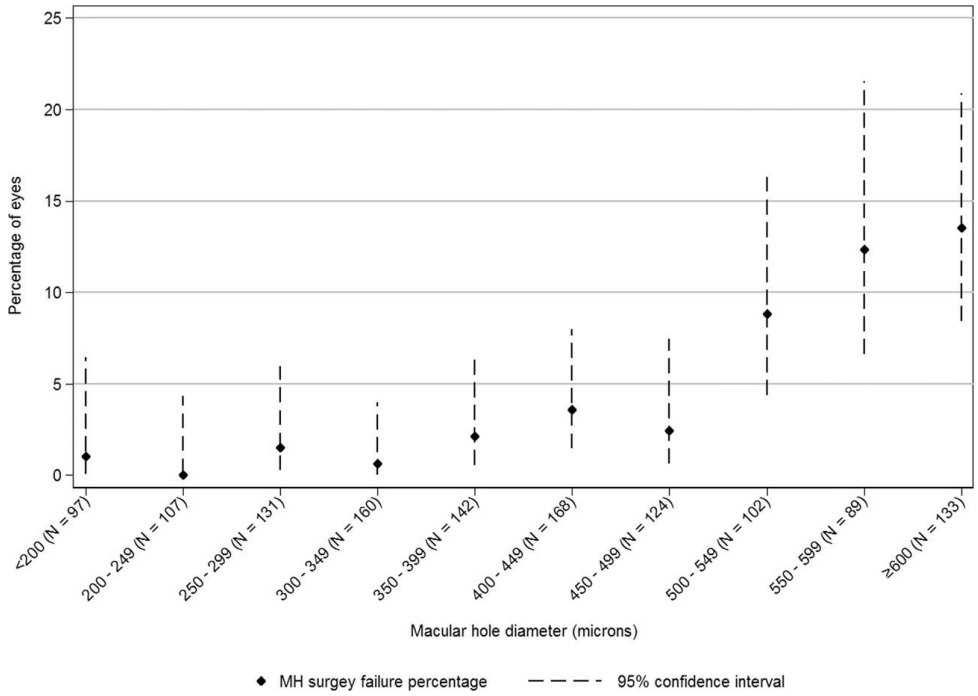

Figure 7. Failure rates in macular hole surgery depending on the MH size. The error bars indicate the 95% confidence interval. Reproduced with permission from Springer Nature (*Eye (Lond)* 2021;35:316–25). Copyright Springer Nature.[14]

In the cases with primary MH closure, Steel et al. reported that 94% of the patients experienced visual gain, and 64% had a visual improvement of at least 3 Early Treatment Diabetic Retinopathy Study (ETDRS) lines. The preoperative MH size is strongly correlated with the final VA; eyes with a small MH are more likely to end up with a good VA compared to eyes with a large MH.[14, 89-91] Relatively few end up with a VA equal to or better than logMAR 0.1, considered as normalVA. Fallico et al. reported that only 28% reach a VA ≤ logMAR 0.1 one year after surgery in a retrospective analysis of 327 cases. If a MH is treated within a few weeks after symptom onset, the chances of ending up with a VA ≤ logMAR 0.1 increases significantly.[90] This implies that MH should be operated relatively soon after symptom onset.

1.5.3 Alternative methods

There are also reports of successful MH closure using only medical treatment.[92-94] Sokol et al. reported in 2021 successful treatment of small MH with only topical medical therapy.[93] The topical treatment consisted of steroids, non-steroidal anti-inflammatory drugs, and carbonic anhydrase inhibitors. This was a small retrospective study with only 14 patients, of whom seven had previously undergone vitrectomy. Small MHs are more likely to close spontaneously, and the treatment mentioned above should be confirmed through prospective randomised trials.

It is possible to isolate the MH from the intraocular fluids by other means than using an endotamponade. In 2020, Stopa et al. reported that 11 out of 12 MH closed without endotamponade. An inverted ILM flap covered the MH and was kept in place by cohesive viscoelastic material.[95] Lally & Kasetty reported a closure rate of 85% in a group of MH <400 µm without any tamponade or use of inverted ILM flap.[96] The ILM was peeled in a conventional manner 360° around the hole. In the latter study, posterior vitreous detachment was absent in all eyes. The relieve of any VMT combined with small-sized MH may explain why endotamponade seemed unnecessary. Although these studies were small with 12 and 20 patients, they show that it is possible to achieve acceptable closure rates in small MH without the use of endotamponade.

Ocriplasmin was approved in 2012 as a nonsurgical treatment for VMT.[97] The drug is injected through pars plana and achieves pharmacologic vitreolysis and vitreomacular separation.[98, 99] Due to relatively low MH closure rates and reports of Ocriplasmin-related side effects, it never became an established alternative in MH treatment. According to a meta-analysis from 2022, the overall closure rate for Ocriplasmin was 34% (95% CI, 30–37%).[99] The closure rate was negatively correlated with the MH size with 47% closure rate for small MH (≤250 µm), 24% closure rate for medium sized MH (250–400 µm), and only 6% closure rate for large MH (≥400 µm).[99]

As patients with MH are prone to develop an MH in their fellow eye, it was suggested to investigate if early vitrectomy in the fellow eye would prevent MH development.[37] de Bustros et al. conducted in 1994 a prospective, randomised trial to examine whether early vitrectomy would prevent MH formation in the fellow eye.[100] All patients had a full-thickness MH in one eye and a stage 1 MH in the fellow eye. According to Gass, 56% of stage 1 MH progressed to a full-thickness MH.[37] The fellow eye was randomised to vitrectomy or observation. A total of 62 patients were included, 27 patients were randomised to the vitrectomy group and 35 patients to the observational group. An MH developed in 10 (37%) in the vitrectomy group compared to 14 (40%) in the observation group (P=0.81). This trial was conducted in the early days of macular surgery and ILM peeling was not performed, which may explain the high rate of MH development even in vitrectomised eyes. Optical coherence tomography was also not available, and some of the stage 1 MH may have been misdiagnosed as full-thickness MH.

1.6 Rationale for the studies in this thesis

Some studies on the prevalence of MH have been published, e.g. the Beaver Dam Eye Study and the Baltimore Eye Survey.[18, 19] These studies were conducted before established MH treatment, and at that time, the prevalence was an appropriate measure of the disease burden. MH surgery is well established in today's developed countries, and patients with MH are treated consecutively. Thus, prevalence is no longer a well-suited measure for the disease burden. McCannel et al. investigated the MH incidence in Olmsted County, USA, and Darien-Smith et al. conducted a study on MH incidence in an Australian population.[24, 26] None of these studies applied the OCT-based classification published by the IVTS Group and so far there have been no studies on the MH incidence in Europe.[2] Hence, there is a lack of studies on the incidence of MH, especially studies using OCT to verify the presence of MH. We have studied this in Paper I.

The incidence of MH is reported to be 7.8 persons with MH per 100 000 inhabitants per year and 7–16.7 % of persons with MH in one eye also develop a MH in the fellow eye.[8, 24, 26-32] Hence, the fellow eye of a patient with MH is more likely to develop an MH than an eye in the general population. This indicates that MH formation does not occur by random chance alone; some persons are more susceptible than others. Is it possible to identify the individuals who are at the most significant risk? Paper II address this question.

As discussed in section 1.3, the initial appearance of the Müller cell cone damage may differ. Outer retinal defects, foveal pseudocyst, intraretinal splits, and subfoveal fluid are all retinal abnormalities that are reported to be more frequent in fellow eyes which subsequently develop an MH.[49, 101, 102] Choi et al. found that all fellow eyes with an outer retinal defect subsequently developed an MH.[49] The aforementioned finding could justify a preventive vitrectomy in selected cases, but further studies are needed.

Face-down positioning is still considered by many to be superior to an NSP regimen. Although NSP would ease the postoperative discomfort related to positioning, many surgeons fear that an NSP regimen will decrease the bubble-fovea

contact time. By monitoring the head position during the first 24 hours, it is possible to get an indirect measure of the fovea-fluid contact time. We study this in paper III.

There is a lack of prospective randomised studies comparing air and SF_6 tamponade. The use of air would decrease the postoperative drawbacks related to tamponade. Considering that Forsaa & Krohn demonstrated a 95% closure rate for MH <400 µm, it is possible that air could be equal to or not inferior to SF_6 in the surgical management of MH. This is studied in Paper IV.

2. Aims

This thesis' main aim is to investigate the epidemiology of primary MH and to decrease the burden associated with MH surgery while maintaining good anatomical results.

We specifically aimed to:

1. Investigate the incidence of primary MH in a well-defined Norwegian population, and classify the MHs according to the IVTS classification. (Paper I)

2. Assess the risk of MH formation in the fellow eye, and to evaluate baseline characteristics and OCT features that precede MH formation in the fellow eye. (Paper II)

3. Evaluate the closure rate of MH after nonsupine postoperative positioning, and to investigate the correlation between postoperative positioning compliance and closure rate. (Paper III)

4. Investigate if air is non-inferior compared SF_6 gas for MH ≤400 μm in diameter. (Paper IV)

3. Methods

3.1 Patients and study design

Paper I and Paper II are retrospective studies conducted at the Department of Ophthalmology at Stavanger University Hospital. The Department of Ophthalmology is the only centre for vitreoretinal surgery in Rogaland County and serves a population of approximately 450 000 inhabitants. As some patients in the northern part of the county may be referred elsewhere, only patients living in the southern 18 municipalities of Rogaland County were included (see map Figure 8).

Figure 8. The blue area represents the 18 municipalities studied in Paper I and II.

The patients were identified by a search in our patients' files using the International Classification of Diseases (ICD) procedure code for pars plana vitrectomy, CKD 65. For Paper I this search was for the period January 1, 2008, to December 31, 2014. Macular holes were identified by a manual review of the patients' medical records. Some patients who were not operated due to spontaneous closure, were identified through the screening logs of four prospective studies on MH.

For Paper II, a case-control study, the search was extended to December 31, 2018. The cases in Paper II were the persons who developed an MH in the fellow eye, the controls were the persons with MH in one eye who did not develop an MH in the fellow eye.

Paper III and IV are both prospective multicentre studies conducted at the Departments of Ophthalmology at Stavanger University Hospital, Haukeland University Hospital, Trondheim University Hospital, and the University Hospital of North Norway. For Paper IV, the Department of Ophthalmology at Oslo University

Hospital was added to the study group. Paper III is a prospective multicentre study investigating the closure rate in MH surgery when applying a nonsupine postoperative positioning regimen. Paper IV is a prospective, randomised noninferiority trial.

3.2 Background parameters and outcome measures

In Paper I and II the cause of MH, age, sex, duration of symptoms, laterality, and VA were recorded. Visual acuity was measured using ETDRS or Snellen charts. Optical coherence images of the eye with MH were examined for the presence or absence of VMT and ERM, and the MH was classified according to the IVTS classification.[2]

In Paper I, all images were examined and graded by three retina specialists. In cases with discrepancies, mutual agreement was achieved through discussions. The OCT images in Paper II were only examined and graded by one retina specialist. A spectral domain-OCT of each case in Paper I was exported and used as the basis for schematic macula drawings.

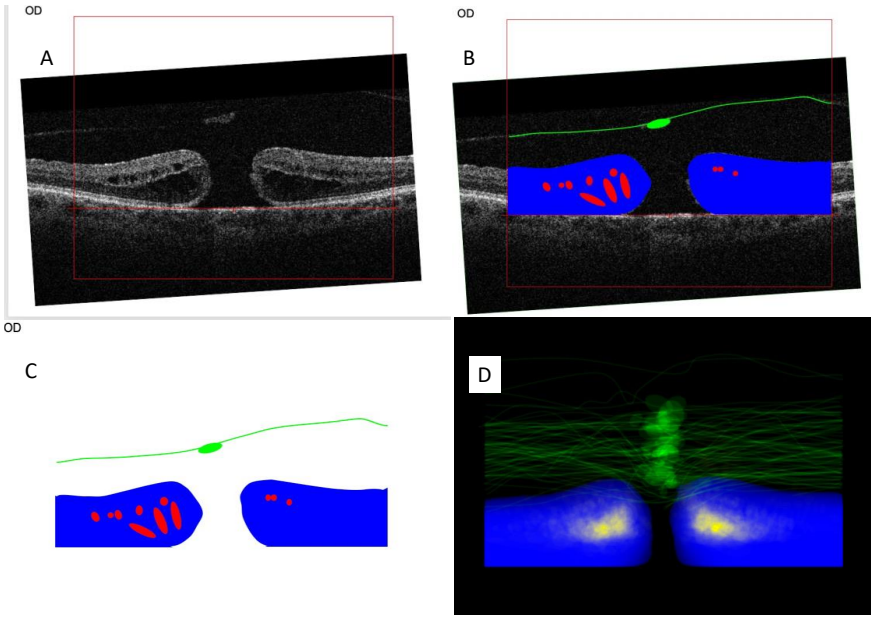

Figure 9. The process of producing superimposed colour coded maps. (A) An OCT image was centred vertically and horizontally. (B) Schematic colour coded drawings of important structures such as the retina contour (blue), intra retinal cysts (red) and posterior hyaloid (green). (C) The drawings were then merged and filtered (D). In (D), intraretinal cysts are coded yellow. © Jørgen Krohn

Images of the left eyes were mirrored, so that all eyes appeared as right eyes. The retinal contour, the shape of the MH, VMT, ERM, intraretinal cysts, posterior hyaloid membrane, and any pseudo-operculum were then drawn by using the drawing tools of PowerPoint (Microsoft Corp., Redmond, WA, USA). Different colours were used to indicate each structure. By using a custom-made MATLAB program (The MathWorks, Natick, MA, USA), the drawings were merged, filtered and presented as colour-coded maps (Figure 9). The colour intensity correlated with the number of overlapping tissue structures.

In Paper II, OCT images of the fellow eye taken at the time the patient presented with an MH in the first eye were reviewed for the presence of VMT, ERM, outer retinal defects, intraretinal cysts, intraretinal splits, and foveolar detachment.

The primary outcome in Paper I was the annual incidence rate of MH, whereas in Paper II the main outcome was the percentage of fellow eyes that subsequently developed an MH. Secondary outcome in Paper II was the difference in frequency of retinal abnormalities in the fellow eyes which develop MH compared to the fellow eyes which did not develop an MH. The status of PVD in the fellow eye was also recorded and classified as follows:

I) No PVD: no signs of PVD; the posterior vitreous cortex is attached to the retinal surface.
II) Perifoveal PVD: the posterior vitreous cortex attached to the fovea but detached from the retinal surface around the fovea.
III) Foveal PVD: the posterior vitreous cortex not attached to the fovea, but attached to the optic disc. Cases where it was difficult to determine the relationship between the vitreous cortex and the optic disc were classified as foveal PVD.
IV) Complete PVD: the posterior vitreous cortex detached from fovea and the optic disc.

In Paper III and IV the age, sex, laterality, intraocular pressure, VA, duration of symptoms, and lens status were recorded. The OCT images of the eye with MH were reviewed for the presence of VMT and ERM, and the MH was classified according to the IVTS classification.

The primary outcome in Paper III and IV was the closure rate after a single surgery confirmed by OCT at least two weeks after surgery. Secondary endpoint in Paper III was the time spent in supine position during the first 24 hours. A positioning measuring device was attached to the patient's forehead. This device was a clock connected to a tilt switch. The clock was activated when the head was in a supine position, and the accumulated time spent in this position was recorded. In Paper IV, subgroup analyses were planned on closure rates for small (≤250 μm) and medium-

sized (>250 µm and ≤400 µm) MH. Secondary endpoints in Paper IV were intraocular pressure (IOP) on the first postoperative day and VA at the last follow-up.

3.3 Surgical procedure (Paper III and IV)

The surgery consisted of a standard 23- or 25-gauge pars plana vitrectomy with induction of posterior hyaloid separation and dye-assisted peeling of the ILM. The ILM peeling was circumferential around the MH, and the ILM peeling size was decided by the individual surgeon. In Paper III, 26–30% SF_6 gas was used as tamponade, whereas in Paper IV the patients were randomised to air or 26% SF_6 gas.

All patients in Paper III followed an NSP regimen for 3–5 days, and all patients in Paper IV followed an NSP regimen for 3 days. In Paper III, the tennis ball technique (TBT) was applied to some patients depending on the surgeons' preferences. The TBT regimen consisted of a tennis ball fastened to the back of the nightshirt to prevent the patient from sleeping in the supine position. This technique was in 2016 proven by Forsaa & Krohn to reduce the time spent in supine position during sleep.[103] All participants in Paper IV used the TBT regimen to decrease the time spent in supine position. In Paper IV, the surgery had to be completed before 12pm to standardise the time spent upright position until bedtime.

Randomisation procedure (Paper IV):

The randomisation procedure took place intraoperatively, immediately after the fluid-air exchange and was performed by a web-based randomisation and data collection system at the Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology, Trondheim, Norway. The randomisation was stratified by small (≤250 µm) and medium-sized (>250 µm and ≤400 µm) MH.

3.4 Statistics

Continuous variables were described by the mean and standard deviation (SD) when normally distributed, otherwise by median and range. Categorical data were

summarised by numbers and proportions. The Student´s t-test was used to compare normally distributed continuous data between independent populations. When continuous data were not normally distributed, the Mann-Whitney U test was applied. The chi-square test or Fisher´s exact test was used to compare categorical values. In Paper I we used the binomial test to compare nasal VMT to temporal VMT. A two-tailed P-value ≤0.05 was considered statistically significant.

Snellen VA scores were converted to logarithm of the minimum angle of resolution (logMAR) for statistical calculations. In Paper III, we used the Benjamini-Hochberg procedure to correct for multiple testing. In Paper I, linear and logistic regression analyses were applied to investigate associations between different OCT parameters, e.g. linear regression analysis on the impact of duration of symptoms on the MH diameter. In the multivariable regression modelling, variables with a *P*-value <0.2 in univariable modelling and variables considered to be of important relevance were included. Backward and forward stepwise variable selections were used to help find the final multivariable models.

The annual incidence rate was reported as the number of persons per 100 000 inhabitants per year with MH (individual incidence) and the number of MHs per 100 000 inhabitants per year (eye incidence). To be able to compare our reported incidence rate with similar studies, the crude incidence was age- and sex-adjusted to the Norwegian population, the 2013 European standard population, the 2000 census figures for the United States white population, and the World Health Organization standard population.[104-107]

In Paper IV, statistical calculations were made separately for all included patients (intention to treat (ITT) group) and for the group of participants without violations to the study protocol (per protocol (PP) group).

Sample size calculations

Paper I and Paper II are retrospective studies. Thus, no sample size calculations were performed. The time period of patient inclusion was chosen because high quality OCT examinations were likely available and MH surgery was well established in the region. Paper III aimed to investigate the correlation between positioning compliance and closure rate. The sample size was calculated using SPSS SamplePower version 3.0 (SPSS, Inc, Chicago, IL, USA). Preliminary data from a previous trial investigating the effect of the TBT regimen was used as basis for the sample calculations.[103] The mean time in supine position was 6 minutes and 34 seconds, and the threshold for non-compliance was set to 30 minutes. As a result, 320 patients were needed to achieve a power of 80%.

The sample size in Paper IV was based on the high closure rates reported in Paper III. Initially, we used the sample size calculator at www.sealedenvelope.com and an anticipated closure rate of 97%. The noninferiority margin was set to 10 percentage points difference in closure rate, power to 80%, and significance level to 2.5%. With these settings, the sample size was estimated to be 92 patients, 46 in each group. However, at the interim analysis, our sample size calculation turned out to be inappropriate. The sample size calculator at www.sealedenvelope.com assumes a normal distribution. As the closure rate approximate 100%, this assumption is no longer valid. A new sample size estimation was performed by simulations of different scenarios. We used the R-package ExactCIdiff to calculate the exact confidence intervals (CI).[108, 109] The simulations showed a required sample size of 150 patients, assuming a success rate of 97.5% among patients with standard treatment and a noninferiority margin of 10 percentage points. If there truly is no difference between the two treatments, 150 patients were required to be 83.7% sure that the lower limit of a two-sided 95% CI will exclude a difference in favour of the SF_6 group of more than 10%.

3.5 Ethical approval

Paper I was a part of a retrospective quality of chart review (Norwegian Center for Research Data (NSD) identifier 22069). An approval by The Regional Committee for Medical and Health Research Ethics was deemed unnecessary by the NSD. Paper II–IV were approved by The Regional Committee for Medical and Health Research Ethics (ref: 2018/954/REK Vest, 2014/879/REK sør-øst B, 2018/785/REK sør-øst C). All four studies adhered to the Declaration of Helsinki. The Regional Committee for Medical and Health Research Ethics decided that informed written consent was not required for participants in Paper II. However, all living potential participants in Paper II was offered the ability to decline study participation. In Paper III and IV, all participants gave their informed written consent prior to study participation.

4. Results

4.1 Paper I

4.1.1 Study group

Between January 1, 2008, and December 31, 2014, 177 eyes with MH in 166 patients were identified. The mean age at the time of diagnosis was 69.3 years (SD, 9 years). A total of 152 eyes in 142 patients (86%) had primary MH, whereas 25 eyes in 25 patients (14%) had secondary MH. Among the 152 eyes with primary MH, 103 (68%) were in female patients. Thus, the male-to-female ratio was 1:2.2. Bilateral MHs occurred in 10 out of 142 patients (7%) with primary MH.

4.1.2 Incidence

The overall crude annual eye incidence in Southern Rogaland was 7.5 MHs per 100 000 inhabitants. When adjusted for age and sex to the Norwegian population, the eye incidence was 9.3 per 100 000 per year. The age and sex-adjusted eye incidence for females and males were 12.8 and 5.9 per 100 000, respectively. Table 2 summarises the incidence rates for primary MHs with age and sex adjustments to relevant reference populations.

