

Air vs Perfluoropropane Gas in Pneumatic Retinopexy

A Randomized Noninferiority Trial

Suthasinee Sinawat, MD; Tanapat Ratanapakorn, MD; Thuss Sanguansak, MD; Sirinada Prompol, BNs; Malinee Laopaiboon, PhD; Yosanan Yospaiboon, MD

Objective: To evaluate whether air is as effective as perfluoropropane gas in treating rhegmatogenous retinal detachment by pneumatic retinopexy.

Methods: In a double-blind, randomized, clinically controlled noninferiority trial, eligible patients were randomized into 2 treatment groups by using block randomization and treated by pneumatic retinopexy using filtered air or perfluoropropane gas.

Main Outcome Measures: Retinal reattachment rate and final visual recovery.

Results: One hundred twenty-six patients were recruited. Half (63 patients) were assigned to receive filtered air during pneumatic retinopexy and half received perfluoropropane gas. The single-procedure reattachment rate was higher for the perfluoropropane gas group (73.0% [46 patients]) than for the air group (60.3% [38]), but the difference was not statistically significant (risk difference, -12.7%; 95% confidence interval, -29.0% to 3.6%). The final reattachment rate after additional pneu-

matic retinopexy and/or surgical procedures was 92.1% (58) in the air group and 96.8% (61) in the perfluoropropane gas group. This result showed an equivalent effect on the final reattachment rate (risk difference, -4.7%; 95% confidence interval, -12.7% to 3.2%). Final visual acuity did not differ significantly between groups.

Conclusion: Pneumatic retinopexy using filtered air is associated with a nonsignificantly lower initial reattachment rate than using perfluoropropane gas but results in an equivalent final reattachment rate and final visual recovery.

Application to Clinical Practice: Air is an acceptable alternative to perfluoropropane gas when treating rhegmatogenous retinal detachment by pneumatic retinopexy.

Trial Registration: clinicaltrials.gov Identifier: NCT00120445

Arch Ophthalmol. 2010;128(10):1243-1247

Author Affiliations:

Department of Ophthalmology, Faculty of Medicine (Drs Sinawat, Ratanapakorn, Sanguansak, and Yospaiboon), Srinagarind Hospital (Ms Prompol), and Department of Biostatistics and Demography, Faculty of Public Health (Dr Laopaiboon), Khon Kaen University, Khon Kaen, Thailand.

PNEUMATIC RETINOPEXY IS A commonly used technique to repair rhegmatogenous retinal detachment (RRD). In this procedure, a gas bubble is injected into the vitreous cavity and placed over the retinal break by manipulating the patient's head position. The break is closed, and retinopexy seals the break.^{1,2} Subretinal fluid is then reabsorbed by the retinal pigment epithelium. This technique has several potential advantages in the management of uncomplicated RRD. It has been shown that pneumatic retinopexy involves less tissue manipulation, has less morbidity, and has better functional visual results compared with scleral buckling and vitrectomy.³⁻¹¹ Some researchers used air instead of expansile gas in an attempt to minimize vitreous disturbance and reported satisfactory results. Carim¹² demonstrated

that using air in pneumatic retinopexy was successful in selected cases. Yospaiboon and Sajjapong¹³ also reported satisfactory results using filtered air in this procedure, particularly in patients with phakic eyes. The reattachment rate and visual recovery were comparable to those when using expansile gas.

To the best of our knowledge, no clinical trial has compared air and expansile gas in pneumatic retinopexy. We hypothesized that both air and expansile gas are similarly effective as agents in pneumatic retinopexy. Perfluoropropane (C₃F₈) gas is expensive, and, in settings where C₃F₈ gas is not available or affordable, such as developing countries or remote areas, air would be a reasonable alternative. Therefore, we conducted a double-blind, randomized, controlled study to evaluate whether air is as effective as C₃F₈ gas in treating RRD by pneumatic retinopexy. We

