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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;6:828-834 © 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.

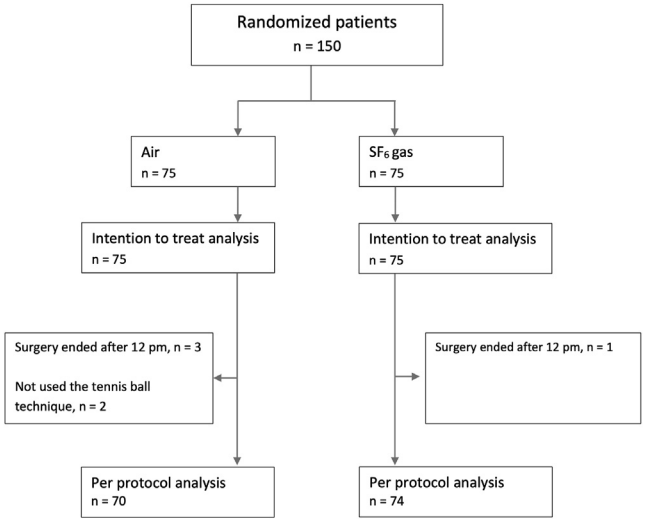


**Figure 1.** Flow diagram showing the patients through the study.

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

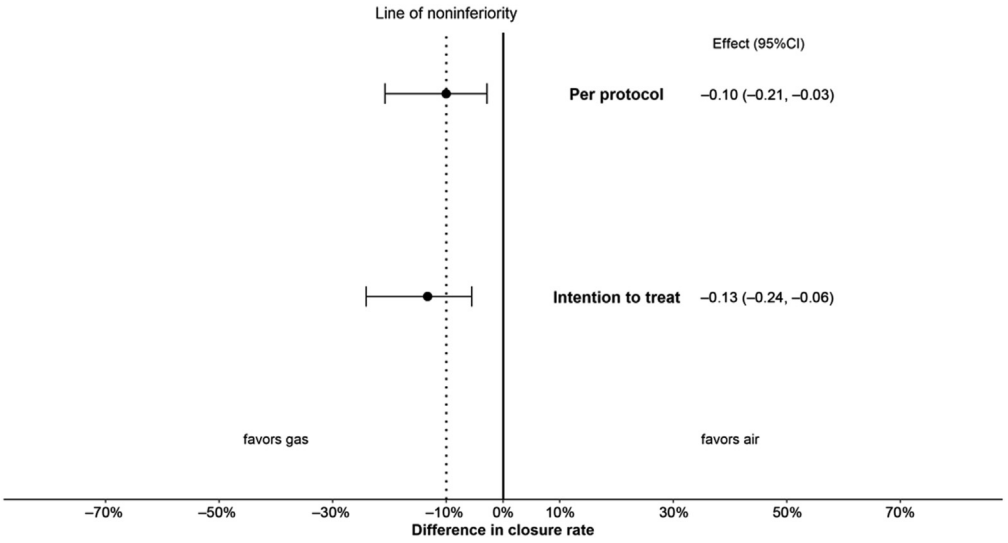


**Figure 2.** Graph showing the 2-sided 95% CI for the difference in proportions with the noninferiority margin of 10% for both intention-to-treat and per-protocol analyses. Noninferiority could not be proven. CI = confidence interval.

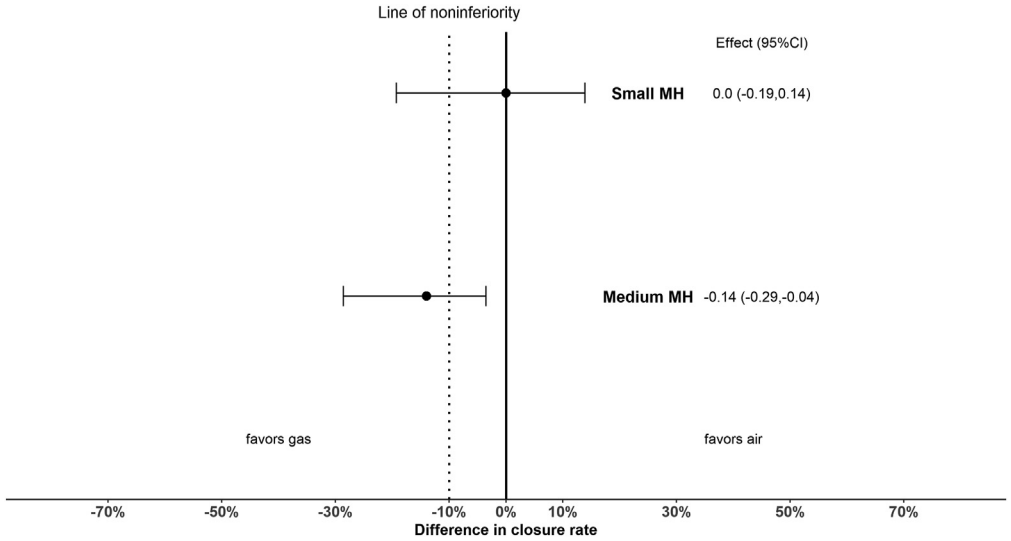


**Figure 3.** Graph showing the 2-sided 95% CI for the difference in proportions with the noninferiority margin of 10% for small and medium-sized macular holes in the per-protocol analysis. The study was not powered to conclude in these subgroups. Noninferiority could not be proven. CI = confidence interval.

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: April 7, 2022. 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.

Author Contributions:

Conception and design: Lindtjørn, Krohn, Austeng, Fossen, Haugstad, Varhaug, Basit

Data collection: Lindtjørn, Krohn, Austeng, Fossen, Haugstad, Varhaug, Basit

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

Overall responsibility: Lindtjørn, Krohn, Austeng, Fossen, Haugstad, Varhaug, Basit

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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