Annual incidence per 100 000 inhabitants

	Present Study					Mc Cannel et al.[24] *	Darian-Smith et al.[26] **
	Crude	**Norway[104]**	**Europe 2013[105]**	**USA white population 2000[107]**	**WHO[106]**		
Individual							
All	5.9	7.4	11.1	8.5	4.5	7.8	4.1
Female	8.1	10.0	15.4	12.3	5.9	10.9	
Male	3.9	4.9	6.8	4.5	3.1	4.3	
Eye							
All	6.4	7.9	11.3	8.6	4.8	8.7	
Female	8.7	10.7	15.4	12.3	6.3	12.2	
Male	4.1	5.2	7.2	4.7	3.3	4.8	

Table 2. Incidence rates of primary macular holes with sex-and age-adjusted rates for different reference populations and compared to two relevant previous studies.
*Age and sex-adjusted to the USA white population 2000
** Crude incidence
WHO = World Health Organization

The annual incidence of MH increased with age and peaked in the eighth decade of life (Figure 10).

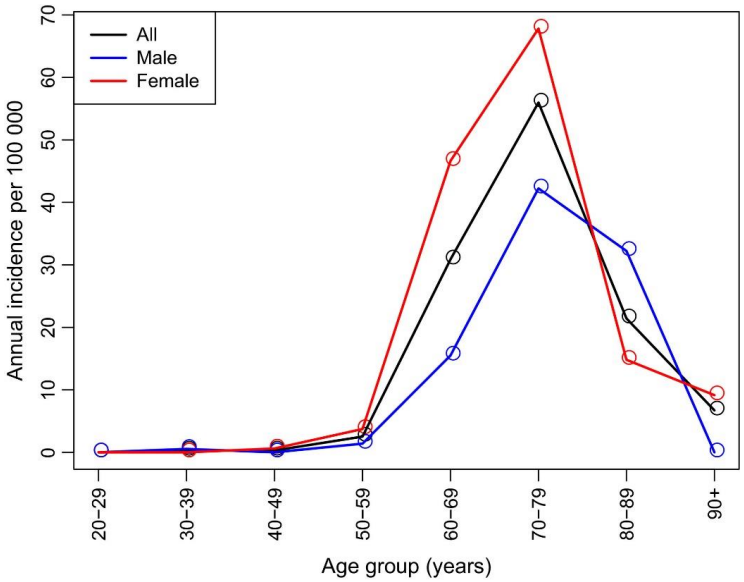

Figure 10. Annual incidence of primary macular holes per 10-year age intervals by sex distribution.

4.1.3 IVTS classification

Of 152 patients with primary MH, 151 patients had an OCT images of sufficient quality to identify morphological structures and information about the vitreoretinal interface. In 150 patients, a macular cube OCT scan was available, making it possible to measure the midline diameter and base diameter of the MHs. The mean MH size was 435 µm (SD=176). Twenty (13%) MH were classified as small, 47 (31%) as medium, and 83 (55%) as large. Vitreomacular traction was present in 52 (34%) eyes and ERM in 55 (36%) eyes. The VMT was more often attached to the nasal side of the MH rim than the temporal side (*P*=0.002) (Figure 11).

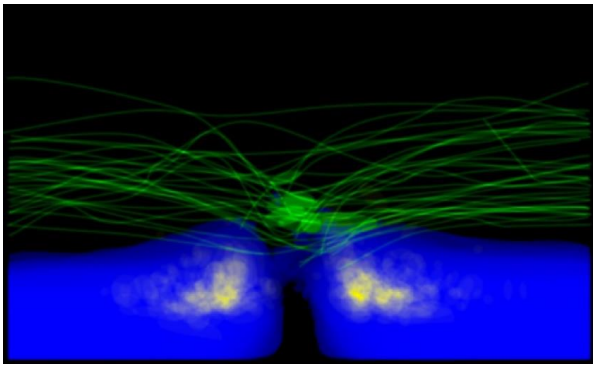

Figure 11. Colour map of merged macular drawings of macular holes with vitreomacular traction. The posterior hyaloid is coded green, intraretinal cysts yellow and retinal contour blue. The right side of the picture represents the nasal side.

4.1.4 Visual function and duration of symptoms.

The mean VA in patients with small MH was 0.55 logMAR (SD=0.16). This was statistically significantly better than the VA eyes with medium or large-sized MH, which presented with 0.63 logMAR (SD=0.17) and 0.75 logMAR (SD=0.21), respectively (P <0.0001). The median duration of symptoms was 5.0 months (range, 1–26). Multivariable linear regression showed that the MH size was highly associated with VA and duration of symptoms (Table 3). Reduced VA and a longer duration of symptoms were associated with larger MH.

Table 3. Multivariable linear regression

	P	*β*	B	95% CI for B	*n*
MH diameter*					
Visual acuity†	<0.0001	0.387	312.5	186–439	149
Duration†	0.004	0.236	7.1	2.4–11.8	127

CI = confidence interval, MH = macular hole, * = Dependent variable. † = Independent variable

4.2 Paper II

4.2.1 Study group

A total of 229 patients underwent surgery for primary MH in the period between January 1, 2008, and December 31, 2018. Twenty patients were classified with bilateral disease of whom six patients presented with bilateral MHs. Among these six patients, two had an old MH in the fellow eye unsuitable for surgery. Two patients had been treated for MH in the fellow eye prior to the study period. Thus, 12 patients subsequently developed an MH in the fellow eye during the study period (bilateral group). In 209 patients with unilateral disease, nine were excluded due to missing OCT images of the fellow eye, one due to poor OCT quality, one because of a prosthesis in the fellow orbit, and another patient was excluded because of previous vitrectomy in the fellow eye. As a result, 197 patients were included in the unilateral group. The mean age in the unilateral group was 70.6 years (SD=8.6), compared to 71.7 years (SD=4.8) in the bilateral group (P=0.5).

The male-to-female ratio was 1:5 in the bilateral group and 1:1.9 in the unilateral group (*P*=0.35)

4.2.2 Risk of bilateral disease

Twenty patients presented with a history of bilateral disease or subsequently developed an MH. Two patients were excluded from the overall risk calculation due to previous surgery in the fellow eye. Thus, the overall risk of bilateral MH formation was 8.8% (95% CI, 5.8–13.2%). The risk of subsequent MH formation was 5.7% (95% CI, 3.3–9.8%). The median observational time was 54 months (range, 3–138 months) and the median time to MH formation in the fellow eye was 17 months (range, 5–83 months).

4.2.3 Optical coherence tomography findings

The posterior vitreous detachment tended to be at a more advanced stage in the unilateral group compared to the bilateral group, but the difference was not statistically significant (Table 4). Outer retinal defects were more common (41.7%) in the bilateral group compared to unilateral group (6.6%) (*P*=0.001). This was the only difference that remained significant after correction for multiple testing. Figure 12 illustrates the risk of MH formation depending on different variables, which were present in the fellow eye at the time the first eye was operated for MH. Among the patients with an outer retinal defect in the fellow eye, 27.8% (95% CI, 12.5–50.9%) of the eyes subsequently developed an MH.

Table 4. Baseline demographics and optical coherence tomography features of the fellow eye.

	Bilateral group (*n* = 12)	Unilateral group (*n* = 197)	*p*
Age, mean (SD), years	71.7 (4.8)	70.6 (8.6)	0.509*
Sex, male/female	2/10	68/129	0.345†
Pseudophakia, *n* (%)	2 (16.7)	31 (15.7)	1.0†
Interval between both eyes, median (range), months	17 (5–83)	NA	
Vitreoretinal relationship, *n* (%)			
No PVD	2 (16.7)	19 (9.6)	0.352†
Perifoveal PVD	7 (58.3)	81 (41.1)	
Foveal PVD	3 (25.0)	74 (37.6)	
Complete PVD	0	23 (11.7)	
Retinal abnormalities, *n* (%)			
VMT	3 (25.0)	33 (16.8)	0.438†
Epiretinal membrane	4 (33.3)	50 (25.4)	0.512†
Outer retinal defects	5 (41.7)	13 (6.6)	**0.001**†
Intraretinal splits	4 (33.3)	27 (13.7)	0.083†
Pseudocysts	4 (33.3)	20 (10.2)	0.036†
Foveolar detachment	0	6 (3.0)	1.0†

MH = macular hole; NA = not applicable; PVD = posterior vitreous detachment; SD = standard deviation; VMT = vitreomacular traction.

* Students t-test.

† Fisher's exact test.

P-values that remained statistically significant after applying the Benjamini-Hochberg procedure for multiple testing are presented in bold.

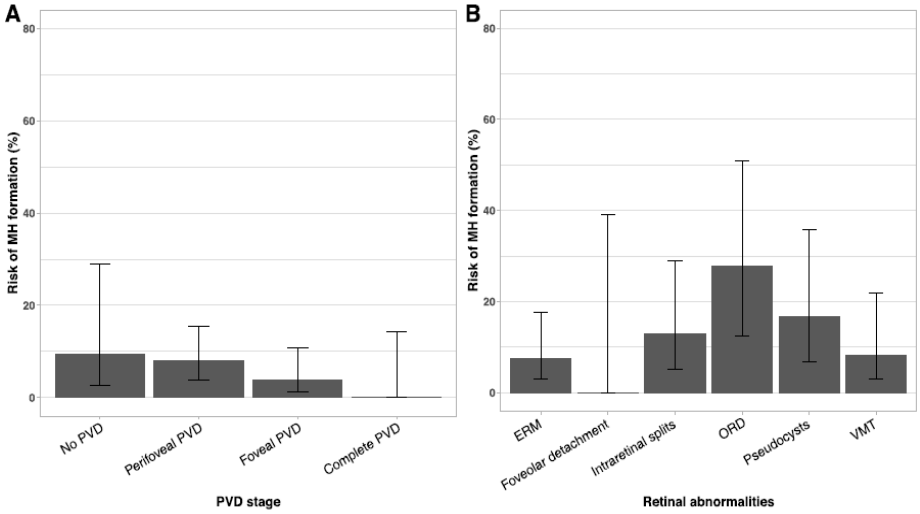

Figure 12. Bar graphs illustrating the risk of subsequent MH formation in the fellow eye depending on (**A**) PVD stage and (**B**) the presence of retinal abnormalities in the fellow eye at the time the first eye was examined for MH.
ERM = epiretinal membrane; MH = macular hole; PVD = posterior vitreous detachment; ORD = outer retinal defects; VMT = vitreomacular traction.

4.2.4 Additional analysis:

After the paper was published, I have done some additional analyses. The risk of MH development in the fellow eye can be considered as a time to event analysis. The Kaplan-Meier estimator was therefore applied to calculate and illustrate the risk of MH formation in the fellow eye. Figure 13 illustrates the cumulative risk of MH formation including 6 patients who presented with bilateral disease.

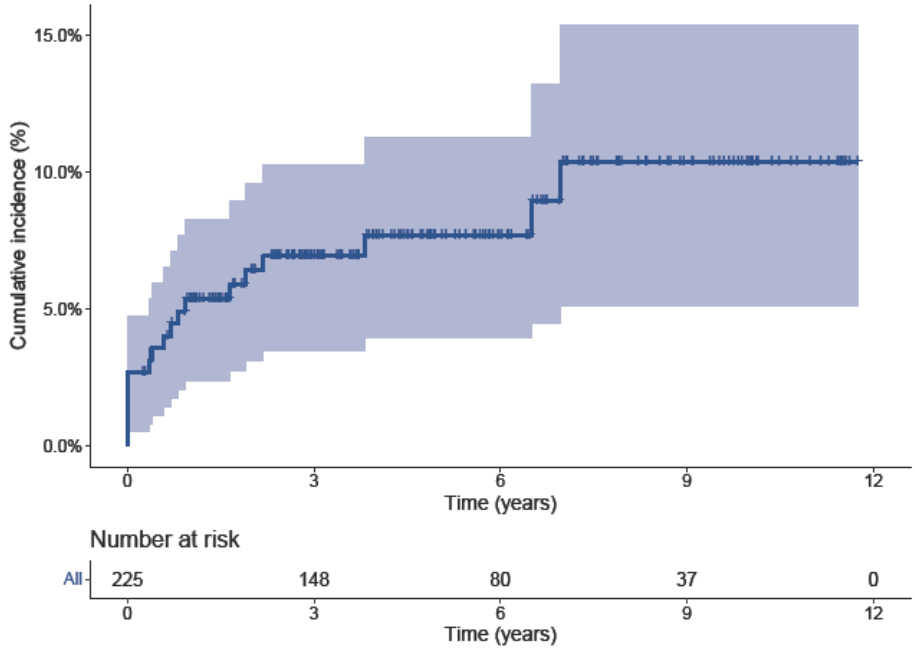

Figure 13. Cumulative incidence curve of macular hole formation in the fellow eye. The blue area represents the 95% confidence interval.

The cumulative risk of MH formation in the fellow eye nine years after MH formation in the first eye was 10.4% (95% CI, 5.1–15.4%). When applying the log-rank test, both outer retinal defects and pseudocysts appeared statistically significantly more often in the bilateral group than in the unilateral group (Table 5).

Table 5. Optical coherence tomography features of the fellow eye.

	Bilateral group (n = 12)	Unilateral group (n = 197)	P
Vitreoretinal relationship, *n* (%)			
No PVD	2 (16.7)	19 (9.6)	0.4**
Perifoveal PVD	7 (58.3)	81 (41.1)	
Foveal PVD	3 (25.0)	74 (37.6)	
Complete PVD	0	23 (11.7)	
Retinal abnormalities, *n* (%)			
VMT	3 (25.0)	33 (16.8)	0.5**
Epiretinal membrane	4 (33.3)	50 (25.4)	0.3**
Outer retinal defects	5 (41.7)	13 (6.6)	**<0.001****
Intraretinal splits	4 (33.3)	27 (13.7)	0.06**
Pseudocysts	4 (33.3)	20 (10.2)	**0.01****
Foveolar detachment	0	6 (3.0)	0.6**

PVD = posterior vitreous detachment; VMT = vitreomacular traction.
P-values that remained statistically significant after applying the Benjamini-Hochberg procedure for multiple testing are presented in bold.
**log-rank test

Figure 14 illustrates the cumulative incidence curve in eyes with a present outer retinal defect compared to those without an outer retinal defect. The cumulative incidence for patients with present outer retinal defect was 36.5% (95% CI, 2.1–58.8%)

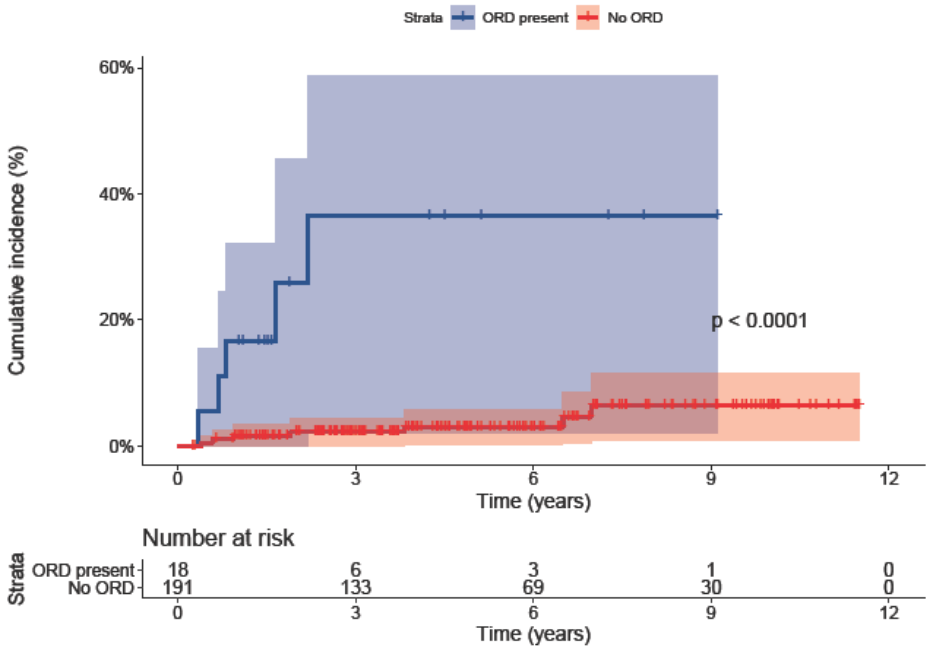

Figure 14. Cumulative incidence curve with corresponding 95% confidence interval in eyes with present ORD compared to those without ORD.
ORD = outer retinal defect.

4.3 Paper III

4.3.1 Participants

A total of 205 participants were enrolled in the study between December 2014 and June 2017. One patient was lost to follow-up due to a stroke and it remained unknown whether this patient´s MH closed or not. Another patient was examined too early after surgery, failing to meet the endpoint measurement criteria, despite the MH was closed 10 days after surgery. A total of 203 patients met the criteria for the closure rate calculation. Four patients had unreliable recorded time spent in supine position and thus were excluded from the compliance calculations.

4.3.2 Anatomic results

Two hundred and two of 203 MHs were closed after single surgery, and the closure rate was thus 99.5% (95% CI, 97.3–99.9%). The study was terminated after inclusion of 205 participants because of the very high closure rate. We considered it unlikely to find a meaningful correlation between compliance and closure rate even with the planned 320 participants.

4.3.3 Patient compliance

Among the 205 enrolled patients, 131 patients used the TBT in addition to the NSP regimen. The overall median time spent in supine position was 29 seconds (range, 00:00:00–01:52:28). Without the TBT, the median time was 1 minute and 21 seconds (range, 00:00:00–01:47:48). Patients using the TBT spent only a median of 19 seconds (range, 00:00:00–01:52:28) in the supine position during the first 24 hours after surgery.

4.4 Paper IV

4.4.1 Participants:

One hundred and fifty patients were included between September 2018 and December 2020, with 75 patients in each group. Fifty MHs were classified as small and 100 MHs as medium-sized MH. The mean age was 69.5 years (SD, 6.8 years)

and 49% of the participants were male. Six patients were excluded from the PP analysis because of violations to the study protocol.

4.4.2 Anatomic results

Intention to treat analysis

Ten of the patients in the air group had an open MH at examination 3–8 days after surgery. Three of them were observed for a few days (range, 3–13 days) to wait for hole closure, which did not happen. All 10 patients with an open MH underwent a second surgery with SF_6 gas installation. No MHs were open in the gas group at the examination 2–8 weeks after surgery. As a result, the closure rate for MH ≤400 μm was 86.7% (95% CI, 76.4–93.1%) in the air group and 100% (95% CI, 93.9–100%) in the gas group. Among the small MH, 21 out of the 22 MHs in the air group closed, whereas all 28 small MHs in the gas group closed.

Per protocol analysis

In the air group, 63 out of 70 patients achieved MH closure. All 74 patients in the gas group achieved closure. Hence, the closure rates for air and gas were 90% (95% CI, 79.9–95.5%) and 100% (95% CI, 93.9–100), respectively. Figure 15 illustrates the differences in closure rates between the air and gas groups for both the ITT and PP analysis. In the subgroup small MH, all 20 patients in the air group and all 28 patients in the gas group achieved primary hole closure. Figure 16 illustrates the closure rate differences between the air and gas group for small and medium-sized MH in the PP analysis.

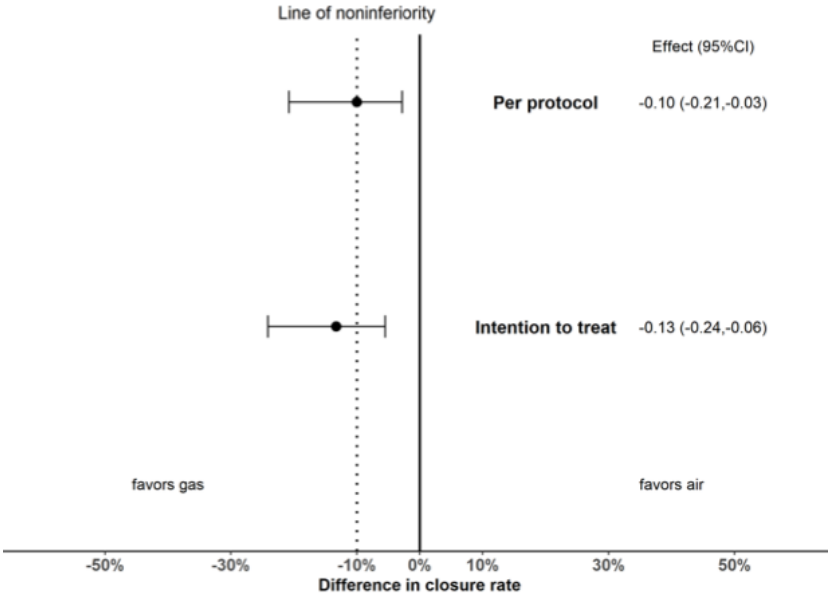

Figure 15. Graph showing the 2-sided 95% confidence interval (CI) for difference in proportions with the noninferiority margin of 10% for both the intention to treat analysis and the per protocol analysis. Noninferiority could not be proven.