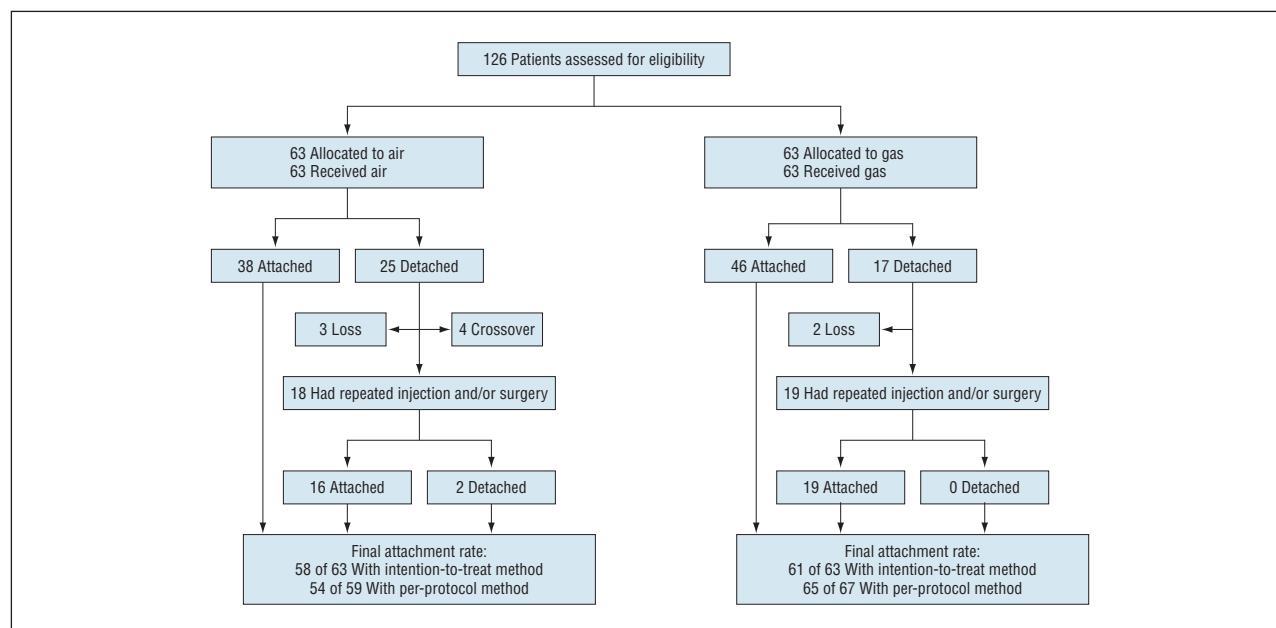


Figure 1. Study flowchart.

selected C_3F_8 gas because it was commonly used for pneumatic retinopexy at our hospital.

METHODS

A hospital-based, double-blind, randomized, clinically controlled noninferiority trial was conducted in a vitreoretinal center at Srinagarind Hospital, Khon Kaen University, in Thailand. This trial followed the tenets of the Declaration of Helsinki and was approved by the Khon Kaen University Ethics Committee for Human Research. All patients with RRD who visited the center between April 1, 2004, and October 31, 2008, were recruited. The eligibility criteria were having a superior retinal break between the 8-o'clock and 4-o'clock positions, having a single retinal break not larger than 2.5 clock hours, having multiple breaks not more than 3 clock hours away, having no or minimal proliferative vitreoretinopathy (PVR), being able to physically and mentally cooperate in postoperative head positioning, having at least 12 weeks of follow-up, and being capable of giving informed consent. Patients were excluded if they had only 1 eye or had ocular media opacities, advanced glaucoma, aphakia, pseudophakia, or a history of previous ocular surgical procedures. Recruited patients were allocated into 2 groups by block randomization with varying block size. Patients were treated by pneumatic retinopexy using filtered air or C_3F_8 gas (**Figure 1**).