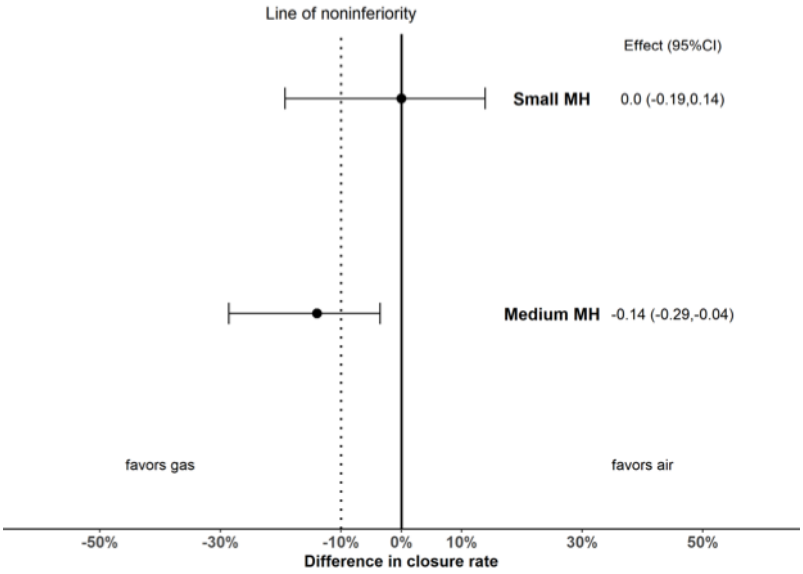

Figure 16. Graph showing the 2-sided 95% confidence intervals (CI) for difference in proportions with the noninferiority margin of 10% for small and medium sized macular holes in the per protocol analysis.

5. Discussion

This section is divided into a discussion of the methods followed by a clinical discussion of the results.

5.1 Methodological discussion

A study's validity can be divided into internal and external validity. The internal validity expresses the degree to which the measured results represent the truth in the studied population. External validity is the study's ability to generalise the results to other populations or settings.[110] The external validity is dependent on a high degree of internal validity. However, a high internal validity does not necessarily imply that the results can be extrapolated to other settings. Measurement errors affect the internal validity and can be divided into random errors and systematic errors.[111] A systematic error, also called bias, skews the results in a specific direction and is not affected by the sample size.[112]

Random error

A random error is the variation in the outcome measure that is due to chance alone. The random error is reduced by increasing the sample size and thereby improving the outcome precision. In both Paper I and Paper II we chose the population of the southern 18 municipalities of Rogaland County as the basis for our investigations. Although the population of southern Rogaland is relatively high, approximately 350 000 in 2014, the outcome event is rare. A larger inclusion area would have gained more patients, but the resulting systematic error would probably cause an underestimation of the incidence; patients living in the outskirts of the abovementioned 18 municipalities are more likely referred elsewhere. To increase the precision of the studies in Paper I and II, we collected data from a long time period. In Paper I we collected data from a period of seven years and in Paper II we collected data from a period of 11 years. Paper II, which is a case-control study, is clearly susceptible to random error. The main outcome event, subsequent MH formation in the fellow eye, occurred only in 12 patients. The random error could have been

further decreased by adding data from additional years or by collaboration with other vitreoretinal clinics. Paper III and IV are both prospective trials and the sample sizes were determined in advance to keep the random error at an acceptable level.

Systematic errors

All four papers in this thesis have some risk of bias. Paper I and Paper II are both retrospective studies and associated with lack of data. Both studies rely on the premise that people with MH will be examined and treated at the Department of Ophthalmology at Stavanger University hospital. Some patients may not notice the MH occurrence, particularly in the non-dominant eye or in an amblyopic eye. Other patients may have been examined for an MH by an external ophthalmologist, but refused to undergo surgery for various reasons. These patients are likely not included in the incidence calculations. Thus, our reported incidence is probably somewhat underestimated. Selection bias occurs when there is a systematic difference between the participants selected for the study compared to those who were not selected, which is the case in Paper I and II. In addition, Paper II relies on the assumption that patients will contact the same eye clinic if they experience an MH formation in the fellow eye. Some patients may not be satisfied with our clinic and motivated to go elsewhere when an MH occurs in the fellow eye. Others may have moved out of the catchment area of Stavanger University Hospital. In Paper III, patients attending an NSP regimen are compared to patients attending an NSP regimen accompanied with the TBT. This division into two groups was not randomised and thus prone to selection bias. However, the purpose of the study was not to compare these two groups and this selection bias is unlikely to influence the primary outcome. Paper III and IV are prone to inclusion bias. People attending a prospective trial may be more compliant than those who choose not to participate. The postoperative compliance is important in MH surgery. If persons who refuse study participation are less compliant, the closure rate may be skewed in the direction of a higher closure rate. Paper IV is a randomised controlled trial and any baseline differences between the groups were due to chance alone. However, the treatment was not blinded neither for the patients nor for the health care providers. Thus, some degree of skewness in

postoperative care may have existed. In cases with air as tamponade, the instructions about avoiding supine position may unconsciously have been more thorough than for patients receiving gas as tamponade.

In Paper I, we tried to improve the measurement bias by using three investigators when reviewing and grading the OCT scans. Some of the retinal abnormalities are subtle and susceptible to misclassification, especially with only one investigator. The observer bias in Paper II would probably have been reduced if multiple investigators took part in the OCT analysis. When analysing the OCT images in Paper II, the investigator was not aware of whether the patient subsequently developed an MH or not, but may have recognised some of the names and thereby be prone to an expectation bias. Furthermore, patients with many OCT examinations on different dates were probably more likely to subsequently have developed an MH in the fellow eye. This systematic error may have overestimated the number of retinal abnormalities in the bilateral group.

Confounding is a variable that is associated with both the dependent and independent variable and blurs the effect of the independent variable on the dependent variable. In Paper II, confounding is probably present. From other studies we know that VMT can be associated with female sex.[113] It would therefore be desirable to establish a statistical model which adjusts for possible confounders and collinearity. However, there were too few cases with subsequent MH formation to allow more than one variable in a logistic regression model. A rule of thumb in logistic regression is that the numbers of variables in a model should not exceed the number of cases or events divided by ten.[114] Although the proportion of women was higher in the bilateral group compared to the unilateral group in Paper II, the difference was not statistically significant. The difference could be due to chance alone or the sample size was too small to detect the difference.

Type I and type II error

Type I error, also called α error or false positive, is to detect a difference that in reality does not exist. To control the type 1 error to 5% or lower, we set the $\alpha \leq 0.05$. The chance of making at least one type 1 error is $1 - (1-\alpha)^n$, where n is the number of statistical tests performed. When multiple statistical testing is performed, the risk of at least one type 1 error increases (Figure 17).

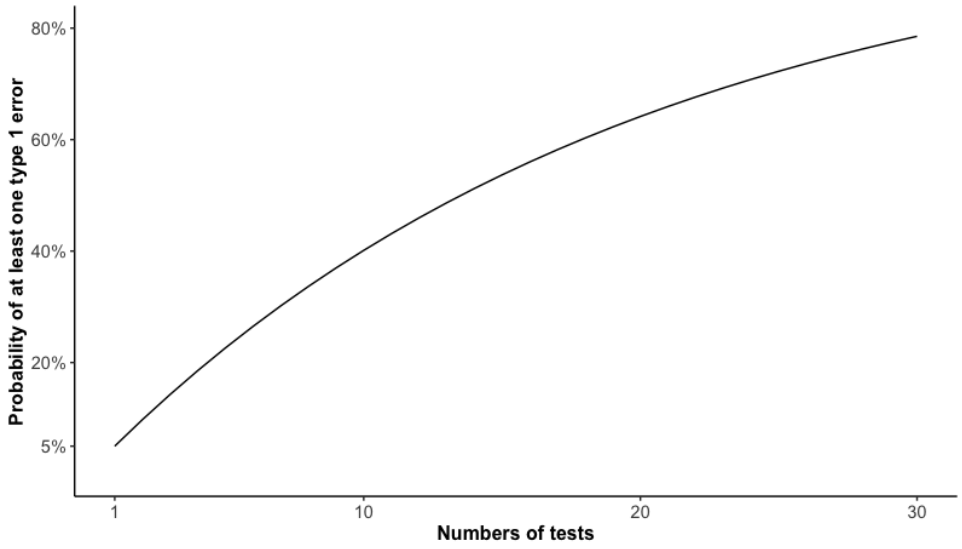

Figure 17. Probability of at least one type 1 error in multiple testing when *P*=0.05.
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In Paper I and III, no measures were taken to keep the false discovery rate low although multiple tests were performed. In Paper II, the Benjamini-Hochberg procedure was applied to keep the false discovery rate below 5%. [115] Multiple testing was also performed in Paper IV. However, it did not affect the primary outcome.
Type II error, also called β error or false negative, is not to detect a difference that exists. To keep the probability of type II error low, scientists calculate the sample size ahead of the study start. The power is equal to 1-β and it is desireable to have a power

of 80% or 90%. However, this only applies to prospective studies. It is not meaningful to do a post hoc power analysis of retrospective studies after the data are collected to help interpret insignificant results.[116, 117] The wide confidence intervals in Paper II indicate that the sample size was too small. The trial described in Paper III ended before the planned 320 participants were included. Given the high closure rates, we realised that we could not consider any correlation between compliance and closure rate. The premise of the power calculation in Paper III was that the closure rate in the non-compliant group was 80%. In retrospect, this assumption was probably false, and the difference in closure rate between compliant and non-compliant patients is perhaps less than assumed. Paper IV's initial sample size calculation assumed normally distributed closure rate data, which is not the case when the closure rates approximate 100%. However, as described in section 3.4, this was corrected, and a new sample size was calculated. The sample size of 150 patients was well suited to detect a possible difference in closure rates. Paper IV also aimed to investigate any difference in closure rates between the air and gas group in small and medium-sized MH. The difference in closure rate in medium holes was statistically significant. But the non-difference in closure rate between air and gas in small MH should be interpreted with caution as the study was not powered to detect such a difference, and the probability of a type II error is substantial.

External validity

Macular hole formation typically occurs in the seventh or eighth decade of life. Incidence rates of MH will therefore vary between populations with different age compositions. The crude incidence of MH is expected to be lower in a young population than in an older population. To compare our incidence rates of MH, we adjusted our incidence rates to different reference populations. Our reported risk of MH formation in the fellow eye is comparable to similar studies.[8, 24, 50] However, when it comes to identifying predictors of MH formation in the fellow eye, Paper II has some problems regarding bias and thereby the internal validity, which affects the external validity. Both Paper III and IV have high internal validity, but it is uncertain whether our results can be generalised. They are both multicentre studies, which

strengthen the external validity. The earlier mentioned inclusion bias affects the external validity. An overview of the number of patients considered eligible, and the number of included patients would help the reader assess the inclusion bias. In addition, we only included patients who had their MH surgery completed before noon. In the everyday clinical setting, surgery often ends after noon. Nevertheless, the external validity in Paper III and IV is probably high.

Ethical considerations

In Paper II, we used OCT to identify intraretinal abnormalities, associated with subsequent MH formation. A reasonable question to raise is, how to handle a potential abnormality that has a high predictive value MH formation? Would we offer newly diagnosed patients with such an abnormality a preventive vitrectomy? The right approach would probably be to address this dilemma in a prospective randomised trial.

The noninferiority design was chosen for Paper IV, and considered the best option when you want to prove that an alternative treatment is not unacceptably worse than the standard treatment. When planning a noninferiority trial, the crucial point is to determine the noninferiority margin. How much can we tolerate that the closure rate is lowered and still recommend air tamponade for our patients? We resolved this issue through a plenary discussion among the vitreoretinal surgeons involved in the study. However, we do not know if this reflects the patients' opinion regarding the noninferiority margin. We could have conducted a qualitative or semi-qualitative study with a questionnaire among well-informed patients to clarify this issue.

5.2 Clinical discussion of the results

The age and sex-adjusted incidence of primary MH was 7.9 eyes per 100 000 inhabitants per year when adjusted to the Norwegian population. Table 2 shows the incidence adjusted to different standard populations and illustrates how important it is to consider the age and sex composition when comparing incidence and prevalence data across diverse populations. Adjusted to the 2000 census for the U.S. white

population, the incidence was 8.6 eyes per 100 000 inhabitants per year. This was almost the same as the findings of McCannel et al. who reported age- and sex-adjusted incidence of 8.7 eyes per 100 000 inhabitants per year in a similar population.[24] In a nationwide registry based study on MH in South-Korea, the reported incidence was 3.14 eyes per 100 000 per year.[118] This study from Cho et al. only included patients who were operated for MH and those covered by the Korean National Health Insurance (NHI) service. The Korean NHI covers 97% of the population and thus cannot explain the low reported incidence alone. However, inclusion bias may explain the low incidence. Only patients who underwent surgery and only patients with the diagnosis code H35.33, from the sixth edition of Korean Classification of Diseases (KCD-6, an adaption of the tenth edition of the International Classification of Diseases [ICD-10]), were included. Thus, a significant proportion of patients with MH may have been excluded from the study. Unfortunately, we were not able to perform age and sex adjustment of our incidence estimates to the same populations as reported by Cho et al. and Darian-Smith al. Direct comparison should therefore be interpreted with cautions. As figure 10 illustrates, the risk of MH formation peaked in the eighth decade of life. This is in accordance with Ali et al. who reported an increasing risk of MH formation until the age of 75.2 years, followed by decreasing risk thereafter.[25] Similar to other epidemiological studies, we found a female predominance. The male-to-female ratio was 1:2.2 in our research. Cho et al. reported a male-to-female ratio of 1:2.15, and Darian-Smith et al. reported a male-to-female ratio of 1:2.[25, 26] It remains unknown why women are more likely to develop MH than men. Chuo et al. found that menopause was a significant risk factor for PVD even after correction for age, and it is known that PVD plays a crucial role in primary MH development.[119] It is thus possible that the postmenopausal drop in oestrogen level increases the likelihood of MH development.[120] We also found that 86% of the MHs were classified as primary, which is in accordance with other studies. McCannel et al. reported 92% to be idiopathic MH, and Darien-Smith et al. reported 87% to be of primary origin.[24, 26] A strength of our study is the OCT verification of all MH. Before OCT was widely available, the MH diagnosis was often based on the results of slit lamp examinations

and symptoms alone. Macular pseudoholes are challenging to differentiate from a full-thickness MH based on fundoscopy alone, and patients with full-thickness MH do not always present with a positive Watzke Allen test.[121] Epidemiological studies on MH should therefore use OCT when diagnosing an MH.

In Paper I, we reported that 7% of the patients have bilateral disease. For Paper II, we extended the 7-year period studied in Paper I to include the four years from 2015 through 2018 in order to further investigate the risk of MH formation in the fellow eye. In Paper II, we reported an overall risk of bilateral MH formation of 8.8% and the risk of subsequent MH formation of 5.7%. This is in accordance with the risk assessments reported by McCannel et al., Furashova & Matthè, and Lewis et al.[10, 24, 50] Other studies have reported higher rates of fellow eye involvement. Choi et al. reported that 14.9% of patients with MH presented with bilateral MH or subsequently developed MH in the fellow eye. Kumagai et al. reported that 16.7% had bilateral involvement within 10 years after an MH occurred in the first eye.[27, 49] Our reported risk probably underestimates the actual risk of bilateral involvement since several patients in the unilateral group may develop MH in the fellow eye after ended data collection. The applied method for risk calculation did not take the differences in observation times into account. As described under section 4.2.4, the Kaplan-Meier estimator is a better method of calculating the risk, as it allows different observation times. When applying the Kaplan-Meier estimator, the overall risk of bilateral involvement in our study population was 10.4% (95% CI, 5.1–15.4%) in our study population. Similar to Kumagai et al., Ezra et al. applied the Kaplan-Meier estimator to calculate the risk of MH in the fellow eye and reported a risk of 15.6%.[28] However, Ezra et al. only included patients without PVD in the fellow eye, thereby overestimating the actual risk of bilateral disease.

No eyes with complete PVD developed MH, but we did not find any statistically significant differences regarding the PVD stage in the fellow eye between the unilateral and bilateral group. It has been demonstrated that complete PVD is negatively associated with MH formation, and it seems likely that foveal PVD is negatively associated with MH formation.[28, 49, 50] However, three patients with foveal

PVD subsequently developed MH. Macular hole development in eyes with foveal PVD has also been described in previous studies.[45, 122] Hence, we cannot exclude MH formation even though the vitreous is detached from the macular region. Bringmann et al. emphasise that damage to the Müller cell cone is essential in MH pathogenesis.[48] The three patients with foveal PVD who subsequently developed MH had an epiretinal membrane at baseline examination. This may have caused tangential traction to a foveola with pre-existing damaged Müller cell cone.

In Paper II, only outer retinal defects were statistically significantly more common in the bilateral group than in the unilateral group. However, when the more appropriate log-rank test was applied, intraretinal pseudocysts were also statistically significantly more common in the bilateral group. This is in accordance with the findings reported by Choi et al. and Takahashi et al.[49, 122] All five patients with an outer retinal defect in the study by Choi et al. subsequently developed an MH, which implies a positive predictive value of 100%. Michalewska et al. conducted a prospective study of 131 fellow eyes in patients with an MH and followed them with OCT examinations every two months for six months.[123] Four out of five patients who developed an MH had an elevation or defect in the photoreceptors prior to MH development. Still, only three out of six patients with an elevation of the photoreceptor layer subsequently developed an MH. It is likely that the lesions, described by Michalewska et al. as triangular elevation of the photoreceptor layer, to some degree equal what we in Paper II and Choi et al. have referred to as outer retinal defects. Thus, the high positive predictive value of outer retinal defects reported by Choi et al. is not confirmed, neither by Paper II nor by the study by Michalewska et al. Patients with MH have significantly more often retinal abnormalities and vitreoretinal interface changes in their fellow eye than in a matched healthy population.[102, 124] Thus, it is difficult to identify a retinal abnormality with a very high positive predictive value. The results of Paper II are valuable when counselling patients about the risk of MH formation in the fellow eye.

In Paper III, we investigated the closure rate after single surgery with SF_6 as tamponade combined with an NSP regimen. The closure rate was 99.5% (95% CI,

97.3–99.9%), and in only one case did the MH not close. Consequently, we could not investigate any correlation between closure rate and compliance. The TBT significantly reduced the time spent in supine position, but we cannot conclude that the this technique improves the closure rate. According to a study by Alberti & la Cour, minor interruptions of the gas-foveal contact do not affect the closure rate.[125] This may be because such minor interruptions last too short and do not allow the fluid to be absorbed by the retinal tissue and cause new tissue swelling. The closure rate in Paper III was surprisingly high considering that it was a multicentre study, and over 50% of the MH were classified as large. The study provides strong evidence for abandoning FDP. However, it is still controversial whether NSP is sufficient to achieve acceptable closure rates. In 2019, two meta-analyses concluded that FDP is unnecessary for MH <400 μm, but significantly increases the closure rate for MH >400 μm.[13, 72] Our study was not a comparison between different positioning regimens and will therefore not affect the results of meta-analysis comparing NSP and FDP in MH surgery. In a registry-based study by Essex et al., NSP was found to be non-inferior to FDP, with a noninferiority margin of 5%.[12] Pasu et al. conducted a prospective randomised trial including only MH ≥400 μm and reported that FDP did not achieve significant higher closure rates compared to NSP. However, the VA three months after surgery was better in the group who attended the FDP regimen.[73]

Paper IV showed that air as tamponade was not non-inferior to SF_6 gas for MH ≤400 μm in diameter. The closure rate for air was statistically significantly lower than for SF_6 gas, and the 95% CI for the difference in closure rate did not exceed the value of 0, neither in the ITT analysis nor in the PP analysis (Fig.15). Thus, air was inferior to SF_6 gas for MH ≤400 μm in diameter. Air was also inferior to SF_6 gas in the subgroup analysis of medium-sized MH. In the subgroup of small MH, the sample size was too small to draw any conclusions. Our study is the largest randomised controlled trial comparing air to SF_6 for MH ≤400 μm in diameter. A meta-analysis from 2022, which aimed to review the effect of different tamponades on the closure rates, found no difference between air and SF_6 gas regarding closure rates.[76] This meta-analysis included only three studies comparing air to SF_6. All three studies were retrospective,

and two of them (Hasegawa et al. and Usui et al.) applied FDP as postoperative positioning regimen.[84, 85] Our study could potentially have altered the conclusion of this meta-analysis. A bubble meniscus height of 60% in the air group on the first postoperative day indicates that air should be sufficient to isolate the MH for at least the first 24 hours after surgery, even when applying an NSP regimen. In a pooled analysis of 11 different studies investigating the time to MH closure, 79.5% of the MH were closed 24 hours after surgery (Paper IV). Hence, a significant proportion of patients requires more than 24 hours to achieve closure. Air does not sufficiently isolate the hole from the intraocular fluid in this group beyond 24 hours after surgery.

All eyes with SF_6 as tamponade in Paper IV achieved primary closure and thereby confirmed the high closure rates achieved by our study group in Paper III using SF_6 gas in combination with an NSP regimen. In conclusion, SF_6 gas should be preferred over air in MH surgery, and an NSP regimen is sufficient to achieve excellent closure rates for MH ≤400 μm. For MH ≤250 μm, air may be considered an alternative to SF_6 gas depending on the patients´ preferences, but this needs to be investigated in future studies.

6. Conclusions and future perspectives

The incidence of primary MH in Norway is similar to comparable populations. Macular holes typically occur in the seventh or eighth decade of life and affect women twice as often as men. Individuals who develop a primary MH in one eye have a significantly increased risk of MH formation in the fellow eye compared to the general population. We identified some intraretinal abnormalities, which indicate an even greater risk of MH formation in the fellow eye. However, we did not find any markers that predict MH formation in the fellow eye with high certainty. An interesting idea is to perform preventive vitrectomy in eyes with an increased risk of MH formation. Future studies on identifying markers of MH formation in fellow eyes should be prospective, longitudinal, and based on regular OCT examinations. We demonstrated excellent closure rates with SF_6 tamponade combined with an NSP regimen even in eyes with large MH. Whether an NSP regimen is non-inferior to an FDP regimen for large MH is still not settled. Air was inferior to SF_6 gas for MH ≤400 μm. However, in the subgroup of small MH (≤250 μm), we think non-inferiority for air compared to SF_6 gas may exist. Future studies on air as a tamponade in MH surgery should focus on small MH. The inconvenience associated with MH surgery has significantly decreased over the last three decades, but there are still issues to study in order to tailor the treatment depending on the preoperative findings and patients´ preferences.

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Acta Ophthalmologica

Epidemiology and morphology of full-thickness macular holes

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ABSTRACT.

Purpose: **To investigate the incidence of full-thickness macular holes (FTMHs) and their morphological features according to the International Vitreomacular Traction Study (IVTS) classification.**

Methods: **The clinical records of all new patients with FTMH, referred between 2008 and 2014, were reviewed for demographics, cause of the FTMH, age at diagnosis, symptom duration, laterality, visual acuity (VA), axial length and lens status. A detailed analysis of the patients' spectral domain optical coherence tomography (SD-OCT) images was performed, and the primary FTMHs were classified in clinical stages according to the IVTS classification. From the SD-OCT, accurate macula drawings were made by means of a computer-drawing software. By merging these drawings and displaying them as colour-coded maps, the morphology and shape of the FTMH were visualized.**

Results: **The study included 177 eyes (152 primary and 25 secondary FTMH) in 166 patients. In primary FTMH, the male-to-female ratio was 1:2.2. The age- and gender-adjusted annual incidences of primary FTMH were 7.9 eyes and 7.4 individuals per 100 000 inhabitants. Mean primary FTMH minimum linear diameter (MLD) and basal diameter (BD) were 435 μm and 872 μm, respectively, and 13% were classified as small, 31% as medium and 55% as large. Vitreomacular traction (VMT) and epiretinal membrane (ERM) were present in 34% and 36% of the eyes, respectively.**

Conclusion: **This study provides data on the incidence rates of FTMH adjusted to different standard populations. The morphological analysis and novel computational visualization technique offer new insight into the structural complexity of FTMH and how VMT and ERM significantly influence FTMH configuration.**

Key words: classification – epidemiology – full-thickness macular hole – incidence – macular hole – morphology

Acta Ophthalmol. 2018: 96: 397–404

doi: 10.1111/aos.13618

Introduction

A full-thickness macular hole (FTMH) can be defined as an anatomical defect in the fovea with interruption of all neural retinal layers from the internal limiting membrane to the retinal pigment epithelium (Duker et al. 2013), causing reduced VA and a central visual field scotoma. The recent IVTS Group defined FTMH as primary when caused by vitreous traction, and secondary when due to other pathological processes (Duker et al. 2013).

Several large-scale population-based studies have reported the prevalence of FTMH to range between 0.2 and 3.3 per 1000 individuals (Rahmani et al. 1996; Mitchell et al. 1997; Wang et al. 2006; Sen et al. 2008). However, data on FTMH epidemiology are scarce, and to the best of our knowledge, only two studies have provided reliable data on the incidence of this condition. McCannel et al. (2009) reported an annual incidence of idiopathic FTMH, adjusted for age and gender, of 7.8 individuals and 8.7 eyes per 100 000 inhabitants in Olmsted County, MN, USA. Darian-Smith et al. (2016) found an annual incidence of 4.1 individuals per 100 000 inhabitants in Tasmania, Australia.

A detailed study on the morphology of FTMH, based on a widely acknowledged classification system and a

nationally representative, epidemiological sample, has not been previously published. The aims of this study were to determine the annual incidence of FTMH in a well-defined Norwegian population, to classify the FTMH according to the IVTS Group classification system (Duker et al. 2013), and to visualize the morphological features of FTMH in this cohort of patients.

Materials and Methods

Patients

The study was conducted at the Department of Ophthalmology at Stavanger University Hospital, which is the only tertiary referral hospital for vitreoretinal surgery in the county of Rogaland. It serves a population of approximately 450 000 inhabitants. A large fjord separates the county into Southern and Northern Rogaland. Only the population of Southern Rogaland, which per January 2014 counted 352 632 inhabitants, was included in this study.

As part of a retrospective quality of care review (Norwegian Social Science Data Services identifier 22069), an initial search was performed in our patient files, using the International Classification of Diseases (ICD) procedure code for pars plana vitrectomy (PPV), CKD 65, for the 7-year period between 1 January 2008 and 31 December 2014. Subsequently, all patients treated for FTMH were identified by a manual review of the patients' records. All patients with newly diagnosed FTMH underwent surgery with exception of a few cases, where the FTMH spontaneously closed prior to planned treatment. The latter were identified through the screening log of four prospective studies on FTMH (Clinical Trials identifiers; NCT02011165, NCT01680068, NCT02028481 and NCT02295943). The study followed the official ethical regulations for clinical research and the tenets of the Declaration of Helsinki.

Background parameters, optical coherence tomography imaging and macula drawings

The following parameters were retrieved from the patient files; gender, cause of the FTMH as defined by the IVTS group (Duker et al. 2013), age at the time of diagnosis, duration of symptoms, laterality, best-corrected visual acuity (BCVA) in logMAR, axial length and lens status. Full-thickness macular holes (FTMHs) were defined as primary or secondary. Based on a detailed analysis of the patients' SD-OCT images, the primary FTMHs were classified in clinical stages according to the IVTS Group classification system, that is small $\leq$250 μm, medium between >250 and $\leq$400 μm, and large >400 μm. (Duker et al. 2013) The FTMH MLD was measured by SD-OCT (Topcon 3D OCT 1000, and Topcon 3D OCT 2000; Topcon Corp., Tokyo, Japan), using the calliper function and software as described in the IVTS Group classification (Duker et al. 2013). The MLD was measured at the narrowest point in the mid-retina, roughly parallel to the retinal pigment epithelium. In addition, the largest BD was measured. The presence of ERM, identified as a hyper-reflective structure on the retinal surface and evident VMT on one or more of the OCT line scans, was also evaluated. All images were reviewed and graded by three retina specialists (VAF, BL and JK), and discrepancies were discussed until mutual agreement was reached.

One SD-OCT image of each case, displaying the correct MLD, was exported and used as the basis for the schematic macula drawings made by the last author (JK). The SD-OCT images of left eyes were flipped across the vertical axis, so that all eyes were displayed as right eyes. The drawing tools of the computer software POWERPOINT (Microsoft, Redmond, WA, USA) were used to manually draw the retinal contour, the shape of the FTMH, intraretinal cysts, ERM and the posterior hyaloid membrane including any pseudo-operculum. Each structure was drawn in different colours. All the drawings were then entered into a database of centrally and horizontally positioned macula drawings. By means of a custom-made MATLAB program (The MathWorks, Natick, MA, USA), the collection of digital macula drawings was divided into separate collections for each vitreoretinal structure and FTMH subgroup. The drawings were subsequently filtered and merged to produce colour-coded maps, where the colour intensity was proportional to the number of overlapping tissue structures. Finally, the structure-specific maps were merged into composite colour maps, where the retina, intraretinal cysts, and any ERM and posterior hyaloid membranes including pseudo-opercula, were represented by shades of blue, yellow, red and green, respectively. Separate colour maps were made for various FTMH subgroups.

Statistical analysis

Annual incidence rates were presented as the number of persons per 100 000 inhabitants per year with FTMH in either or both eyes (individual incidence) and as the number of FTMH per 100 000 inhabitants per year regardless if they occurred as unilateral or bilateral cases (eye incidence). Age- and gender-adjusted annual incidence rates were calculated by direct standardization with 5-year intervals for age using as reference population, respectively, the 2013 European standard population, the 2000 census figures for the United States white population, the World Health Organization (WHO) standard population, and the Norwegian population. Exact population data for the beginning of each year from 2008 to 2015 for Southern Rogaland and all of Norway were obtained from Statistics Norway (2016). From these data, interpolated mid-year populations were found and used in the calculations.

Categorical data were summarized by numbers and proportions, and continuous data were described by mean and standard deviation when normally distributed, otherwise by median and range. The chi-square test was used to analyse differences between categorical data, while the Mann–Whitney *U*-test was used for continuous data. Poisson regression analysis was used to test for differences in crude incidence between genders. The binomial test was used to compare nasal to temporal VMT. Uni- and multivariable linear regression models were applied to evaluate possible associations between diameters (MLD and BD), and other parameters. Dependent variables that were not normally distributed were log-transformed. For the dichotomous response variables VMT and ERM, uni- and multivariable logistic regression modelling were used. In the multivariable regression modelling, variables with a p value <0.2 in univariable modelling and variables considered to be clinically relevant were included. Backward and forward stepwise variable selections were used to help find the final multivariable models.

Two-tailed p values ≤0.05 were considered statistically significant. The statistical analyses were performed using IBM SPSS version 23.0 (SPSS Inc., Chicago, IL, USA) and R3.1.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patients

Between 1 January 2008 and 31 December 2014, the procedure PPV (CKD 65) was performed 1375 times in patients from Southern Rogaland. From these records, 173 eyes with FTMH in 162 patients were identified. In addition, the screening logs of four prospective studies on FTMH revealed four patients with unilateral FTMH. In these cases, the FTMH had closed after cataract surgery prior to the planned vitreoretinal surgery. Thus, the study included a total number of 177 eyes in 166 patients with FTMH. Mean age of the patients at the time of diagnosis was 69.3 years (SD = 9) (range, 27–92 years). A total of 152 eyes in 142 patients (86%) had primary FTMH, and 25 eyes in 25 patients (14%) had secondary FTMH. Secondary FTMHs were caused by retinal detachment in 12 patients, trauma in five, complication to vitreoretinal surgery in five, high myopia in two, and following intravitreal injection of ocriplasmin (Jetrea; Thrombogenics, Leuven, Belgium) in one patient.

One hundred and three of 152 (68%) eyes with primary FTMH were in female patients, corresponding to a male-to-female ratio of 1:2.2. Bilateral primary FTMH occurred in 10 of 142 individuals (7%). Patient demographics and clinical data of the primary versus secondary FTMH and differences between genders are presented in Table 1.

Incidence

All FTMH eye incidence

The overall crude annual incidence of FTMH in Southern Rogaland over the study period was 7.5 per 100 000 inhabitants. The crude annual incidence was found to be 10.4 and 4.7 per 100 000 inhabitants for females and males, respectively. Adjusted for age and gender of the Norwegian population, the annual incidence was 9.3 per 100 000. For females and

Table 1. Demographic and morphological characteristics of primary and secondary full-thickness macular hole (FTMH)

	FTMH				Primary FTMH									
					Gender			IVTS classification						
	Total	Primary	Secondary	p*	*n*	Female	Male	p*	*n*	Small	Medium	Large	p*	*n*
Eyes, *n* (%)	177	152	25			103	49	**<0.0001**	152	20 (13)	47 (31)	83 (55)		150
Right, *n* (%)	99 (56)	88 (58)	11 (44)	0.195	177	55 (53)	33 (67)	0.104	88	12 (60)	31 (66)	44 (53)	0.350	87
Female, *n* (%)	121 (68)	103 (68)	18 (72)	0.673	177					13 (65)	33 (70)	56 (68)	0.905	102
Age, mean (SD), years	69.3 (8.8)	70.2 (7.7)	64.1 (12.9)	**0.028**	177	69.7 (6.9)	71.1 (9.0)	0.116	152	70.3 (6.3)	71.4 (6.3)	69.3 (8.5)	0.400	150
FTMH diameter, mean (SD), μm	445 (201)	435 (176)	524 (349)	0.630	167	442 (183)	422 (160)	0.580	150	182 (40)	325 (47)	560 (127)	**<0.0001**	150
Basal diameter, mean, μm (SD)	892 (385)	872 (333)	1088 (714)	0.380	164	863 (319)	890 (362)	0.982	149	551 (232)	707 (206)	1041 (307)	**<0.0001**	149
VMT, *n* (%)	53 (32)	52 (34)	1 (7)	**0.028**	166	40 (39)	12 (25)	0.075	151	9 (45)	19 (40)	24 (29)	0.241	150
ERM, *n* (%)	60 (36)	55 (36)	5 (33)	0.812	166	28 (27)	27 (55)	**0.001**	151	10 (50)	11 (23)	34 (41)	0.056	150
BCVA, mean logMAR (SD)	0.78 (0.42)	0.68 (0.20)	1.36 (0.77)	**<0.0001**	177	0.70 (0.22)	0.66 (0.17)	0.333	152	0.55 (0.16)	0.63 (0.17)	0.75 (0.21)	**<0.0001**	150
Duration, median, months (range)	5.0 (1–36)	5.0 (1–26)	1.0 (1–36)	**<0.0001**	152	5.0 (1–24)	5.0 (1–26)	0.585	130	3.5 (1–12)	3.5 (1–26)	7.0 (1–24)	**0.001**	128
Axial length, median, mm (range)	23.6 (21.5–31.4)	23.5 (21.5– 28.7)	24.2 (21.5–31.4)	0.055	160	23.2 (21.5–28.7)	23.9 (22.4–28.3)	**0.0002**	141	23.9 (22.4–28.3)	23.3 (21.8–27.9)	23.5 (21.5–28.7)	0.071	139

BCVA = best-corrected visual acuity, ERM = epiretinal membrane, IVTS = International Vitreomacular Traction Study Group, SD = standard deviation, VMT = vitreomacular traction.
*p values based on the chi-square test for categorical variables, the Kruskal-Wallis test when three categorical variables, and the Mann–Whitney *U*-test for two continuous variables. Poisson regression analysis was used to test for differences in crude incidence between genders. Bold numbers indicate significant p values.

Table 2. Incidence of primary full-thickness macular hole (FTMH), with rates adjusted for gender and age compared to different reference populations and to findings in previous studies

	Annual incidence per 100 000 inhabitants						
	Present study						
	Crude	Norway	Europe 2013	USA white population 2000	WHO	Mc Cannel et al.	Darian-Smith et al.
Individual							
All	5.9	7.4	11.1	8.5	4.5	7.8	4.1
Female	8.1	10.0	15.4	12.3	5.9	10.9	
Male	3.9	4.9	6.8	4.5	3.1	4.3	
Eye							
All	6.4	7.9	11.3	8.6	4.8	8.7	
Female	8.7	10.7	15.4	12.3	6.3	12.2	
Male	4.1	5.2	7.2	4.7	3.3	4.8	

WHO = World Health Organization.

males, the adjusted annual incidence was 12.8 and 5.9 per 100 000, respectively.

All FTMH individual incidence

The overall crude annual incidence of individuals with FTMH in one or both eyes was 7.1 per 100 000 inhabitants. The crude annual incidence of individuals with FTMH in one or both eyes was found to be 9.7 and 4.4 per 100 000 for females and males, respectively. Adjusted for age and gender of the Norwegian population, the annual incidence of individuals with FTMH was 8.7 per 100 000. For females and males, the adjusted annual incidence was 11.9 and 5.5 per 100 000, respectively.

Primary FTMH eye incidence

The crude annual incidence of primary FTMH was 6.4 per 100 000. The crude annual incidence was found to be 8.7 and 4.1 per 100 000 for females and males, respectively. Adjusted for age and gender of the Norwegian population, the annual incidence of primary FTMH was 7.9 per 100 000. For females and males, the adjusted annual incidence was 10.7 and 5.2 per 100 000, respectively (Table 2).

Primary FTMH individual incidence

The crude annual incidence of individuals with primary FTMH in one or both eyes was 5.9 per 100 000 inhabitants. The crude annual incidence of individuals with primary FTMH in one or both eyes was found to be 8.1 and 3.9 per 100 000 for females and males, respectively. Adjusted for age and gender of the Norwegian population, the annual incidence of individuals with primary FTMH was 7.4 per 100 000. For females and males, the adjusted annual incidence was 10.0 and 4.9 per 100 000, respectively (Table 2).

Primary FTMH incidences adjusted for different populations

The adjusted annual eye incidence rates standardized to the 2013 European standard population, the 2000 census figures for the United States white population, and the WHO standard population, were 11.3, 8.6 and 4.8 per 100 000 inhabitants, respectively. Similar figures for the adjusted annual individual incidence rates were 11.1, 8.5 and 4.5 (Table 2).

Macula colour maps

Different morphological features of the FTMH were visualized by merging the macula drawings and displaying the overlapping macular structures on the colour-coded maps. In Fig. 1A, all the macular drawings were merged, including both the primary and secondary FTMH with all the tissue structures. The primary FTMHs were divided into two groups according to the median duration of symptoms (Fig. 1B,C). A high number of attachments of the posterior vitreous membranes to the FTMH edges were visualized on the image of FTMH with short symptom duration (Fig. 1B). A larger MLD and BD were seen in the eyes with long symptom duration (Fig. 1C). A gradual increase in MLD was seen in the primary FTMH which were grouped according to the IVTS classification system as small, medium and large (Figs. 1D–F). In these images, a difference in the distribution of intraretinal cysts could also be demonstrated. In the small FTMH, the cysts were clustered closer to the hole, whereas they were more diffusely distributed around the boundaries of the large FTMH. A similar cyst distribution was also found in primary FTMH with and without VMT, respectively (Figs 2A,B). In the eyes with VMT, most of the posterior vitreous membranes were attached to the nasal rim of the FTMH (Fig. 2A). In the eyes with VMT (Fig. 2A) and in eyes without ERM (Fig. 2C), the shape of the macular hole resembled that of a cylinder, whereas it in eyes without VMT (Fig. 2B) and eyes with ERM (Fig. 2D) looked more like an hourglass.

Primary FTMH

IVTS classification

Of the 152 eyes with primary FTMH confirmed by SD-OCT, 151 eyes had SD-OCT images of sufficient quality to reveal detailed morphological and structural information of the macular region and vitreoretinal interface. In 150 of these eyes, a horizontal macular cube scanning protocol was documented, which allowed us to classify the FTMH according to the IVTS. Thirteen per cent ($n = 20$) of the FTMH were classified as small, 31% ($n = 47$) as medium, and 55% ($n = 83$) as large (Table 1). Mean MLD and BD were 435 μm (SD = 176) and 872 μm (SD = 333), respectively.

Visual function and duration of symptoms

In patients with small FTMH, the mean VA was 0.55 logMAR (SD = 0.16), which was significantly better than the mean VA of 0.63 logMAR (SD = 0.17) in the group of medium FTMH and 0.75 logMAR (SD = 0.21) in the group of large FTMH ($p < 0.0001$). The median duration of symptoms in patients with small and medium FTMH was both 3.5 months (range, 1–12 months and 1–26 months, respectively), compared with 7.0 months (range, 1–24 months) in the group with large FTMH ($p = 0.001$).

Multivariable linear regression analysis revealed a highly significant positive association between increasing MLD and low VA. Increasing MLD

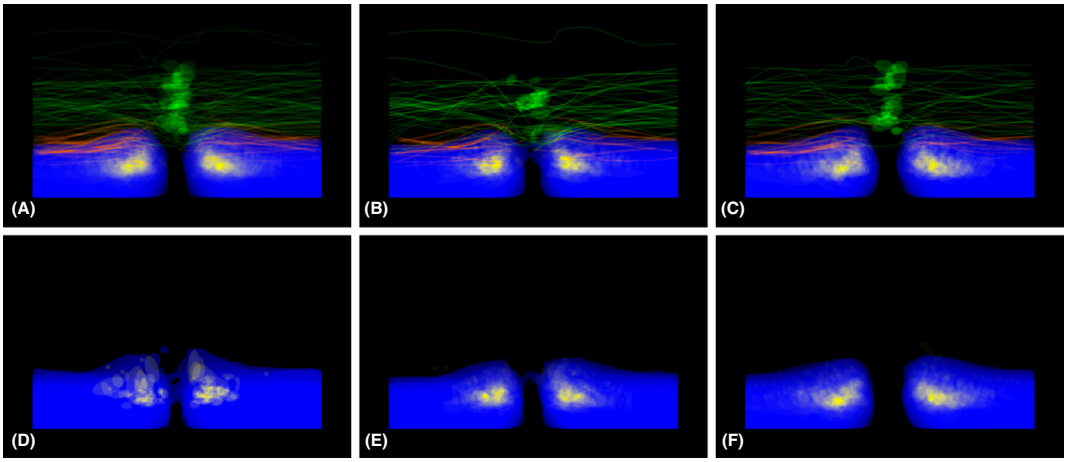

Fig. 1. (A–F) Colour maps made by the merged macula drawings, showing the retina and macular hole configuration (blue), retinal cysts (yellow), epiretinal membranes (red), and posterior hyaloid membranes and pseudo-opercula (green). The nasal and temporal part of the macula corresponds to the right and left side of the images, respectively. Note, that the colour intensity is proportional to the number of overlapping tissue structures. For each macular hole subgroup, the number of merged macula drawings is given in parentheses. (A) All eyes including both primary and secondary full-thickness macular hole (FMTH) with all tissue structures (165). (B) Primary FTMH with a symptom duration of less than or equal to the median value (75). (C) Primary FTMH with a symptom duration longer than the median value (66). (D) Primary FTMH classified as small (≤250 μm) (20). (E) Primary FTMH classified as medium (>250 and ≤400 μm) (47). (F) Primary FTMH classified as large (>400 μm) (83).