One surgical nurse (S.P.) prepared air and C_3F_8 gas for intravitreal injection. An insulin syringe was connected to a filter (Millipore; Bausch & Lomb Inc, Rochester, New York) that had the capacity to filter bacteria at a level of $0.22 \mu m$,¹⁴ and 0.3 mL of filtered air or C_3F_8 gas was drawn into the syringe. Syringes were then coded A or B for use in the treatment of patients in the air or C_3F_8 gas group, respectively. The allocation sequence was generated using computer-generated random numbers with randomly varying block size (SAS statistical software; SAS Institute Inc, Cary, North Carolina). The random allocation sequence was concealed in a sealed opaque envelope, numbered sequentially, and kept by the surgical nurse, who was the only one who knew which code was for air or C_3F_8 gas. The researchers and patients did not know the code, and unblinding was done at the end of the study.

The primary outcomes for both groups were the retinal reattachment rate and the final visual recovery. The retinal reattachment rate was calculated from the number of patients who had an attached retina after surgery divided by the total number of patients treated. The final visual recovery was the difference between the preoperative and postoperative best-corrected visual acuity that improved by 1 or more lines on a Snellen acuity chart was classified as "improved"; postoperative best-corrected visual acuity that decreased by 1 or more lines was classified as "worse."

We considered this an equivalence trial; thus, a formula by Jones et al¹⁵ was used for sample size calculation. We estimated that both groups would have a 90% final reattachment rate. At a 95% confidence level and a power of 80%, an acceptable margin of noninferiority in effectiveness of treatment was 15% for a 1-tailed test. The required number of patients per treatment group was calculated to be 63. For a 1-tailed test, equivalence is declared if the lower 1-sided confidence limit exceeds the defined level. We chose to use the 1-sided test in this study because we wanted to confirm that pneumatic retinopexy using air is not inferior to the procedure using C_3F_8 gas. Equivalence and superiority were both regarded as positive outcomes.

Descriptive statistics were used for the patients' demographic characteristics and clinical findings. Intention-to-treat and per-protocol methods were used to analyze the results and the comparisons between air and C_3F_8 gas. The reattachment rate, final visual recovery, and risk difference with 95% confidence intervals (CIs) were used to compare the differences for categorical outcomes.

RESULTS

A total of 126 patients with RRD were recruited into the trial. We allocated 63 patients to the air group and another 63 patients to the C_3F_8 gas group (**Figure 1**). The demographic characteristics of the patients in each group, including age and sex, and the associated conditions, such as myopia and history of trauma, were similar at study entry. The clinical findings in each group, including the duration of symptoms, type and number of retinal breaks,

Table 1. Demographic Characteristics and Clinical Findings

Characteristic	No. (%) of Patients	
	Air Group (n=63)	C ₃ F ₈ Gas Group (n=63)
Age, mean (SD) [range], y	54.1 (11.3) [28-76]	52.6 (13.5) [16-72]
Sex		
Female	21 (33.3)	20 (31.8)
Male	42 (66.7)	43 (68.2)
Associated conditions		
Myopia	6 (9.5)	5 (7.9)
Trauma	5 (7.9)	3 (4.8)
Duration of symptoms, mean (SD), wk	3.8 (4.0)	4.2 (5.8)
No. of retinal breaks, mean (SD)	1.4 (0.7)	1.4 (1.0)
Extent of detachment, No. of quadrants		
1	7 (11.1)	7 (11.1)
2	22 (34.9)	34 (54.0)
3	24 (38.1)	15 (23.8)
Total detachment, PVR grade ^a		
A	41 (65.1)	41 (65.1)
B	21 (33.3)	21 (33.3)
C1	1 (1.6)	1 (1.6)

Abbreviations: C₃F₈, perfluoropropane; PVR, proliferative vitreoretinopathy.

^aGrading of PVR is explained in Tornambe et al.¹⁶

Table 2. Pneumatic Retinopexy and Surgical Procedures

	No. (%) of Patients	
	Air Group (n=63)	C ₃ F ₈ Gas Group (n=63)
Pneumatic retinopexy, No. of injections ^a		
Single	38 (60.3)	46 (73.0)
Multiple	25 (39.7)	17 (27.0)
Complications	12 (19.1)	13 (20.6)
New or missed break	3 (4.8)	8 (12.7)
Subretinal gas	4 (6.3)	1 (1.6)
Glaucoma	0	2 (3.2)
Epithelial defect	2 (3.2)	0
Other	3 (4.8)	2 (3.2)
Surgical procedures	24 (38.1)	20 (31.8)
Pars plana vitrectomy	19 (30.2)	12 (19.1)
Scleral buckling	1 (1.6)	6 (9.5)
Combined procedure	4 (6.3)	2 (3.2)
Follow-up, range, wk	6-228	6-190

Abbreviation: C₃F₈, perfluoropropane.