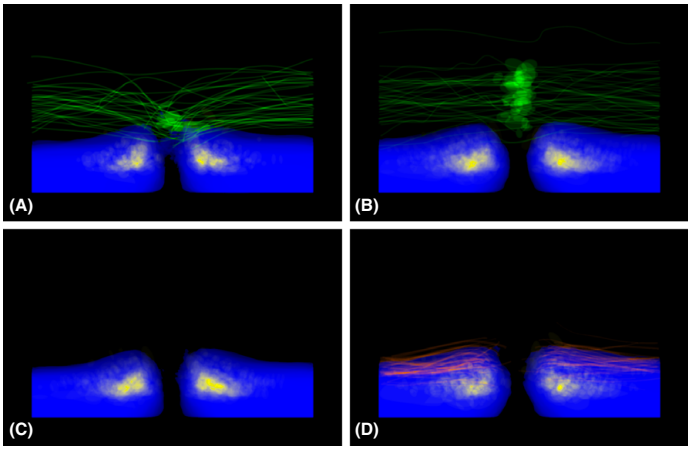

Fig. 2. (A–D) Colour maps made by the merged macula drawings. The image components are as described in Fig. 1. For each macular hole subgroup, the number of merged macula drawings is given in parentheses. (A) Primary full-thickness macular hole (FMTH) with vitreomacular traction (VMT) (52). (B) Primary FTMH without VMT (99). (C) Primary FTMH without epiretinal membrane (ERM) (96). (D) Primary FTMH with ERM (55).

was also significantly associated with long duration of symptoms. Increasing BD had a highly significant positive association with both, low VA and long duration of symptoms. Additionally, a significant positive association between large BD and resolved VMT was found (Table 3 and Fig. 2A,B).

VMT and ERM

On SD-OCT, VMT was present in 52 (34%) eyes and ERM in 55 (36%) eyes (Table 1). Forty-five per cent (n = 9) of the small FTMH had VMT and 50% (n = 10) had ERM. In the group of medium FTMH, 40% (n = 19) had VMT and 23% (n = 11) had ERM, whereas for large macular holes 29% (n = 24) had VMT and 41% (n = 34) had ERM.

The focal area of vitreomacular attachment was significantly more often localized at the nasal than the temporal rim of the FTMH. In 58% (n = 30) of the cases, the vitreous was attached only nasally, in 19% (n = 10) only temporally, and in 23% (n = 12) both nasally and temporally (p = 0.002) (Fig. 2A).

Multivariable logistic regression analysis revealed that when MLD and BD are considered together, the chance of VMT increases with increasing MLD and decreasing BD. Thus, the regression model indicates shape differences where large MLD diameter together with relatively small BD increases the chance of VMT. Significant positive associations were also found between the presence of ERM and reduced MLD, increased BD, male gender and long duration of symptoms (Table 4 and Fig. 2A,B).

The regression models showed that relative large MLD together with small BD increase the likelihood of VMT and absence of ERM, while relative small MLD together with large BD increase the likelihood of resolved VMT and the presence of ERM. This indicates that the shape of the macular hole differs between

Table 3. Multivariable linear regression model

	p	β	B	95% CI for B	*n*
FTMH diameter*					
BCVA	<0.0001	0.387	312.5	186.0–438.9	149
Duration	0.004	0.236	7.10	2.38–11.82	127
Basal diameter†					
BCVA	<0.0001	0.341	546.18	302.58–789.79	148
Duration	0.0002	0.297	17.83	8.64–27.01	126
VMT	0.009	−0.203	−137.42	(−240.19)–(−34.65)	148

BCVA = best-corrected visual acuity, FTMH = full-thickness macular hole, VMT = vitreomacular traction.
Included variables in the multivariable regression analysis: *BCVA, duration, and VMT, †BCVA, duration, VMT and epiretinal membrane.

Table 4. Multivariable logistic regression model

	p	OR	95% CI for OR	*n*
VMT*				
FTMH diameter	0.013	1.004	1.001–1.007	150
Basal diameter	<0.0001	0.996	0.994–0.998	149
ERM†				
FTMH diameter	0.026	0.995	0.991–0.999	150
Basal diameter	0.004	1.003	1.001–1.005	149
Gender	0.007	0.312	0.135–0.726	151
Duration	0.05	1.085	1.000–1.177	129

ERM = epiretinal membrane, FTMH = full-thickness macular hole, VMT = vitreomacular traction.
Included variables in the multivariable regression analysis: *FTMH diameter, basal diameter, gender, ERM, and lens status, †basal diameter, gender, duration and VMT.

patients with VMT and patients with ERM, which is illustrated in Fig. 2.

Difference between genders

In females, the annual incidence of primary FTMH was higher than in males up to the age of 80 years, and this difference reached statistical significance in the 60–69 years group ($p < 0.0001$). From 80 to 89 years of age, the incidence was higher among males, but this difference was not statistically significant ($p = 0.140$) (Fig. 3).

The mean age at diagnosis was 69.7 years (SD = 6.9) for females and 71.1 years (SD = 9.0) for males ($p = 0.116$) (Table 1). The mean MLD in female patients was 442 μm (SD = 183) compared with 422 μm (SD = 160) in males ($p = 0.580$). Neither the VA nor the recorded duration of symptoms differed significantly between genders. Female patients had a mean VA of 0.70 logMAR (SD = 0.22) and a median duration of symptoms of 5.0 months (range, 1–24 months), while the corresponding figures for males were 0.66 logMAR (SD = 0.17) ($p = 0.333$) and 5.0 months (range, 1–26 months) ($p = 0.585$), respectively.

Among the female patients, 39% ($n = 40$) had VMT compared to 25% ($n = 12$) of the male patients ($p = 0.075$). Twenty-seven per cent ($n = 28$) of the females and 55% ($n = 27$) of the males had ERM ($P = 0.001$). The median axial length of female eyes was 23.2 mm (range, 21.5–28.7 mm), and for male eyes it was 23.9 mm (range, 22.4–28.3 mm) ($p = 0.0002$) (Table 1). Multivariable logistic regression analysis revealed a positive association between the presence of ERM and male gender ($p = 0.002$) (Table 4).

Primary versus secondary FTMH

Patients with primary FTMH were significantly older than those with secondary FTMH [70.2 years (SD = 7.7) and 64.1 years (SD = 12.9), respectively ($p = 0.028$)]. Eyes with primary FTMH also had a significantly better VA of 0.68 logMAR (SD = 0.20) compared to 1.36 logMAR (SD = 0.77) in eyes with secondary FTMH ($p < 0.0001$). Patients with primary FTMH had a significantly longer median duration of symptoms compared to those with secondary FTMH (5 months (range, 1–26 months) and 1 month (range, 1–36 months), respectively ($p < 0.0001$) (Table 1).

Discussion

In this study, 86% of the FTMH were classified as primary, which is similar to previously reported rates. McCannel et al. (2009) reported 92% of the macular holes to be idiopathic, whereas

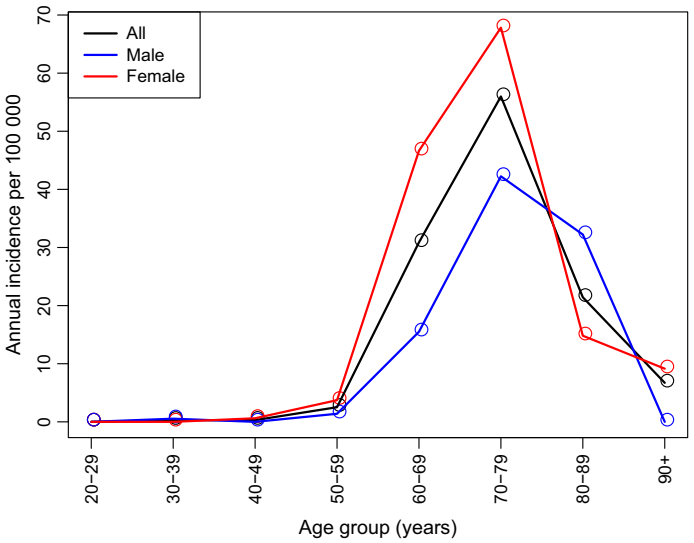

Fig. 3. Annual incidence of primary FTMH per 10-year age intervals by gender. FMTH = full-thickness macular hole.

Darian-Smith et al. (2016) found a frequency of 87% idiopathic macular holes in their material. With a male-to-female ratio of 1:2.2, the expected female predominance in patients with primary FTMH was confirmed. The two previous studies on FTMH incidence found somewhat similar relations; McCannel et al. (2009) reported a male-to-female ratio of 1:3.3 and Darian-Smith et al. (2016) reported a ratio of 1:2. The high proportion of females is also consistent with previous reports on FTMH prevalence, presenting male-to-female ratios varying from 1:1.2 in India to 1:7 in China (Wang et al. 2006; Sen et al. 2008).

Bilateral primary FTMH occurred in 7% of the patients, which is in accordance with the finding of 7% by Darian-Smith et al. (2016). Their mean observation period of 6 years compares well with the 7 years of observation in the present study. McCannel et al. (2009) reported a frequency of 12% bilateral macular holes during 10 years of observation. A prospective observational study found 7% fellow eye involvement after six or more years of follow-up.(Chew et al. 1999) In two studies of fellow eyes without posterior vitreous detachment (PVD) in patients with unilateral FTMH, the estimated risk of fellow eye involvement was found to be 11% and 16% over a period of two and five years, respectively (Ezra et al. 1998; Niwa et al. 2005). In one study not specifying the presence of PVD in fellow eyes, the authors found an incidence rate of bilateral idiopathic FTMH of 13% within 48 months (Lewis et al. 1996). The frequency of 7% fellow eye involvement found in the present study is probably too low. It is likely that a longer period of observation would have resulted in a higher rate of bilateral FTMH, as some patients probably developed a FTMH in the other eye outside the study period.

The present study allows an estimation of FTMH incidence in a northern European, predominantly Caucasian population. The age- and gender-adjusted annual eye incidence of primary FTMH in South Western Norway between 2008 and 2014 was 7.9 per 100 000 inhabitants. As demonstrated in Table 2, the incidence varies greatly between populations. When adjusting our incidence data to other populations, we found an annual FTMH incidence of 11.3 using the 2013 European standard population as reference, and a much lower incidence of 4.8 when the WHO standard population was used. This is a result of differences in the demographic profiles, as the European population is older than the WHO standard population. Such age disparities make direct comparisons of crude incidence rates between populations unreliable and illustrate the needs to report adjusted rates with a common reference population for fair comparisons. When adjusting to the 2000 census for the United States white population, the annual incidence was 8.6 per 100 000 inhabitants. This is similar to the incidence of 8.7 reported by McCannel et al. (2009) in a study from Olmsted County, MN, USA, where they adjust to the same United States white population, and where the study population like ours comprises Caucasians of northern European heritage. In the Australian study from Tasmania by Darian-Smith et al. (2016), there is unfortunately no information on eye incidences. They reported an annual individual incidence of only 4.1 per 100 000 in a population of mainly Caucasian and northern European origin where they adjust to the Australian population. This is considerably lower than the corresponding incidence of 7.4 in the present study, but an extrapolation of the Australian findings to the Norwegian population could not be made.

Our study is the first to provide detailed SD-OCT-derived morphological characteristics of FTMH based on a nationally representative epidemiological data set. The mean MLD was 435 μm, and 55% of the FTMH were classified as large, 31% as medium and 14% as small. Both the MLD and the BD were significantly and positively associated with increased duration of symptoms and reduced VA. Furthermore, increased BD was positively associated with resolved VMT. Forty-five per cent of the small FTMH presented with VMT compared to only 29% of the large FTMH. The same pattern was found in a study by Madi et al. (2015), where the comparable figures were 47% and 10%, respectively. This could be explained by the natural course of the disease, where the initial formation of a primary macular hole is caused by the VMT (Haritoglou et al. 2006). Over time, the FTMH enlarges, and in many cases the VMT spontaneously resolves (Madi et al. 2015). These considerations imply that the distribution of FTMH sizes and presence of VMT can vary substantially by the regional healthcare provision.

Our findings suggest that the release of VMT leads to a relatively greater enlargement of the BD than the MLD. When using multivariable regression to analyse the effect of VMT on the MLD and BD, we found that a small MLD combined with a large BD was inversely associated with the presence of VMT. Consequently, in eyes with VMT, the macular hole looks like a straight cylinder, whereas it may take the form of an hourglass after release of the VMT. This is in accordance with a recent study by Woon et al., who showed that VMT release was the event that had the greatest impact on the increase of the inner diameter of the FTMH. They also found that the BD increased substantially more than the MLD (Woon et al. 2015). Steel et al. (2016) reported that FTMH in a presumably earlier stage with narrow MLD relative to BD, had a greater chance to close following intravitreal ocriplasmin injection. These observations allow us to propose a model of FTMH maturation from a cylinder shape into an hourglass shape, which is accelerated by the release of the VMT. When we performed the same analyses on the effect of ERM on the MLD and BD, we found the opposite pattern. A small MLD combined with a large BD was positively associated with the presence of ERM. This means that the macular hole in eyes with ERM has the shape of an hourglass, whereas it in cases without ERM looks more like a cylinder. It has been postulated that early development of PVD with incomplete vitreoretinal separation in the perifoveal macular region, contributes to ERM in cases with primary FTMH (Johnson 2005; Schumann et al. 2006). Over time, further development and maturation of the ERM takes place and transmission electron microscopy have revealed fibrocellular tissue attached to the ILM in 51% of stage III macular holes compared to 80% in stage IV macular holes (Schumann et al. 2006). This again fits well with our observation of a significant positive association between ERM and duration of symptoms.

We are not aware of previous reports on the considerably higher proportion of nasally compared to temporally located vitreomacular attachments in FTMH. It has earlier been described that the vitreopapillary

adhesion is strong and therefore the last area in the posterior pole to separate during PVD (Foos & Roth 1973; Johnson 2005). We believe that the firm vitreopapillary and peripapillary adherence are a contributing factor to the delayed vitreoretinal separation at the nasal rim of the macular hole.

The female predominance in primary FTMH incidence was strongly significant in the age group of 60–69 years. For the age interval 80–89 years, however, males had the highest incidence rates. Interestingly, the same pattern was found in the material of Darian-Smith et al. (2016). Studies have reported an earlier onset of PVD and a generally higher proportion of PVD in females compared with males (Foos & Wheeler 1982; Yonemoto et al. 1994). Furthermore, a twofold increase in the risk of PVD among females has been reported together with a strong association between PVD and history of menopause (Chuo et al. 2006). There is also evidence that the postmenopausal decline in oestrogen level leads to increased vitreous liquefaction, and that such sudden menopausal hormonal changes increase the likelihood of FTMH (Foos & Wheeler 1982; Larsson & Osterlin 1985; Evans et al. 1998). This has been supported by animal research, where a decreased exposure to sex hormones was associated with a lower concentration of hyaluronan in the vitreous (Larsen 1958). These relations may explain both the differences in FTMH incidences between genders, as well as the trend towards an earlier peak incidence among females.

Our results showed a significantly longer mean axial length in the eyes of male than female FTMH patients. Such gender difference has also has been shown in previous epidemiological studies of general populations (Eysteinsson et al. 2005; Shufelt et al. 2005; Fotedar et al. 2010). The multivariable logistic regression analysis revealed that male FTMH patients had a greater likelihood of coexistent ERM compared to females. We are uncertain how to interpret this finding, which may be coincidental, as the incidence of ERM in the general population has been found to be equally distributed between genders (Klein et al. 1994; Fraser-Bell et al. 2003).

An important limitation of our study is the retrospective data collection, which led to some loss of data and lack of standardization of clinical examinations. The incidences were determined from an observation period of only 7 years, and a longer time interval with a larger sample size would provide more accurate estimates. Further, we cannot completely exclude the possibility that we have missed some patients. Some cases could have been lost due to referral elsewhere or not referred at all, incorrect coding, spontaneous closure or patient's refusal of surgery, and we may therefore have underestimated the actual incidence of FTMH in our region.

In summary, we have classified an epidemiological data set of FTMH according to the new IVTS classification system and determined the annual incidence rates of this condition in our region. Our detailed morphological analysis and the novel computational visualization technique based on SD-OCT have provided new insight into the structural complexity of FTMH and the impact of VMT and ERM on the macular hole configuration.

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Received on April 18th, 2017.
Accepted on September 2nd, 2017.

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Presented in part at the 15th Euretina Congress, Nice, France, September 2015.

Lindtjørn *et al. BMC Ophthalmol (2021) 21:351*
https://doi.org/10.1186/s12886-021-02111-1

BMC Ophthalmology

RESEARCH ARTICLE Open Access

Optical coherence tomography features and risk of macular hole formation in the fellow eye

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Abstract

Background: To investigate the risk of primary macular hole (MH) in the fellow eye, and to evaluate baseline characteristics and optical coherence tomography (OCT) features that precede MH formation in the fellow eye.

Methods: A retrospective review of 229 patients treated for primary MH at Stavanger University Hospital, Norway, from January 2008 through December 2018. The patients were categorised into two groups according to subsequent development of MH in the fellow eye. The OCT findings of the two groups were compared, and associated risk factors for MH formation assessed.

Results: Twenty cases of bilateral MH were identified. The overall bilateral disease risk was 8.8% (95% CI, 5.8–13.2%). Two patients were previously operated in the fellow eye, six patients presented with bilateral MH, and 12 patients subsequently developed MH in the fellow eye. The risk of subsequent MH development was 5.7% (95% CI, 3.3–9.8%). Although the extent of posterior vitreous detachment (PVD) tended to be more progressed in the bilateral group compared with the unilateral group, the difference was not statistically significant. In the bilateral group, 41.7% had outer retinal defects vs 6.6% in the unilateral group ($p = 0.001$), and 33.3% in the bilateral group had intraretinal pseudocysts vs 10.2% in the unilateral group ($p = 0.036$, not significant after multiple testing correction).

Conclusion: Outer retinal defects and intraretinal pseudocysts are associated with an increased risk of MH formation in the fellow eye, and complete PVD indicates a decreased risk of MH formation.

Keywords: Bilateral macular holes - epidemiology - macular hole - optical coherence tomography - risk factors - vitreoretinal surgery

Background

The incidence of primary full-thickness macular hole (MH) is 7.9–8.7 eyes per 100,000 population per year [1, 2]. MH predominately occur in the elderly population with a male-to-female ratio around 1:3 [2]. A small percentage of MHs close spontaneously, varying between 4.0 and 11.5% [3]. If left untreated, the MH size increases over time and severely reduces the visual acuity (VA) to less than 20/200 in the majority of cases [4, 5].

The pathogenesis of MH formation is not yet fully understood. However, it is generally accepted that anteroposterior traction at the vitreoretinal interface is a major contributor to the development of MH [6]. Previous studies on the risk of bilateral MH have estimated the risk to be between 7.0 and 16.7% [1, 2, 4, 7–10]. The use of spectral domain optical coherence tomography (SD-OCT) and swept source optical coherence tomography (SS-OCT) enables detection of subtle retinal abnormalities. Some studies have investigated changes at the vitreoretinal interface and showed that foveal or complete

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posterior vitreous detachment (PVD) indicates a low risk of MH formation [7, 11–13]. Studies on retinal abnormalities in fellow eyes have revealed certain structural changes that are associated with an increased risk of MH formation [7, 11, 14, 15].

Patients with MH often ask for information about the risk of developing MH in their fellow eye, and selected patients with a predicted high risk may require regular follow-up examinations and early surgical intervention. This present study sought to provide some answers to these questions based on the evaluation of retinal morphological changes in the fellow eye of patients with MH. The aims of the study were to determine the risk of developing bilateral MH, and to investigate OCT-based vitreoretinal interface- and intraretinal abnormalities associated with MH formation.

Methods

Study design and participants

This retrospective, observational study was conducted at the Department of Ophthalmology at Stavanger University Hospital in Norway. Stavanger University Hospital is the only referral hospital for vitreoretinal surgery in Rogaland County and serves a population of approximately 450,000 inhabitants. As some residents in the northern part of the county may be referred elsewhere, we only included patients living in the 18 southern municipalities of Rogaland County. The medical records of 276 patients who underwent surgery for MH from January 2008 through December 2018 were reviewed. Inclusion criteria were primary MH with available OCT scans of the fellow eye from the time of primary MH diagnosis or surgery. One patient declined study participation and 46 patients were classified as having secondary MH. We categorised the patients into two groups: A bilateral group comprising subjects who subsequently developed MH in the fellow eye, and a unilateral group with subjects who did not develop MH in the fellow eye during follow-up. Macular OCT imaging was performed at the initial visit and the OCT features of the fellow eye in the two groups were compared.

The study was approved by the Regional Committee for Medical and Health Research Ethics (2018/954 REC west, Norway) and followed the tenets of the Declaration of Helsinki. Written informed consent was sent to all living patients, and the opportunity to decline study participation was offered.

Background parameters and optical coherence tomography imaging

The following patient characteristics were retrieved from the electronic medical records: sex, date of birth, duration of symptoms, laterality, VA in logMAR, date of surgery, and date of death if deceased.

High-resolution OCT images were obtained using SD-OCT or SS-OCT (Topcon 3D OCT 2000 and Topcon DRI OCT Triton; Topcon Corp., Tokyo, Japan) of both eyes when the patient was examined for MH in the first eye. The scanning protocol used for SD-OCT was a macula 3D scan, 512×128 (6×6 mm, spacing 47 µm) centred on the macula, and for the SS-OCT a macula 3D scan, 512×256 (7×7 mm, spacing 23 µm) centred on the macula. The vitreomacular interface of the fellow eye was investigated and the PVD status categorised into the following stages:

I) No PVD: no signs of PVD; the posterior vitreous cortex attached to the retinal surface.
II) Perifoveal PVD: the posterior vitreous cortex attached to the fovea, but detached from the retinal surface around the fovea.
III) Foveal PVD: the posterior vitreous cortex not attached to the fovea, but attached to the optic disc. We classified cases where it was difficult to determine the relationship between the vitreous cortex and the optic disc as foveal PVD.
IV) Complete PVD: the posterior vitreous cortex detached from fovea and the optic disc.

Vitreomacular traction (VMT) was defined as the presence of anatomic distortion of the fovea in combination with perifoveal PVD, as described by Duker et al. [16]. The presence of other retinal abnormalities, such as intraretinal cysts, intraretinal splits, outer retinal defects (ORD), epiretinal membrane (ERM) and foveolar detachment in the central macular region was also registered (Fig. 1). Intraretinal splits were defined as tiny horizontal splits within the foveal region, and intraretinal cysts were defined as round-shaped intraretinal cavities [11, 17].

Statistical analysis

Continuous data were described by mean and standard deviation (SD) when normally distributed, otherwise by median and range. Categorical data were summarised by numbers and proportions. The chi-square test or Fisher's exact test was used for comparing categorical values. The Student's t-test was used to compare normally distributed continuous data, such as age. We used the Wilcoxon signed-rank test to compare related samples. The Wilson score interval was used for estimating binomial proportion confidence intervals (CI). To control the false discovery rate at 0.05, we applied the Benjamini-Hochberg procedure. The statistical analyses and graphics were made using R Project for Statistical Computing, version 4.0.2 (R Foundation for Statistical Computing, Vienna,

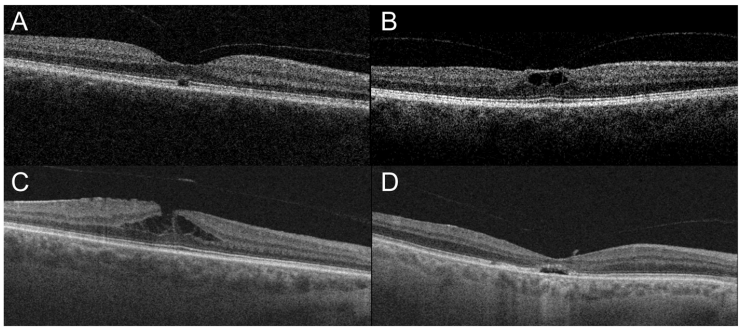

Fig. 1 Optical coherence tomography scans illustrating intraretinal abnormalities we were looking for. **A** Outer retinal defect. **B** Intraretinal pseudocysts. **C** Intraretinal splits. **D** Foveolar detachment

Austria). Two-tailed p-values ≤ 0.05 were considered statistically significant.

Results

Participants

Between January 2008 and December 2018, 229 patients underwent surgery for primary MH. Twenty patients were identified with bilateral disease. Six of the patients presented with bilateral MH, of whom two had an old MH in the fellow eye unsuitable for surgery. Two patients had been operated for a MH in their fellow eye prior to 2008. A total of 12 patients subsequently developed a MH in their fellow eye and were enrolled in the bilateral group. Among the 209 patients with unilateral MH, 9 patients did not have an OCT image of their fellow eye at the initial examination and one patient was excluded due to poor OCT image quality. One patient was excluded due to a prosthesis in the fellow orbit, and one because of previous vitrectomy in the fellow eye. Hence, 197 patients were enrolled in the unilateral group. When calculating the overall risk of bilateral disease, we excluded the two patients with previous surgery in the fellow eye. The mean age at time of operation was 70.6 ± 8.6 years in the unilateral group and 71.7 ± 4.8 years in the bilateral group ($p = 0.50$, Student's t-test). The male-to-female ratio in the bilateral group was 1:5 and 1:1.9 in the unilateral group ($p = 0.35$, Fisher's exact test). Twenty patients presented with a history of MH or subsequently developed a MH in the fellow eye. Hence, the overall risk of bilaterality was 8.8% (95% CI, 5.8–13.2%). The risk of subsequent MH development was 5.7% (95% CI, 3.3–9.8%). Figure 2 illustrates the cumulative frequency of bilateral MH. The median observational time was 54 months (range, 3–138 months). In the bilateral group, the median time interval between the diagnosis of the first and the second MH was 17 months (range, 5–83 months), and 75% of the patients developed the MH in their fellow eye within 32 months. Two of the 12 patients in the bilateral group and 31 of the 197 patients in the unilateral group were pseudophakic in the fellow eye at baseline ($p = 1.0$, Fisher's exact test). In the period until MH development in the fellow eye, two patients in the bilateral group underwent cataract surgery. Consequently, 8 of the 12 patients in the bilateral group were phakic at the time of MH formation in the relevant eye. Table 1 summarises the baseline demographics and OCT features of the two groups.

Optical coherence tomography findings

Foveal PVD in the fellow eye occurred in three patients (25%) in the bilateral group and in 74 patients (37.6%) in the unilateral group ($p = 0.35$). Figure 3 demonstrates the development of MH in a patient with foveal PVD. None of the patients in the bilateral group had a complete PVD compared to 23 patients (11.7%) in the unilateral group ($p = 0.35$). Although not significant, the extent of the PVD in the fellow eye seemed to be more advanced in the unilateral group compared to the bilateral group. The presence of VMT and ERM in the fellow eye was not significantly different between the two groups.

Outer retinal defects were present in 41.7% of the fellow eyes in the bilateral group and in only 6.6% of the fellow eyes in the unilateral group ($p = 0.001$). The presence of ORD had a sensitivity of 41.7% (95% CI, 19.3–68.0%) and specificity of 93.4% (95% CI, 89.0–96.1%) in detecting subsequent MH formation. The presence of pseudocysts was also higher in the bilateral group with 33.3% compared to 10.2% in the unilateral group ($p = 0.036$), but did not remain statistically significant after correction for multiple testing. There were no statistically significant differences regarding the presence of intraretinal

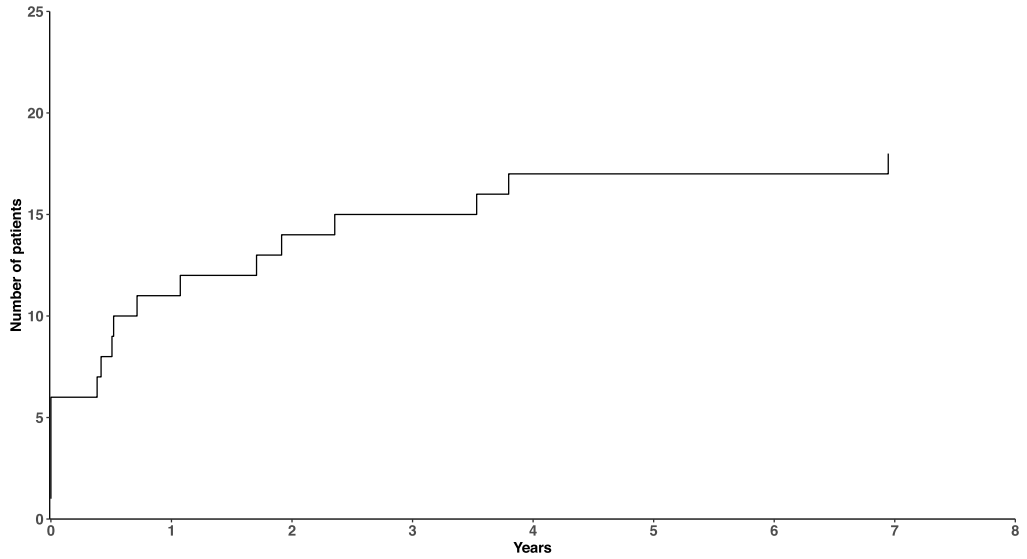

Fig. 2 Cumulative frequency curve of macular hole in the fellow eye after diagnosis of macular hole in the first eye. Six patients who presented with bilateral macular hole at the initial visit were included

Table 1 Baseline demographics and optical coherence tomography features of the fellow eye

	Bilateral group ($n = 12$)	Unilateral group ($n = 197$)	*P*
Age, mean (SD), years	71.7 (4.8)	70.6 (8.6)	0.509*
Sex, male/female	2/10	68/129	0.345†
Pseudophakia, *n* (%)	2 (16.7)	31 (15.7)	1.0†
Interval between both eyes, median (range), months	17 (5–83)	NA	
Vitreoretinal relationship, *n* (%)			
No PVD	2 (16.7)	19 (9.6)	0.352†
Perifoveal PVD	7 (58.3)	81 (41.1)	
Foveal PVD	3 (25.0)	74 (37.6)	
Complete PVD	0	23 (11.7)	
Retinal abnormalities, *n* (%)			
VMT	3 (25.0)	33 (16.8)	0.438†
Epiretinal membrane	4 (33.3)	50 (25.4)	0.512†
Outer retinal defects	5 (41.7)	13 (6.6)	**0.001†**
Intraretinal splits	4 (33.3)	27 (13.7)	0.083†
Pseudocysts	4 (33.3)	20 (10.2)	0.036†
Foveolar detachment	0	6 (3.0)	1.0†

MH Macular hole, *NA* Not applicable, *PVD* Posterior vitreous detachment, *SD* Standard deviation, *VMT* Vitreomacular traction

* Students t-test.

† Fisher's exact test.

p-values that remain statistically significant after applying the Benjamini-Hochberg procedure for multiple testing are presented in bold.

splits and foveolar detachment. All three patients in the bilateral group with foveal PVD in the fellow eye displayed ERM, ORD and a visible pseudo-operculum in the same eye. Among the patients with ORD in the fellow eye, 27.8% (95% CI, 12.5–50.9%) subsequently developed a MH. The presence of ORD was the strongest predictor of MH development in the fellow eye (Fig. 4). Table 2 shows a comparison of VA, MH diameter and duration of symptoms between the first and the second eye, for which no significant differences were found.

Discussion

In this study, we found an overall risk of bilateral MH of 8.8%, illustrating a profoundly higher probability of MH in the fellow eye compared to the risk of first eye MH in the general population [1, 2]. The risk of subsequent MH formation was 5.7%. These results are in accordance with those of McCannel et al., Furashova & Matthè, and Lewis et al. [2, 4, 18]. Other studies however, have reported a higher risk of bilateral MH formation [7, 8]. Ezra et al. reported a bilateral risk of 15.6%, but their study was based on a subgroup of fellow eyes without PVD, which may have caused overestimation of the overall risk of bilateral MH formation [9]. Ali et al. reported that Asian-Americans had a 177% increased risk of MH formation compared to Caucasians [19]. Ethnic susceptibility to MH formation may partly explain why Kumagai et al. and

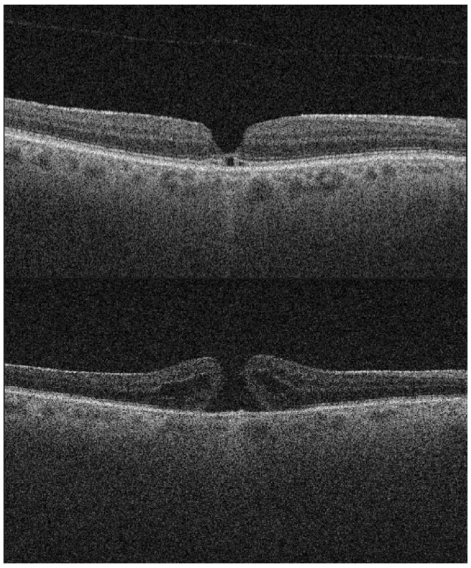

Fig. 3 The upper image shows an optical coherence tomography scan of the fellow eye of a patient with macular hole at the initial visit. Outer retinal defects, foveal posterior vitreous detachment and a thin epiretinal membrane are present. The lower image, captured four months later, shows that the patient has developed a full-thickness macular hole

Choi et al. reported a higher risk of bilateral MH formation [7, 8]. Our calculated risk may be underestimated as individuals in the unilateral group may develop a MH in the fellow eye after ended data collection. Our study relied on the high probability of patients developing a MH in their fellow eye being readmitted to the Stavanger University Hospital. Still, we cannot fully exclude the risk that some patients have moved out of our catchment area or been referred elsewhere with a MH in the fellow eye. We did not investigate the family history of MH in our patients. Kay et al. reported a significantly higher frequency of MH among family members of patients with bilateral MHs, which may indicate a genetic predisposition in some individuals [20].

Although not statistically significant, PVD had reached a more progressed stage in the unilateral group, and no fellow eye with complete PVD developed full-thickness MH. Several studies have demonstrated that complete PVD is negatively associated with the development of MH [7, 18]. Surprisingly, three eyes with foveal PVD subsequently progressed to a full-thickness MH. Hence, VMT is not the only contributor to MH development and foveal or complete PVD does not rule out the possibility of MH formation. However, the presence of ORD and a pseudo-operculum in these three cases indicate previous vitreomacular traction and a weakened foveal structure. In a study by Takahashi et al., five out of 16 patients with foveal PVD subsequently developed a MH [11]. Besirli & Johnson described two cases with foveal PVD who developed MH, where OCT imaging revealed foveal contour irregularities consistent with previous vitreomacular traction [21]. Peeling of the internal limiting membrane improves the closure rates after MH surgery, which indicates the presence of tangential traction forces on the retinal surface [22]. In a prospective study on 34 individuals with lamellar MH, Bottoni et al. detected two patients with PVD and concomitant ERM who subsequently developed full-thickness MH [23]. A post hoc evaluation of the three patients with foveal PVD and MH formation in our study revealed that two of the cases had a thick ERM and one had a thin ERM. Recently, Bringmann et al. described different modes of MH formation and emphasised that MH formation is caused by disruption of both Müller cell cones and the external limiting membrane [24]. A plausible theory explaining our three cases with foveal PVD and MH formation, is that initially, vitreomacular traction caused structural damage to the fovea. Subsequently, this vulnerability facilitated the formation of a full-thickness MH induced by tangential traction by the ERM on the retinal surface.

Outer retinal defects were significantly more frequent in the bilateral group. In accordance with Choi et al., we found the presence of ORD to have the highest positive predictive value of developing MH, with a sensitivity of 41.7% in predicting MH formation [7]. However, while Choi et al. reported a specificity of 100%, we found it to be 93.4%. In our study, five out of 18 patients with ORD developed a MH. In contrast, all five eyes with ORD in the study by Choi et al. developed a MH. Nevertheless, many of our patients in the unilateral group had retinal abnormalities in the fellow eye. This is in accordance with the findings of Chhablani et al. and Kumagai et al., reporting that retinal abnormalities and vitreofoveal interface changes are more common in fellow eyes of patients with MH than in a matched healthy population [15, 25].

In the bilateral group, we found no significant differences between the first and the second eye regarding preoperative VA, MH size or duration of symptoms. One would expect that patients would seek medical assistance at an earlier stage when suffering from a MH in their fellow eye. In Norway, patients need a referral from a health care professional to access specialised hospital departments, which may explain some of the delay from onset of symptoms to treatment.

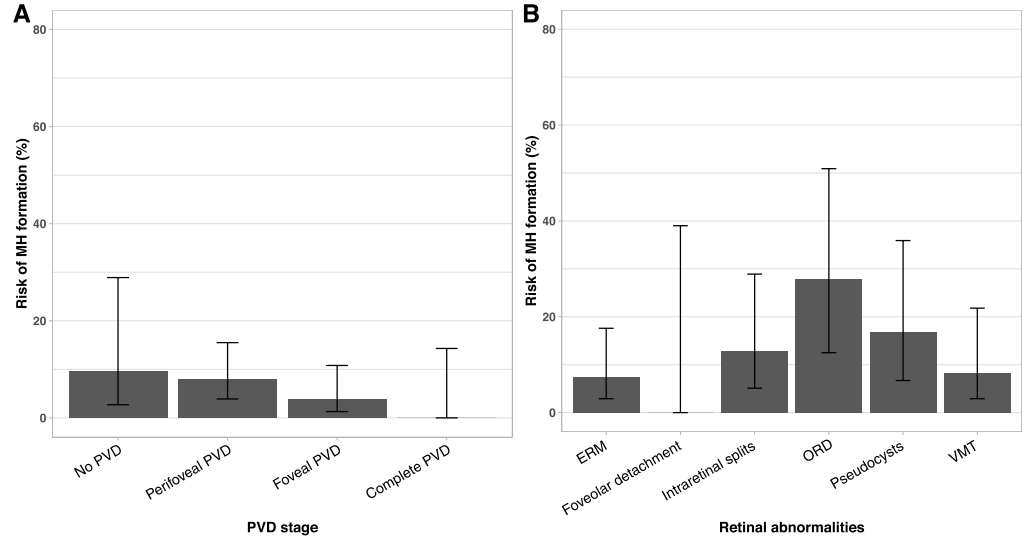

Fig. 4 Bar graph illustrating the risk of subsequent MH formation in the fellow eye depending on **A** PVD stage and **B** the presence of retinal abnormalities. ERM = epiretinal membrane; MH = macular hole; PVD = posterior vitreous detachment; ORD = outer retinal defects; VMT = vitreomacular traction

Table 2 Comparison of first and second eye in the bilateral group

	First eye	Second eye	*P*
Preoperative VA, mean (SD), logMAR	0.63 (0.14) (*n*=10)	0.63 (0.19) (*n*=12)	0.81*
MH diameter, mean (SD), µm	356 (177) (*n*=12)	388 (169) (*n*=12)	0.52*
Duration of symptoms, median (range), months	5 (1−8) (*n*=10)	4 (1−12) (*n*=12)	0.76*

MH Macular hole, *SD* Standard deviation, *VA* Visual acuity

* Wilcoxon signed-rank test

The present study has several limitations including its retrospective design and a relatively small sample size. We only examined the OCT images of the fellow eye captured at the time when the first eye was examined for a MH. A longitudinal study design with repeated OCT examinations could have revealed other transient retinal abnormalities and vitreoretinal interface changes. OCT images were available for 94% of the fellow eyes in the unilateral group and for all of the fellow eyes that subsequently developed MH. Due to the retrospective study design, two different OCT systems, SS-OCT and SD-OCT, were used in the study. SS-OCT provides narrower spacing and better detection of deeper signals, posterior to the retinal pigment epithelium (RPE). However, both SS-OCT and SD-OCT use the Fourier domain detection techniques and allow detection of subtle retinal changes anterior to the RPE [26].

Conclusion

Our study provides useful information when counselling patients with MH. This patient group has a substantially increased risk of developing a MH in the fellow eye compared to the general population. The presence of complete PVD indicates a minimal risk of developing a MH, while the presence of ORD reveals a significantly higher risk of MH formation.

Abbreviations

CI: Confidence interval; ERM: Epiretinal membrane; MH: Macular hole; OCT: Optical coherence tomography; ORD: Outer retinal defects; PVD: Posterior vitreous detachment; RPE: Retinal pigment epithelium; SD: Standard deviation; SD-OCT: Spectral domain optical coherence tomography; SS-OCT: Swept source optical coherence tomography; VA: Visual acuity; VMT: Vitreomacular traction.

Acknowledgements

Not applicable.

Authors' contributions
BL, JK and VAF contributed to the study conception and design. Measurements, data collection and data analysis were performed by BL. BL wrote the first manuscript draft. BL, JK and VAF contributed in the commenting and editing process of the manuscript. All authors have read and approved the final version of the manuscript.

Funding
This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Availability of data and materials
The dataset is available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study was approved by the Regional Committee for Medical and Health Research Ethics (2018/954 REC west, Norway). Passive informed consent was obtained from all living patients included in the study. A letter informing about the study was sent to all living patients who had underwent MH surgery at Stavanger University Hospital from 2008 to 2018. Patients who wished to decline participation, could contact us by letter, e-mail, SMS or phone. The regional ethic committee approved this method of consent. All data were anonymised before use.

Consent for publication
Not applicable.

Competing interests
None of the authors have any conflicting interests to disclose.

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Received: 9 May 2021 Accepted: 16 September 2021
Published online: 29 September 2021

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Publisher's Note

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Nonsupine Positioning after Macular Hole Surgery

A Prospective Multicenter Study

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Purpose: To evaluate the postoperative closure rate of full-thickness macular holes (MHs) after nonsupine positioning, which means that the patients avoid upward gaze and a supine sleeping position, and to investigate the correlation between postoperative positioning compliance and closure rate.

Design: Prospective, multicenter study (ClinicalTrials.gov identifier, NCT02295943).

Participants: Patients undergoing primary surgery for primary MH.

Methods: Patients underwent pars plana vitrectomy with internal limiting membrane peeling and sulfur hexafluoride gas tamponade followed by 3 to 5 days of nonsupine positioning. A positioning measuring device that recorded the time spent in the supine position was attached to patients' forehead after surgery for 24 hours.

Main Outcome Measures: Anatomic closure rate of MH at 2 weeks or more after surgery and the time spent in supine position during the first 24 hours after surgery.

Results: A total of 205 participants were included, of whom 2 were lost to follow-up. Two hundred two of 203 MHs closed after a single operation, giving a closure rate of 99.5% (95% confidence interval, 97.3%−99.9%). The median time of supine positioning during the first 24 hours was 28 seconds (range, 0:00:00−01:52:28). Because of the very high closure rate, a correlation between positioning compliance and closure rate could not be established.

Conclusions: Pars plana vitrectomy with internal limiting membrane peeling followed by a short-term nonsupine positioning accomplished a very high MH closure rate. Thus, face-down positioning was not necessary to achieve excellent closure rates in this study. *Ophthalmology Retina 2019;3:388-392 © 2018 by the American Academy of Ophthalmology*

See Editorial on page 385.