^a*P* < .001.

extent of the detached retina, and grading of PVR, were also similar (**Table 1**). The interventions, including pneumatic retinopexy and other surgical procedures, are given in **Table 2**. Patients in the air group needed statistically significantly more injections (*P* < .001) than did those in the C₃F₈ gas group.

In this study, the initial reattachment rate for the air group was 71.4% (5 of 7 patients) for those with a retinal detachment extending 1 quadrant, 63.6% (14 of 22) for those with a retinal detachment extending 2 quadrants, 66.7% (16 of 24) for those with a retinal detachment extending 3 quadrants, and 30.0% (3 of 10) for those

Table 3. Reattachment Rate and Final Visual Recovery

	No. (%) of Patients		Risk Difference (95% CI)
	Air Group (n=63)	C ₃ F ₈ Gas Group (n=63)	
Reattachment rate			
Initial	38 (60.3)	46 (73.0)	-12.7 (-29.0 to 3.6)
Final	58 (92.1)	61 (96.8)	-4.7 (-12.7 to 3.2)
Final visual recovery			
Improved	33 (52.4)	36 (57.1)	-4.8 (-2.2 to 12.6)
Stable	23 (36.5)	18 (28.6)	7.9 (-8.4 to 24.2)
Worse	7 (11.1)	9 (14.3)	-3.2 (-14.8 to 8.4)

Abbreviations: C₃F₈, perfluoropropane; CI, confidence interval.

with total detachment. The initial reattachment rate for the C₃F₈ gas group was 85.7% (6 of 7 patients) for those with a retinal detachment extending 1 quadrant, 67.6% (23 of 34) for those with a retinal detachment extending 2 quadrants, 66.7% (10 of 15) for those with a retinal detachment extending 3 quadrants, and 100% (7 of 7) for those with total detachment.

The incidence rate of complications was 19.0% (12 of 63 patients) in the air group and 20.6% (13 of 63) in the C₃F₈ gas group (Table 2). There was no statistically significant difference in the number of complications from pneumatic retinopexy between the groups. Of interest, the incidence of new or missed breaks was 4.8% (3 patients) in the air group and 12.7% (8 patients) in the C₃F₈ gas group.

After the initial procedure, 4 patients in the air group in whom the reattachment failed were treated with C₃F₈ gas. Following the intention-to-treat principle, we did not exclude these 4 patients who crossed over from the analysis. Three patients in the air group and 2 in the C₃F₈ gas group were lost to follow-up. We assumed that they left the study because of an unsatisfactory result, and we included these patients in the group with detached retinas during analysis. Retinal reattachment rates evaluated after a single procedure were 38 of 63 patients (60.3%) in the air group and 46 of 63 (73.0%) in the C₃F₈ gas group (**Table 3**). The difference in initial reattachment rates was -12.7% (95% CI, -29.0% to 3.6%), which was not statistically significant (**Figure 2**). The final reattachment rates after repeated pneumatic retinopexy and/or additional surgical procedures was 92.1% (58 of 63 patients) in the air group and 96.8% (61 of 63) in C₃F₈ gas group. The difference in final reattachment rates was -4.7% (95% CI, -12.7% to 3.2%), indicating an equivalent effect of air and C₃F₈ gas on the final reattachment rate.

Although the intention-to-treat method can preserve the value of the randomization, substantial discontinuation or crossover between treatments will cause it to underestimate the magnitude of the treatment effect. Therefore, using intention-to-treat analysis might make the groups more similar and increase the likelihood that the treatments will be equivalent. We also used the per-protocol method to analyze our data. The final reattachment rates after repeated pneumatic retinopexy and/or surgical procedures were 91.5% (54 of 59 patients) in the air group and 97.0% (65 of 67) in the C₃F₈ gas group.