Full-thickness macular hole (MH) has an incidence of 7.9 eyes per 100 000 persons per year, and the condition has a significant impact on the quality of life of affected individuals.[1,2] Surgery normally consists of pars plana vitrectomy, peeling of the internal limiting membrane (ILM), and insufflation of an intraocular gas. The main effect of the gas tamponade is to isolate the MH from intraocular fluid. This, in turn, allows for absorption of the subfoveal fluid by the retinal pigment epithelium, and finally, fusion of the retinal edges.[3] Face-down positioning ensures that the MH is sufficiently isolated from the intraocular fluid. However, the postoperative face-down regimen is challenging for patients, and strict patient compliance is rarely achieved.[4,5] Because Tornambe et al[6] reported successful MH surgery without postoperative face-down positioning in 1997, there is growing evidence supporting a postoperative regimen in which patients avoid upward gaze and a supine sleeping position.[7–10]

The most critical period after surgery is the first 24 hours, in which 82% of the MHs close.[11] If an MH does not close during the first 3 days, it is likely to remain open.[12] We consider a continuous gas−fovea contact during the first postoperative 24 hours to be essential to achieve MH closure. This point is supported by our previous study on air tamponade in combination with a nonsupine positioning (NSP) regimen in which only 70% of MHs closed.[11] Possibly, the rapid absorption of intraocular air allowed early contact between the intraocular fluid and the hole, leading to an interrupted healing process. There is probably a threshold for the duration an MH can be in contact with fluid without interfering with the healing and closure of the hole.

Patients who assume a supine position for some periods will have longer fluid−foveal contact than compliant patients. By measuring the time spent in the supine position, hereafter called *supine time*, we obtained an indirect measurement of the fluid−foveal contact. The main objectives of the present study were to evaluate the MH closure rate after an NSP regimen and to investigate the correlation between the closure rate and the duration of fluid−foveal contact.

https://doi.org/10.1016/j.oret.2018.12.006
ISSN 2468-6530/19

Methods

Study Design and Participants

This prospective, multicenter study was conducted at the Departments of Ophthalmology at Stavanger University Hospital, Haukeland University Hospital, Trondheim University Hospital, and the University Hospital of North Norway between December 2014 and November 2017. We obtained informed written consent from all participants. The study was approved by the Regional Committee for Medical and Health Research Ethics, South-East Norway, and complied with the tenets of the Declaration of Helsinki. The study is registered at ClinicalTrials.gov with the identifier NCT02295943.

Inclusion criteria were primary MH, duration of symptoms of less than 24 months, and written informed consent. Exclusion criteria were previous vitrectomy, secondary MH, myopia of more than 6 diopters, and age younger than 18 years. The primary outcome measure was primary anatomic closure of the MH assessed by OCT 2 weeks or more after surgery.

Ophthalmologic Examination and Surgical Procedures

Preoperative examination consisted of visual acuity (VA) assessment, Goldmann applanation tonometry, slit-lamp biomicroscopy, funduscopy, and OCT imaging of the macula. Visual acuity was measured using Early Treatment Diabetic Retinopathy Study (ETDRS) or Snellen charts. When a Snellen chart was used, VA was converted to logarithm of the minimum angle of resolution (logMAR) units for statistical analysis.[13] The participants also were asked their preferred sleeping position, and the investigators scored the expected patient compliance to the forthcoming postoperative positioning regimen on a 4-point scale (0 = no compliance to 3 = very high compliance). This scoring of expected patient compliance was based on a purely subjective evaluation of the study participants' behavior and response during the preoperative examination. The size of the MH was defined as its minimum horizontal linear diameter and classified according to the International Vitreomacular Traction Study Group classification.[14]

Ten experienced surgeons (including BL, DA, KF, OH, PV, SB, and VF) performed the surgeries, which consisted of a standard 3-port pars plana vitrectomy with induction of posterior hyaloid separation and dye-assisted peeling of the ILM. Subsequently, the diameter of the ILM peeling was estimated in optic disc diameters before intraocular sulfur hexafluoride (26%−30%) was installed. In phakic patients, the decision to perform a phacovitrectomy or a sole vitrectomy was made by the surgeon.

Immediately after the surgery, a positioning measuring device was attached to the patient's forehead, as previously described.[15] Briefly, this device consists of a tilt switch connected to a watch capable of recording the accumulated time the patient has kept the head in the supine position. If a patient positioned face down, the measuring device was not activated, and the time spent in the face-down position was recorded as NSP. The patients were instructed to follow an NSP regimen, which meant that they could maintain their daily activities but had to avoid upward gaze and a supine sleeping position at any time for 3 to 5 days after surgery. Based on the surgeon's preference, the tennis ball technique (TBT) could be applied. The TBT regimen consisted of a tennis ball attached to the back of the nightshirt during sleep to prevent the patient from sleeping in a supine position. No patients were instructed to position face down.

On the following day, approximately 24 hours after surgery, the total time the patient had spent in the supine position was recorded. The patients' compliance was categorized into 3 levels, as described earlier:[15] compliant, with less than 1 minute of supine time; moderately compliant, with 1 to 30 minutes of supine time; and noncompliant, with more than 30 minutes of supine time. Two weeks or more after surgery, OCT verification of MH closure and measurement of VA were obtained.

Statistical Analysis

The power analyses on sample size were calculated using SPSS SamplePower version 3.0 (SPSS, Inc, Chicago, IL). Preliminary data on the 24 first patients from an earlier trial on NSP served as the basis for the power analysis.[15] Mean supine time in that sample was 6 minutes and 34 seconds, and the threshold for noncompliance to the NSP regimen was set to 30 minutes. These data then were log transformed for the power analysis to 4.4 and 7.5, respectively. One goal of the study was to test the null hypothesis that there is no relationship between predictor 1 (supine time) and the closure rate. Under the null, the closure rate (0.90) is the same at all values of predictor 1, or, equivalently, the odds ratio is 1.0, the log odds ratio (β) is 0.0, and the relative risk is 1.0. Power was computed to reject the null under the following alternate hypotheses. For predictor 1 values of 4.4 and 7.5, the expected closure rates are 0.90 and 0.80, respectively. This corresponds to an odds ratio of 0.44, a β (log odds ratio) of −0.26, and a relative risk of 0.89. This effect was selected as the smallest effect that would be important to detect, in the sense that any smaller effect would not be of clinical or substantive significance. It was also assumed that this effect size was reasonable, in the sense that an effect of this magnitude could be anticipated in this field of research. In these computations, we assumed that the mean predictor 1 value would be 4.4, with a standard deviation (SD) of 2.0, and that the event rate at this mean would be 0.90. The significance level (α) was set at 0.05 with a 2-tailed test. For this distribution (predictor 1 mean of 4.4, SD of 2.0), baseline (event rate of 0.90 at the mean), effect size (log odds ratio of −0.26), sample size (n = 320), and α (0.05, 2-tailed) power is 0.80.

The Mann−Whitney *U* test was used for comparisons between groups containing continuous variables, and the chi-squared test was used for comparing categorical variables. The Wilcoxon signed-rank test was used to compare preoperative and postoperative VA, and the Spearman's correlation was used to compare the investigators' preoperative compliance scoring and actual supine time. A 2-tailed *P* value of 0.05 or less was considered statistically significant. Statistical analyses were made using SPSS statistics software version 24 (SPSS, Inc).

Results

Participants

Between December 2014 and June 2017, 205 participants with MH were enrolled in the study. In 4 patients, the recorded supine time was considered unreliable because the positioning monitoring device loosened during sleep in 3 patients and was accidentally removed during morning care in 1 patient. Consequently, 201 patients achieved valid measurements of the supine time during the first 24 hours after surgery. One patient was lost to follow-up because of a stroke, and we were not able to determine if this patient's MH had closed. Another patient was examined too early after surgery, failing to meet the primary end point. This patient therefore was excluded from the closure rate calculation, although the MH was closed at the examination 10 days after surgery. We were able to obtain postoperative OCT imaging and VA

Table 1. Baseline and Perioperative Characteristics of the Study Participants

Parameters	Entire Cohort (n = 205)
Male gender, no. (%)	71 (35)
Age (yrs), mean (SD)	69.8 (6.5)
Pseudophakia, no. (%)	41 (20)
Duration of symptoms (mos), mean (SD)	6.3 (4.6)
Median preoperative VA	
logMAR (range)	0.7 (0.2−1.8)
Snellen	20/100
MLD (μm), mean (SD)	411 (161)
BD (μm), mean (SD)	850 (268)
MH size (μm), no. (%)	
Large (>400)	105 (51)
Medium (>250−≤400)	66 (32)
Small (≤250)	34 (17)
VMT, no. (%)	65 (32)
ERM, no. (%)	63 (31)
Phacovitrectomy, no. (%)	147 (72)
SF_6 concentration (vol%), median (range)	30 (26−30)
Diameter of ILM peeling (ODD), median (range)	2.25 (1.0−4.5)
Type of dye used for ILM peeling, no. (%)	
Indocyanine green	60 (29)
Brilliant blue G	87 (42)
Trypan blue	58 (28)

BD = base diameter; ERM = epiretinal membrane; ILM = internal limiting membrane; logMAR = logarithm of the minimum angle of resolution; ODD = optic disc diameter; MH = macular hole; MLD = minimum linear horizontal diameter; SD = standard deviation; SF_6 = sulfur hexafluoride; VA = visual acuity; VMT = vitreomacular traction.

measurements in 204 patients, of whom 203 met the criteria for the primary end point.

Table 1 summarizes the baseline and perioperative characteristics. The mean age was 69.8 years (SD, 6.5 years), and the mean duration of symptoms was 6.3 months (SD, 4.6 months). Based on their minimum horizontal linear diameter, 51% of the MHs were classified as large (>400 μm), 32% as medium (>250 to ≤400 μm), and 17% as small (≤250 μm). All patients were instructed to adhere to the NSP regimen, whereas 131 of them combined it with the TBT.

Anatomic Results

Two hundred two of 203 MHs were closed after primary surgery, which corresponds to a closure rate of 99.5% (95% confidence interval, 97.3%−99.9%; Table 2). Given the planned sample size of 320 participants, the very high closure rate of the 205 enrolled patients made it unlikely that we would be able to determine any correlation between the supine time and the closure rate. For that reason, we decided to terminate the study.

Patient Compliance

The overall median supine time for the first 24 hours after surgery was 29 seconds (mean, 00:07:07; range, 00:00:00−01:58:28). Without the use of the TBT, the median supine time was 1 minute and 21 seconds (mean, 00:11:07; range, 00:00:00−01:47:48), compared with only 19 seconds (mean, 00:04:48; range, 00:00:00−01:52:28) with the TBT ($P = 0.02$).

Compliance Scoring

The investigators' preoperative scoring of patient compliance on the 4-point scale correlated significantly with the patients' actual compliance ($r = -0.301$; $P < 0.01$; Fig 1). There was no significant difference between the patients' self-reported preferred sleeping position (supine, face-down, or side) and their supine time.

Functional Results

Median VA improved significantly, with 3.8 ETDRS lines (mean, 4.0 ETDRS lines; range, −1.0 to 14.8 ETDRS lines) from 0.7 logMAR (mean, 0.7 logMAR; range, 0.15−1.8 logMAR) to 0.3 logMAR (mean, 0.3 logMAR; range, −0.11 to 1.48 logMAR) during the study ($P < 0.001$; Table 2). This is approximately equivalent to an improvement in Snellen VA from 20/100 to 20/40. Most patients (78.1%) gained more than 2 ETDRS lines.

Discussion

We studied the MH closure rate after surgery when using an NSP regimen. Unfortunately, a sample size of 205 patients, of whom 203 showed a closure rate of 99.5%, was not sufficient to determine any correlation between the time spent in the supine position and the MH closure rate. We assumed that enrollment of another 115 patients would not alter the study's ability to meet its end point, and therefore we terminated the study after the enrollment of 205 patients. To investigate a correlation between supine time and MH closure is not practicable when the closure rate approximates 100%. The rationale for anticipating a 90% closure rate in the present study lies in the result of other prospective trials, in which the closure rates after surgery with ILM peeling range between 84% and 93%.[10,16–19] Moreover, prospective, multicenter studies with many participating surgeons are likely to achieve inferior results compared with other studies, as was the case in a previous study on retinal detachment.[20] With this in mind, it was surprising to achieve the extraordinary high closure rate of 99.5%.

All patients were instructed to avoid upward gaze and a supine sleeping position after surgery for 3 to 5 days. Therefore, this study provides strong evidence for abandoning the unpleasant face-down positioning regimen after MH surgery. Our results confirm the findings by Tadayoni et al[10] and Alberti and la Cour,[7] who in randomized controlled studies showed that postoperative NSP was noninferior to face-down positioning. The present study was not randomized, which may weaken the impact of our findings. Nevertheless, given such a high closure rate, a randomized trial probably would have limited additional value.

The TBT regimen led to a significantly shorter median supine time during sleep of 00:00:19 compared with 00:01:21 in the group not following the TBT regimen. Although our study was not designed to investigate the comparison of NSP and NSP plus TBT, this finding confirms the results of an earlier study on postoperative positioning compliance.[15] In the present study, the difference in compliance did not have any effect on the closure rate. According to a study by Alberti and la Cour,[21] intraocular

Table 2. Anatomic and Functional Results

	Cohort	Nonsupine Positioning	Nonsupine Positioning with Tennis Ball Technique	*P* Value	No. of Analyzed Eyes
MH closure, no./total (%)	202/203 (99.5)	74/74 (100)	128/129 (99.2)	0.45	203
Time in supine position, hours:minutes:seconds				0.002	201
Median (range)	00:00:28 (00:00:00–01:52:28)	00:01:21 (00:00:00–01:47:48)	00:00:19 (00:00:00–01:52:28)		
Mean (SD)	00:07:07 (00:18:03)	00:11:07 (00:23:09)	00:04:48 (00:13:51)		
Median postoperative VA				0.40	203
logMAR (range)	0.3 (−0.1 to 1.5)	0.3 (0.0–1.5)	0.3 (−0.1 to 1.2)		
Snellen	20/40	20/40	20/40		
Median VA gain (range), ETDRS lines	3.8 (−1.0 to 14.8)	3.0 (0.0–14.8)	4.0 (−1.0 to 11.8)	0.11	203
SRF, no./total (%)	63/191 (33.0)	25/74 (33.8)	38/117 (32.5)	0.85	191
Median time to last examination (range), wks	5 (2–111)	5 (2–23)	5 (2–111)	0.01	203

ETDRS = Early Treatment Diabetic Retinopathy Study; logMAR = logarithm of the minimum angle of resolution; MH = macular hole; SD = standard deviation; SRF = subretinal fluid; VA = visual acuity.

fluid interrupted the gas–foveal contact a median of 44 times over 24 hours in the setting of an NSP regimen. Consequently, several minor interruptions of the gas–foveal contact do not interfere substantially with MH closure. Two possible reasons for the low impact of such interruptions on the healing process need attention. First, when the gas–foveal contact prevents influx of fluid into the retina, the retinal pigment epithelium pump effectively reduces the intraretinal edema and facilitates fusion of the MH edges.[22] Minor interruptions of the gas–foveal contact are probably too short to allow intraocular fluid to accumulate in the retinal tissue and keep the MH open. Consequently, there could be some tolerance for fluid during the process of MH closure. Second, MHs already may have sealed before these interruptions. As reported by Kikushima et al,[23] the postoperative healing process starts immediately, and they observed closure of MH as soon as 20 minutes after surgery. In the present study, the interval from surgery to bedtime was likely to exceed 8 hours. Thus, it is likely that some of the MHs already had closed before the patients went to sleep, making the nocturnal positioning compliance irrelevant. This also could explain the fact that in 15 patients (7.5%), the MH closed despite more than 30 minutes (range, 00:34:17–01:52:28) in the supine position. In these patients, longer periods of contact between the MH and the intraocular fluid seemed to be well tolerated.

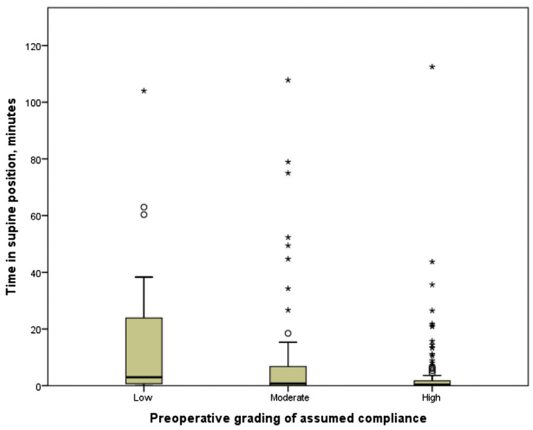

Figure 1. Box plot illustrating the 3 groups of assumed compliance scored by the investigators during the preoperative examination and the actual supine time after surgery. The length of the box indicates the interquartile range (IQR) and the whiskers represent the 1.5 IQR. The line within the box shows the median. Outliers are indicated with a circle (o), and extreme outliers are indicated with an asterisk (*).

The investigators' subjective preoperative scoring of the patients' positioning compliance proved to correlate significantly with their actual compliance. With this in mind, it makes sense to enhance the patient's ability to follow the NSP regimen by means of the TBT in those who are assumed to have a low level of compliance.

To our knowledge, this is the largest prospective study on positioning of patients after MH surgery to date. It demonstrates that a short-term NSP regimen combined with a short-acting intraocular tamponade like sulfur hexafluoride is probably sufficient to obtain excellent closure rates. A tennis ball attached to the back of a patient's nightshirt is a useful tool to support patient compliance. Further studies are needed to understand the process of MH closure in relation to interruptions of the gas–foveal contact.

Acknowledgments. The authors thank Mr. Kenneth Juvik and Mr. Rolf Haakonsen, Clinical Engineering Department, Haukeland University Hospital, for manufacturing the positioning monitoring device; and Laila Tjelta Hashemi, MD, Nils-Erik Boonstra, MD, Erlend Ulltang, MD, and Nina Krøll Angelsen, MD, for helping with inclusion, treatment, and follow-up of study participants.

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Footnotes and Financial Disclosures

Originally received: October 20, 2018.
Final revision: December 20, 2018.
Accepted: December 24, 2018.
Available online: December 31, 2018. Manuscript no. ORET_2018_436.

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Financial Disclosure(s):
The author(s) have no proprietary or commercial interest in any materials discussed in this article.

HUMAN SUBJECTS: Human subjects were included in this study. The human ethics committees at Regional Committee for Medical and Health Research Ethics, South-East Norway, approved the study. All research adhered to the tenets of the Declaration of Helsinki. All participants provided informed consent.

No animal subjects were included in this study.

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Obtained funding: N/A

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Abbreviations and Acronyms:
ETDRS = Early Treatment Diabetic Retinopathy Study; **ILM** = internal limiting membrane; **logMAR** = logarithm of the minimum angle of resolution; **MH** = macular hole; **NSP** = nonsupine positioning; **SD** = standard deviation; **TBT** = tennis ball technique; **VA** = visual acuity.

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Air versus Sulfur Hexafluoride Gas Tamponade for Small and Medium-Sized Macular Holes

A Randomized Noninferiority Trial

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Purpose: To investigate whether air tamponade is noninferior to sulfur hexafluoride (SF_6) gas tamponade for small ($\leq$ 250 μm) and medium-sized ($>$ 250 μm and $\leq$ 400 μm) macular holes (MHs).

Design: Multicenter, randomized controlled, noninferiority trial.

Participants: Patients aged $\geq$ 18 years undergoing surgery for primary MHs of $\leq$ 400 μm in diameter.

Methods: The patients in both groups underwent conventional pars plana vitrectomy with peeling of the internal limiting membrane. At the end of the surgery, the patients were randomized to receive either air or SF_6 gas tamponades, stratified by MH size. Postoperatively, the patients followed a nonsupine positioning regimen for 3 days.

Main Outcome Measures: The primary end point was the MH closure rate after a single surgery, confirmed by OCT after 2 to 8 weeks. The noninferiority margin was set at a 10−percentage-point difference in the closure rate.

Results: In total, 150 patients were included (75 in each group). In the intention-to-treat (ITT) analysis, 65 of 75 patients in the air group achieved primary closure. All 75 MHs in the SF_6 group closed after a single surgery. Six patients were excluded from the per-protocol (PP) analysis. In the PP analysis, 63 of 70 patients in the air group and all 74 patients in the SF_6 group achieved MH closure after a single surgery, resulting in closure rates of 90% (95% confidence interval [CI], 79.9%−95.5%) and 100% (95% CI, 93.9%−100%), respectively. For the difference in closure rates, the lower bound of a 2-sided 95% CI exceeded the noninferiority margin of 10% in both ITT and PP analyses. In the subgroups of small MHs, all 20 patients in the air group and all 28 patients in the SF_6 group achieved primary closure.

Conclusions: This prospective randomized controlled trial proved that air tamponade is inferior to SF_6 tamponade for MHs of $\leq$ 400 μm in diameter. *Ophthalmology Retina 2022;■:1−7 © 2022 by the American Academy of Ophthalmology. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).*

Supplemental material available at www.ophthalmologyretina.org.

With an annual incidence of 7.9 to 8.7 eyes per 100 000 individuals, macular hole (MH) is a relatively common indication for vitreoretinal surgery.[1,2] Surgery normally consists of pars plana vitrectomy, peeling of the internal limiting membrane, and the use of an intraocular tamponade. The main function of the tamponade is to isolate the MH from the intraocular fluid, thereby allowing the retinal pigment epithelium (RPE) to absorb the remaining fluid in the MH. The most commonly used intraocular tamponades are sulfur hexafluoride (SF_6), hexafluoroethane, and perfluoropropane. Among these, SF_6 gas has the shortest duration, with a mean duration of 18 days for a gas concentration of 30%, whereas 15% perfluoropropane lasts for approximately 68 days.[3] During this time, the vision is severely impaired, and the patients are restricted from driving and air travel. Therefore, a short-acting gas that still maintains the isolating effect in the macular region is desired. It has previously been shown that the duration of air within the eye after the fluid−air exchange is up to 10 to 11 days, and several studies have reported the use of air as an endotamponade in MH surgeries.[4−14] In these studies, the closure rates ranged from 75% to 100%, partly depending on the MH size. To our knowledge, there have been no prospective studies

https://doi.org/10.1016/j.oret.2022.04.003
ISSN 2468-6530/22

investigating whether air is noninferior to any commonly used tamponading agents. Here, we report the results from a prospective, randomized trial that aimed to determine whether air was noninferior to SF_6 gas in MH surgeries for small ($\leq$ 250 μm) and medium-sized ($>$ 250 μm and $\leq$ 400 μm) MHs.