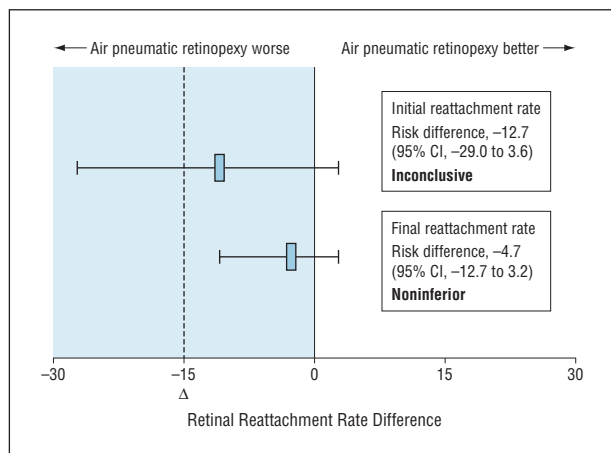


Figure 2. Retinal reattachment rate difference, determined by subtracting the perfluoropropane treatment reattachment rate from the air treatment reattachment rate. The vertical dotted line represents the margin of clinical equivalence; the vertical solid line, the null effect; and the error bars, 2-sided 95% confidence intervals (CIs). The shaded area indicates the zone of inferiority. For the initial reattachment rate difference (upper bar), the 95% CI includes Δ (which indicates the acceptable margin of noninferiority in effectiveness of treatment) and zero, and the difference is nonsignificant but the result regarding noninferiority is inconclusive. For the final reattachment rate difference (lower bar), the 95% CI extends to the right of Δ and includes zero, and the air treatment is noninferior but not shown to be superior.

The difference in final reattachment rates was -5.5% , which was similar to the result from the intention-to-treat analysis. This similarity indicates that pneumatic retinopathy using air is noninferior but not superior to retinopathy using C_3F_8 gas. In other words, there was an equivalent effect on the final reattachment rate. Final visual acuity results were slightly better in the C_3F_8 group compared with the air group, but the difference was not statistically significant ($P=.61$) (Table 3).

COMMENT

The results of this study demonstrate that final visual acuity and reattachment rates after pneumatic retinopathy for RRD were similar when using filtered air or C_3F_8 gas. This finding agrees well with previous studies.^{3,16,17} In a collaborative study of 100 cases, Hilton and coworkers³ demonstrated a reattachment rate of 78% after a single pneumatic retinopathy using C_3F_8 gas, with subsequent procedures resulting in a final reattachment rate of 98%.

Partial vitreal gas filling induces both biochemical and structural alterations and might predispose the eye to PVR, epimacular membrane, and new or missed break formation. From the previous reports, PVR was 5.2%, epimacular membrane was 2% to 4%, and new or missed retinal break formation was 11.7%.¹⁸ Therefore, some researchers used air in an attempt to minimize vitreous disturbance and reported satisfactory results. In 1990, the idea of using nonexpanding gas of short duration in pneumatic retinopathy was first introduced by Carim.¹² He used variable amounts of air (up to 1.0 mL) and had a reattachment rate of 75%. Three years later, Sebag and Tang¹⁹ performed pneumatic retinopathy using 0.8 mL of filtered air, with a reattachment rate of 87% (39 of 45 patients) after a single intravitreal injection. In that case series, paracentesis of the anterior chamber was performed

in all patients. Yospaiboon and Sajjapong¹³ also demonstrated a reattachment rate of 75% following a single injection of 0.3 mL of air for pneumatic retinopathy, with a final reattachment rate of 90% after subsequent procedures. The reattachment rate in phakic eyes was 88% following a single air injection and 94% after subsequent procedures. They concluded that pneumatic retinopathy with air can be performed in selected cases of phakic retinal detachment with a success rate that is comparable to that of the procedure using expansile gases.

Two gas properties, surface tension and buoyancy, play roles in the mechanism of pneumatic retinopathy. A gas bubble occludes the retinal break, permitting the retinal pigment epithelium to remove subretinal fluid, and then presses the retina against the retinal pigment epithelium, sheltering the edge of the break from eddy currents until a chorioretinal scar is formed, sealing the break. Generally, mild chorioretinal adhesion after laser photocoagulation occurs within 24 hours, moderate adhesion in 5 to 7 days, and strong adhesion in 10 to 14 days. Because moderate chorioretinal adhesion was noted 5 to 7 days after retinopathy, the air bubble, with a half-life of 24 to 48 hours and a duration of 5 to 6 days, also has these 2 properties and remains in the eye long enough to carry out its task.

Although some retinal surgeons use pneumatic retinopathy for small or limited detachments only, we routinely attempt the procedure in all patients with RRD—even those with total detachments—as long as they meet the eligibility criteria. Our clinical experience is that pneumatic retinopathy works well.

Reattachment failure occurs for 2 main reasons: (1) persistent vitreous traction on the break such that the buoyancy of the bubble fails to close the break and (2) development of new or sequential breaks, presumably secondary to vitreous traction that is promoted by a bubble. In this study, the incidence of new or missed breaks in the C_3F_8 gas group (12.7%) was comparable to that reported in previous studies (11.7%).¹⁸ The C_3F_8 gas group had a much higher rate of new or missed breaks (compared with 4.8% for the air group), which may be attributed to a greater vitreous traction effect caused by the progressive expansile gas.

As we noted, reattachments in 3 patients in the air group and 8 in the C_3F_8 gas group failed because of a new or missed break. The remaining failures (22 in the air group and 9 in the C_3F_8 gas group) were attributed to too much residual vitreous traction, which allowed the break to flatten or caused a reopening despite chorioretinal adhesion.

Our study is the first, to our knowledge, to directly compare air and C_3F_8 gas in a double-blind, randomized, controlled trial. Furthermore, the number of patients who were lost to follow-up after randomization was minimal. However, we controlled this problem with a sensitivity analysis in which the assumed best (all attached) or worst (all detached) did not change the result of the primary outcome. All these factors strengthen the validity of our conclusions.

The one limitation of this study was the blinding. Although the patients, those administering the intervention, and those assessing the outcomes were unaware of the group assignment, the assessor could determine that

air had been administered because it was reabsorbed faster than expansile gas. The assessor, therefore, might have had selection bias for repeated injections. The crossover also might have biased the study toward equivalency. In those cases, we used both intention-to-treat and per-protocol methods for analysis. The similar results increase the confidence in our conclusions.

In summary, pneumatic retinopathy using air is associated with a nonsignificantly lower initial reattachment rate than is pneumatic retinopathy using C₃F₈ gas but results in an equivalent final reattachment rate and final visual recovery. We recommend using either filtered air or C₃F₈ when treating RRD by pneumatic retinopathy.

Submitted for Publication: October 23, 2009; final revision received May 6, 2010; accepted May 10, 2010.

Correspondence: Yosanan Yospaiboon, MD, Department of Ophthalmology, Faculty of Medicine, Khon Kaen University, 123 Mitraparp Hwy, Muang District, Khon Kaen 40002, Thailand (yosanan@kku.ac.th).

Financial Disclosure: None reported.

Funding/Support: This study was supported by a Senior Research Scholar award from the Thailand Research Fund.

Additional Contributions: Pantipa Wongwai, MD, recruited patients, Pisake Lumbiganon, MD, MS, provided advice concerning the research methods, and Michael G. Morley, MD, assisted with the English presentation of the manuscript.