Methods

Study Design and Participants

This nationwide, multicenter study was conducted at the Departments of Ophthalmology at the University Hospitals of Bergen, Oslo, Stavanger, Tromsø, and Trondheim between September 2018 and December 2020. The inclusion criteria were a primary MH with a diameter of $\leq$ 400 μm, duration of symptoms $\leq$ 24 months, and the ability to provide written informed consent to participate in the study. Primary and secondary MHs were defined according to the International Vitreomacular Traction Study Group classification.[15] The exclusion criteria were age $<$ 18 years, secondary MH, visual acuity (VA) in the fellow eye worse than 20/40, fellow eye already enrolled in the study, previous vitreoretinal surgery in the study eye, and the need for surgery under general anesthesia. The study was approved by the Regional Committee for Medical and Health Research Ethics, South-East Norway (ref. 2018/785), registered at ClinicalTrials.gov with the identifier NCT03572725, and conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent before participating.

The primary end point was the MH closure rate after a single surgery, confirmed by OCT 2 to 8 weeks after the surgery. Subgroup analyses were planned on closure rates after single surgeries for small ($\leq$ 250 μm) and medium-sized ($>$ 250 μm and $\leq$ 400 μm) MHs. The secondary end points were the intraocular pressure (IOP) on the first postoperative day and the VA at the last follow-up.

Treatment Randomization Procedure

The eligible participants were randomized to receive air or 26% SF_6 gas tamponades, stratified by small ($\leq$ 250 μm) and medium-sized ($>$ 250 μm and $\leq$ 400 μm) MHs. The randomization process took place after the fluid−air exchange. The randomization was performed by a web-based randomization and data collection system developed and administered by the Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology, Trondheim, Norway.

Ophthalmic Examination and Surgical Procedures

Preoperative examinations consisted of VA assessment, Goldmann applanation tonometry, slit-lamp biomicroscopy, funduscopy, and OCT of the macula. Visual acuity was measured using the ETDRS or Snellen charts. Snellen values were converted to logarithm of the minimum angle of resolution values for statistical analysis.[16]

The size of each MH was determined according to the International Vitreomacular Traction Study Group classification[15]; it was measured at the narrowest point in the midretina, roughly parallel to the RPE. The surgery consisted of a standard 3-port, 23- or 25-gauge pars plana vitrectomy and dye-assisted peeling of the internal limiting membrane. The size of the peeling area (recorded in optic disc diameters) and the type of vital dye (brilliant blue, trypan blue, or a combination of both) were based on the surgeon's decision. In all phakic patients, a phacovitrectomy with intraocular lens implantation was performed.

Immediately after the fluid−air exchange, the patients allocated to receive the gas tamponade received 26% SF_6 gas. If retinal tears necessitated postoperative positioning, the patients were excluded before randomization. If leakage from a sclerotomy was detected, it was sutured with 7-0 or 8-0 Vicryl. The surgery was to be completed before 12PM to standardize the amount of time for which the patient was in an upright position. Postoperatively, the patients followed a nonsupine positioning (NSP) regimen for 3 days. A tennis ball was attached to the back of their nightshirts to prevent them from sleeping in a supine position. This so-called tennis ball technique is proven to reduce the time spent in the supine position during sleep.[17] On the first postoperative day, the IOP was measured, and the amount of intraocular air or gas was assessed, according to the method previously described by Thompson.[18] We also recorded when the patients went to sleep on the day of the surgery. Each participant in the air group underwent an examination 3 to 8 days after the surgery for the assessment of the macular status by OCT and the measurement of the VA and IOP. In cases with persistent MHs, installation for 26% SF_6 gas was performed, followed by 3 days of NSP. In cases with nearly closed MHs, the patients could be observed for a few more days before retreatment to allow for complete closure. All participants were examined 2 to 8 weeks after surgery with macular OCT and the measurement of VA and IOP.

Statistical Analysis and Sample Size Calculations

Categorical data were summarized by numbers and proportions. Continuous data were described by means and standard deviations when normally distributed; otherwise, they were described by medians and ranges. The Student t test (or the Mann−Whitney U test in cases of nonnormality) was used to compare continuous data. We used the chi-square test or Fisher exact test when comparing categorical variables. A 2-tailed P value of $\leq$ 0.05 was considered statistically significant. Wilson score intervals with continuity corrections were used to calculate confidence intervals for proportions.[19] The results from the intention-to-treat (ITT) group (all included patients) and from the per-protocol (PP) group (only patients who strictly adhered to the study protocol) were separately analyzed and compared. The statistical analyses and graphics were made using R version 4.0.2.[20]

Based on a recent prospective MH study by our group, we expected high closure rates.[21] Thus, we used a procedure for exact confidence interval (CI) calculations implemented in the R-package ExactCIdiff.[20,22,23] Sample size calculations were performed by simulating the power obtained in different scenarios. The simulations showed a required sample size of 150 patients assuming a success rate of 97.5% among patients with standard treatment and a noninferiority margin of 10 percentage points. If there truly was no difference between the 2 treatments, 150 patients were required to be 83.7% sure that the lower limit of a 2-sided 95% CI would exclude a difference in favor of the SF_6 group of $>$ 10%. The noninferiority margin of 10% was considered appropriate because air tamponade is convenient for the patients and provides rapid visual recovery as well as the early lifting of driving and air travel restrictions.

Results

Participants

Between September 2018 and December 2020, we included 150 patients, 75 in each group. The mean age was 69.5 years (standard deviation 6.8 years), and 49% of the participants were men. Table 1 summarizes the baseline and perioperative characteristics, and

Table 1. Baseline and Perioperative Characteristics of the Study Participants

Parameters	Air Group (n = 75)	SF_6 Group (n = 75)
Male, n (%)	32 (42.7)	42 (56.0)
Age, yrs, mean (SD)	68.7 (6.8)	70.3 (6.8)
Symptoms duration, mos, median (range)	3.0 (0.1–12.0)	3.0 (0.1–12.0)
Preoperative VA, logMAR Median (range)	0.52 (0.1–1.6)	0.52 (0.2–1.0)
MH size, µm, median (range)	294 (53–400)	300 (107–395)
MH class, n		
Small	22	28
Medium	53	47
VMT, n (%)	20 (27.0)*	19 (25.3)
ERM, n (%)	24 (32.4)*	18 (24)
Pseudophakic, n (%)	14 (18.7))	16 (21.3)
Phacovitrectomy, n (%)	61 (81.3)	59 (78.7)
ILM peeling size, ODD, median (range)	2.0 (1.0–3.0)	2.0 (1.0–4.0)
Gauge, n		
23	25	30
25	50	45

ERM = epiretinal membrane; ILM = internal limiting membrane; logMAR = logarithm of the minimum angle of resolution; MH = macular hole; ODD = optic disc diameter; SD = standard deviation; SF6 = sulfur hexafluoride; VA = visual acuity; VMT = vitreomacular traction.
*One patient had missing data.

there were no statistically significant differences between the 2 groups. Fifty MHs were classified as small (≤ 250 µm), and 100 MHs were classified as medium-sized (> 250 and ≤ 400 µm).

Four patients were randomized to air or SF_6 gas after 12PM, and in 2 cases, we failed to provide the patient with a tennis ball at the back of the nightshirt. Hence, 6 patients were excluded from the PP analyses. Figure 1 shows the participant flow diagram.

Anatomic Results

In the air group, 10 patients had open MHs when examined 3 to 8 days after surgery. Three of them were observed for a few days (range 3–13 days) to wait for hole closure, which did not occur. Consequently, all 10 patients underwent a second surgery with SF_6 gas installation. Hence, the closure rate in the air group was 85.7% (95% CI, 76.4%–93.1%) in the ITT analysis (Table 2). At their examinations 2 to 8 weeks after surgery, all 75 patients in the SF_6 group presented with MH closure, leading to a closure rate of 100% (95% CI, 93.9%–100%). All 10 MHs that did not close after the first surgery closed after the second surgery with the installation of SF_6 gas.

For the PP analysis, 5 patients in the air group and 1 patient in the SF_6 group were excluded. In the air group, 63 of the 70 patients achieved MH closure after a single surgery. As a result, the closure rate for the air group was 90% (95% CI, 79.9%–95.5%) in the PP analysis (Table 2). Figure 2 illustrates the differences in the closure rates between the air group and the SF_6 group for both ITT and PP analyses. As the lower bound of the 95% CI exceeded the noninferiority margin of 10%, noninferiority could not be proven.

In the subgroup of small MHs, all 20 patients in the air group and all 28 patients in the SF_6 group achieved primary closure in the PP analysis. For the ITT analysis, 21 of 22 patients in the air group and all 28 patients in the SF_6 group achieved primary closure. Figure 3 illustrates the differences in the closure rates between the air group and the SF_6 group for the small and medium-sized MHs in the PP analysis.

On the first postoperative day, the median bubble meniscus heights were 60% (range, 50%–80%) in the air group and 90% (range, 66%–100%) in the SF_6 group ($P < 0.001$; Table S1, available at www.ophthalmologyretina.org). The median interval from the end of the surgery to bedtime was 12.4 hours (range, 7.3–15.7 hours) in the air group and 12.3 hours (range, 7.8–14.7 hours) in the SF_6 group ($P = 0.27$). The median time to the last follow-up was 33 days (range, 12–133 days) in the air group and 23 days (range, 13–127 days) in the SF_6 group ($P < 0.001$).

Visual Acuity and Intraocular Pressure

In both air and SF_6 groups, the patients had median visual gains at the last examination of 3.0 ETDRS lines, ranging from −1.0 to 10.8 and −1.2 to 9.0 ETDRS lines, respectively. In the subgroup of 10 failures in the air group, the median visual gain was 3.5 ETDRS lines (range, 0–10 ETDRS lines). On the first postoperative day, the median IOP was 10 mmHg (range, 2–36 mmHg) in the air group, compared with 14 mmHg (range, 1–38 mmHg) in the SF_6 group ($P < 0.001$).

Discussion

In this noninferiority trial, we could not demonstrate that endotamponade with air was noninferior to that with SF_6 gas for MHs of ≤ 400 µm in diameter. Ninety percent of the PP-treated MHs in the air group achieved primary closure. The closure rate for air tamponade was statistically lower than that for SF_6 gas, and the 95% CI for the difference in closure rates did not exceed the value of 0 in the PP or ITT analyses. Hence, air was inferior to SF_6 for MHs of ≤ 400 µm in diameter.

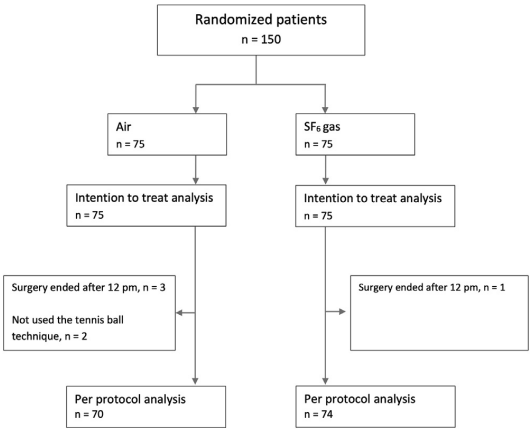

Figure 1. Flow diagram showing the patients through the study.

Table 2. Results of the Intention to Treat and Per-Protocol Analysis

Outcome	Intention-to-Treat Analysis			Per-Protocol Analysis		
	Air Group (n = 75)	*SF_6 Group (n = 75)*	P *Value*	*Air Group (n = 70)*	*SF_6 Group (n = 74)*	P *Value*
Closed after single surgery, n (%)	65 (86.7)	75 (100)	0.001	63 (90)	74 (100)	0.005
95% CI	76.4–93.1	93.9–100		79.9–95.5	93.9–100	
Closed after second surgery, n (%)	75 (100)	75 (100)	> 0.99	70 (100)	74 (100)	> 0.99
Closed small MH after single surgery, n (%)	21/22 (95.5)	28/28 (100)	0.44	20/20 (100)	28/28 (100)	> 0.99
95% CI	75.1–99.8	85.0–100		80.0–100	85.0–100	
Closed medium-sized MH after single surgery, n (%)	44/53 (83.0)	47/47 (100)	0.003	43/50 (86.0)	46/46 (100)	0.01
95% CI	69.7–91.5	90.6–100		72.6–93.7	90.4–100	
VA gain, ETDRS lines, median (range)	3.0 (−1.0 to 10.8)	3.0 (−1.2 to 9.0)	0.79	3.0 (−1.0 to 10.8)	3.0 (−1.2 to 9.0)	0.99
Time to the last follow-up, days, median (range)	33 (12–133)	23 (13–127)	<0.001	33 (12–99)	23.5 (13–127)	< 0.001
IOP at the last follow-up, mmHg, median (range)	14 (6–21)*	14 (7–32)	0.67	14 (6–21)*	14 (7–32)	0.49

CI = confidence interval; IOP = intraocular pressure; MH = macular hole; SF_6 = sulfur hexafluoride; VA = visual acuity.
*One patient had missing data.

The endotamponade isolates the foveal region from the intraocular fluid, thereby allowing the RPE and the Müller cells to absorb the subretinal and intraretinal fluids and the hole edges to appose. The centripetal contraction of perifoveal Müller cells may further contribute to MH closure, and the formation of Müller cell tissue seals the MH.[24] In a pooled analysis of 11 different studies investigating the time to MH closure, 79.5% (95% CI, 74.6%–83.6%) were closed after 24 hours (Table S2, available at www.ophthalmologyretina.org). If an MH is still open on the third postoperative day, it is likely to remain open.[10,25,26] In the present study, we aimed to optimize the tamponade volume and minimize the risk of tamponade interruptions by performing phacovitrectomy in all phakic patients and completing the surgeries before 12PM to increase the time span before sleep. Despite these precautions, we failed to prove the noninferiority of air to SF_6 gas. After 24 hours, a 60% air bubble should be sufficient to keep the fovea separated from the intraocular fluid when in an upright position. Nevertheless, a 90% and longer-lasting SF_6 bubble provides a larger safety margin toward intraocular fluid during the first critical days. This may explain why the overall closure rate was higher in the SF_6 group.

With a 100% closure rate in the SF_6 group, this study demonstrates optimal anatomic results in the setting of NSP. This is in line with the findings of 2 recent meta-analyses concluding that face-down positioning (FDP) is unnecessary in MHs of < 400 μm in diameter.[27,28] In a prospective, multicenter study by our group on MHs of all

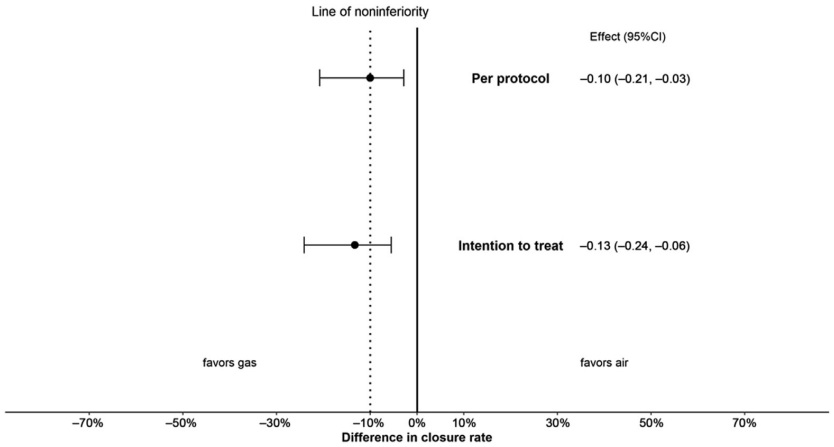

Figure 2. Graph showing the 2-sided 95% CI for the difference in proportions with the noninferiority margin of 10% for both intention-to-treat and per-protocol analyses. Noninferiority could not be proven. CI = confidence interval.

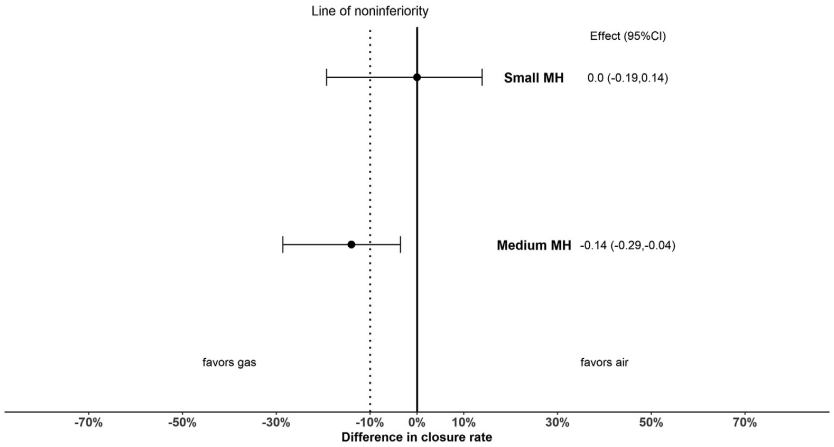

Figure 3. Graph showing the 2-sided 95% CI for the difference in proportions with the noninferiority margin of 10% for small and medium-sized macular holes in the per-protocol analysis. The study was not powered to conclude in these subgroups. Noninferiority could not be proven. CI = confidence interval.

sizes, a 99.5% closure rate was achieved by SF_6 gas tamponade and postoperative NSP.[21] Even though the latter study contradicts the conclusion of the 2 aforementioned meta-analyses that FDP improves the closure rate of large MHs compared with NSP, it is unlikely that the very high closure rates are coincidental. These circumstances inspired the hypothesis that NSP may have some advantages over conventional FDP. The gravitational forces acting on the MH rim during FDP may counteract its adhesion to the RPE and decrease the interstitial hydrostatic pressure in the outer retina, thereby maintaining the macular edema.[29] Further research is needed to confirm this hypothesis.

For small MHs ($\leq$ 250 μm in diameter), there was no difference in the primary closure rates between patients receiving air and those receiving SF_6 gas as tamponade, but the sample size was too small to prove noninferiority in this subgroup. Nevertheless, intraocular air offers several advantages compared with gas. Most importantly, it allows for faster visual rehabilitation and a shorter period of restrictions after surgery. The omission of gas makes the surgical procedure simpler and more cost-effective and reduces the risk of postoperative IOP elevation.[30]

The strengths of the study are its prospective, randomized, multicenter design and the use of both PP and ITT analyses for noninferiority testing. To prove that an alternative treatment is not unacceptably worse than the standard treatment, the noninferiority design is the most appropriate method.[31] When planning such a study, defining the noninferiority margin is crucial. Our noninferiority margin of 10% may be generous and debatable but is in line with those of comparable studies.[32,33] In the study by Essex et al,[32] a prospective noninferiority study on intraocular gases and postoperative positioning, the authors argued for a 5% noninferiority limit. In contrast, Alberti and la Cour[33] chose a 15% noninferiority margin in their prospective study comparing FDP and NSP for MH surgery. The limitations of the present study include the inability to generalize the results to phakic patients and those treated with other positioning regimens. There was an unintended difference in the interval to the last follow-up between the air group and the SF_6 group, but we think it is unlikely that this influenced the outcome.

In conclusion, this prospective randomized controlled trial proved that air tamponade was inferior to SF_6 gas tamponade combined with postoperative NSP for MHs $\leq$ 400 μm in diameter. Based on the results of the present study, we recommend gas tamponade for MHs of $>$ 250 μm. Regarding MHs of $\leq$ 250 μm, the study was not powered to allow definitive conclusions, and a prospective study including more patients with small MHs is required to confirm our results. However, we consider air tamponade a good alternative for MHs of $\leq$ 250 μm, depending on the patients' preferences. A postoperative NSP regimen is recommended for all MHs $\leq$ 400 μm in diameter to provide the best possible patient care.

Footnotes and Disclosures

Originally received: February 18, 2022.
Final revision: March 25, 2022.
Accepted: April 4, 2022.
Available online: ■■■. Manuscript no. ORET-D-22-00119R1.

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Disclosure(s):

All authors have completed and submitted the ICMJE disclosures form.

The authors have no proprietary or commercial interest in any materials discussed in this article.

HUMAN SUBJECTS: Human subjects were included in this study. The study was approved by the Regional Committee for Medical and Health Research Ethics, South-East Norway (ref. 2018/785), registered at ClinicalTrials.gov with the identifier NCT03572725 and was conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent before participating.

No animal subjects were used in this study.

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Obtained funding: Study was performed as part of the authors' regular employment duties. No additional funding was provided.

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Abbreviations and Acronyms:
CI = confidence interval; **FDP** = face-down positioning; **IOP** = intraocular pressure; **ITT** = intention-to-treat; **MH** = macular hole; **NSP** = nonsupine positioning; **PP** = per-protocol; **RPE** = retinal pigment epithelium; **SF_6** = sulfur hexafluoride; **VA** = visual acuity.

Keywords:
Intraocular air, Intraocular gas, Macular hole, Prospective study, Vitrectomy.

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Graphic design: Communication Division, UiB / Print: Skipnes Kommunikasjon AS

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ISBN: 9788230866344 (print)
9788230856826 (PDF)