REFERENCES

- Hilton GF, Grizzard WS. Pneumatic retinopathy: a two-step outpatient operation without conjunctival incision. *Ophthalmology*. 1986;93(5):626-641.
- Dominguez DA, Boyd BF, Gordon S. Repeated insufflation of expansive gas. *Highlights Ophthalmol Lett*. 1986;14:1-14.
- Hilton GF, Kelly NE, Salzano TC, Tornambe PE, Wells JW, Wendel RT. Pneumatic retinopathy: a collaborative report of the first 100 cases. *Ophthalmology*. 1987;94(4):307-314.
- Algvere P, Hallnäs K, Palmqvist BM. Success and complications of pneumatic retinopathy. *Am J Ophthalmol*. 1988;106(4):400-404.
- Chen JC, Robertson JE, Coonan P, et al. Results and complications of pneumatic retinopathy. *Ophthalmology*. 1988;95(5):601-606.
- Lowe MA, McDonald HR, Campo RV, Boyer DS, Schatz H. Pneumatic retinopathy: surgical results. *Arch Ophthalmol*. 1988;106(12):1672-1676.
- McAllister IL, Zegarra H, Meyers SM, Gutman FA. Treatment of retinal detachments with multiple breaks by pneumatic retinopathy. *Arch Ophthalmol*. 1987;105(7):913-916.
- McAllister IL, Meyers SM, Zegarra H, Gutman FA, Zakov ZN, Beck GJ. Comparison of pneumatic retinopathy with alternative surgical techniques. *Ophthalmology*. 1988;95(7):877-883.
- Mortensen KK, Sjolie AK. Retinal detachment treated by pneumatic retinopathy. *Acta Ophthalmol (Copenh)*. 1988;66(2):187-189.
- Prasaritha W, Simaraj P, Lawtiantong T. Pneumatic retinopathy. *Thai J Ophthalmol*. 1989;3:13-16.
- Yospaiboon Y, Sanguansak T, Ratanapakom T, Sinawat S. Surgical outcomes in rhegmatogenous retinal detachment at Srinagarind Hospital. *J Med Assoc Thai*. 2005;88(suppl 9):S69-S76.
- Carim MM. Scleral buckling after failed air injection pneumatic retinopathy. *Arch Ophthalmol*. 1990;108(1):11-12.
- Yospaiboon Y, Sajjapong P. Pneumatic retinopathy using filtered air: a preliminary report. *Thai J Ophthalmol*. 1995;9:139-146.
- Fineberg E, Machemer R, Sullivan P, Norton EW, Hamasaki D, Anderson D. Sulfur hexafluoride in owl monkey vitreous cavity. *Am J Ophthalmol*. 1975;79(1):67-76.
- Jones B, Jarvis P, Lewis JA, Ebbutt AF. Trials to assess equivalence: the importance of rigorous methods. *BMJ*. 1996;313(7048):36-39.
- Tornambe PE, Hilton GF, Brinton DA, et al. Pneumatic retinopathy: a two-year follow-up study of the multicenter clinical trial comparing pneumatic retinopathy with scleral buckling. *Ophthalmology*. 1991;98(7):1115-1123.
- Tornambe PE, Hilton GF; Retinal Detachment Study Group. Pneumatic retinopathy: a multicenter randomized controlled clinical trial comparing pneumatic retinopathy with scleral buckling. *Ophthalmology*. 1989;96(6):772-784.
- Chan CK, Lin SG, Nuthi AS, Salib DM. Pneumatic retinopathy for the repair of retinal detachments: a comprehensive review (1986-2007). *Surv Ophthalmol*. 2008;53(5):443-478.
- Sebag J, Tang M. Pneumatic retinopathy using only air. *Retina*. 1993;13(1):8-12.

100 Years Ago in the Archives

In the various discussions which have taken place, from time to time, as to the advantages and disadvantages of this operation, it has been contended, by the opponents of the operation for the extraction of the cataract in the capsule, that one of the chief objections to this operation is the frequency of the escape of vitreous. This being the only complication which is at all frequent, and the one which is most commonly met with beginners in this operation, I inquired from Major Smith on my arrival in Jullundur in 1906 if any series of cases had ever been published, in which the after-effects of escape of vitreous in this operation were given.

Reference: Lister AEJ. The after-effects of escape of the vitreous during the operation of extraction of cataract in the capsule, by Smith's operation. *Arch Ophthalmol*. 1910;39:1.