

PNEUMATIC RETINOPEXY FOR RETINAL DETACHMENT ASSOCIATED WITH SEVERE CHOROIDAL DETACHMENT

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Purpose: The purpose of this study was to evaluate the role of pneumatic retinopexy as an initial management of retinal detachment associated with hypotony, severe choroidal detachment, and vitritis.

Methods: Retrospective, interventional, noncomparative case series. We included nine eyes from nine patients (six women and three men) with retinal detachment associated with hypotony, severe choroidal detachment, and vitritis managed with pneumatic retinopexy (either SF6 or C3F8) as their initial management between January 1, 1992, and December 31, 2007.

Results: Hypotony and choroidal detachment were rapidly and significantly improved 1 to 3 days after pneumatic retinopexy in all patients. The extent of retinal detachment was decreased in five patients. After vitreoretinal surgery for these five patients, all had attached retina. Complete reattachment of the retina was noted in four patients after pneumatic retinopexy. Two of these patients did not require further surgery because the entire retina remained attached at 6 months and 16 months postoperatively.

Conclusion: Pneumatic retinopexy is a useful initial procedure in managing retinal detachment associated with hypotony, severe choroidal detachment, and vitritis. By rapidly resolving the hypotony and choroidal detachments, it facilitates subsequent surgical repair of this complicated retinal detachment. In addition, complete retinal reattachment after pneumatic retinopexy alone was initially achieved in 33% of eyes.

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Choroidal detachment is a rare complication of rhegmatogenous retinal detachment with an incidence of 2% to 4.5%.^{1,2} The prognosis of conventional scleral buckle surgery with or without drainage of suprachoroidal fluid was unfavorable because of delayed diagnosis, poor retinal reattachment rates with scleral buckling, and high incidence of postoperative proliferative vitreoretinopathy.^{1–3}

Recently, encouraging outcomes were obtained from primary vitrectomy with or without scleral buckle support.^{4–7} Although the overall anatomical success rates were 95% to 100% after one or more operations, the visual outcomes were poor.^{4–7} Many surgeons used systemic steroids for several days to several weeks before operation to reduce the intraocular inflammation and, most importantly, to resolve the choroidal detachment.^{4–7} Delayed surgery and prolonged macular detachment may be factors leading to poor visual outcome in these patients. Patients with persistent choroidal detachment not only require additional procedures, such as sclerotomy and drainage of suprachoroidal fluid during the operation, but also had a higher risk of complications such as improper positioning of infusion cannula and lens touch by instruments.

Pneumatic retinopexy (PR) is a possible alternative to scleral buckling in the treatment of uncomplicated rhegmatogenous retinal detachment.⁸ The single operation success rate was between 70% and

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79.6%.⁸ Although some patients with persistent retinal detachment after PR require further surgery, the gas bubble did not compromise the overall retinal reattachment rate or final visual acuity.^{8,9} However, to the best of our knowledge, PR has not been reported as an initial treatment for retinal detachment associated with severe choroidal detachment. The purpose of the present study was to evaluate the role of PR as an initial management of this particular syndrome to resolve the hypotony and choroidal detachment and to facilitate retinal detachment repair.

Material and Methods

We conducted a retrospective chart review of all patients presenting with rhegmatogenous retinal detachment, hypotony, severe choroidal detachment, and vitritis. Patients who received PR as their initial management between January 1, 1992, and December 31, 2007, were enrolled from 3 different practices. Severe choroidal detachment was defined as a total of 360° or near total choroidal detachment, which was diagnosed preoperatively by either indirect ophthalmoscopic examination or B-scan ultrasonography. Exclusion criteria were 1) only localized or limited choroidal detachment; 2) history of open-globe ocular trauma; and 3) history of previous vitreoretinal surgery. Data collected included the patient's age, gender, initial visual acuity, clinical manifestations, surgical procedures, late complications, and final visual outcome. Main outcome measures in this study were resolution of choroidal detachment and retinal reattachment after PR or subsequent surgery. Successful reattachment of retina after PR alone is defined as reattachment of retina for more than 1 month after PR.

The representative surgical procedures were briefly described as follows: after discussion of the potential benefits and risks of PR and possible subsequent vitreoretinal surgeries, written informed consent was obtained from all patients. Pneumatic retinopexy was done in the office with sulfur hexafluoride (SF6) or perfluoropropane (C3F8) according to the decision of an individual doctor. A volume of 0.3-mL SF6 or 0.6-mL C3F8 was injected into the vitreous cavity through the pars plana. Cryotherapy was done if possible at the same time. Patients were instructed to either position facedown or maintain a position that allowed the gas bubble to tamponade the retinal breaks. Topical steroid and antibiotics with or without oral steroid were given. Patients were followed 1 to 3 days after the pneumatic procedure. As a precaution, we alert all patients receiving PR regarding the risk of rapid intraocular pressure increase. Patients are instructed to come back to our clinic immediately if they were to experience

severe headache, eye pain, redness of the eye, or any other symptoms related to ocular hypertension. Temporary antiglaucoma agents were prescribed if intraocular pressure measured higher than 30 mmHg. Patients with reattachment of the entire retina were managed by either cryotherapy or laser photocoagulation around the retinal breaks. If retinal detachment persisted or recurred, further vitreoretinal surgery such as pars plana vitrectomy, scleral buckle, or a combination of both was performed within 1 week after resolution of the choroidal detachments.

The vitrectomy and scleral buckle surgery were done under either general or local anesthesia. The patients were prepped and draped in the usual sterile ophthalmic manner including 5% Betadine into the cul-de-sac. After 360° peritomy, the recti muscles were isolated and placed on 4-0 silk ties. Encircling buckling was used to support the vitreous base region. Either a silicone strip or a sponge was secured in each quadrant by a 5-0 nylon horizontal mattress suture. The silicone strip was brought together using a silicone sleeve. If external drainage of subretinal fluid was done, BSS (Alcon Laboratories, Fort Worth, TX) was injected into the vitreous cavity to maintain a firm eye to prevent redevelopment of choroidal detachment. The vitrectomy technique entailed a conventional 3-port pars plana approach with the sclerotomies placed 3 mm to 3.5 mm posterior to the limbus. An infusion cannula was fixated into the inferotemporal sclerotomy. The infusion was turned on after it was ensured to be well within the vitreous cavity. Vitrectomy was performed using high-speed cutting and very low suction. Perfluorocarbon liquid was placed into the eye to stabilize the retina and displace subretinal fluid anteriorly. The peripheral vitreous was trimmed down in all quadrants, aided by scleral indentation by the assistant to release any vitreous traction. During fluid-gas exchange, the subretinal fluid was then removed using the cannulated extrusion needle. The buckle was then adjusted to create a moderate buckling height. Endolaser photocoagulation was then placed around the retinal breaks. The vitreous cavity was then filled with either long-acting gas (20% SF6 or 14% C3F8) or silicone oil at the end of surgery. In patients using long-acting gas, a prone position or facedown position was required for patients until the absorption of most part of gas bubble.

Results

Nine eyes of nine patients were included in this study. All of them presented with hypotony, mild to moderate vitritis, bullous retinal detachment, and

severe choroidal detachment. Two (Cases 6 and 8) representative fundus illustrations are shown in Figure 1. Table 1 summarizes the clinical manifestations and treatment courses of these patients. The presenting vision ranged from hand motion to 4/200. The average initial intraocular pressure was 3.3 mmHg (range: 0–9 mmHg). Five eyes were pseudophakic, three eyes were phakic, and one eye was aphakic. Seven eyes had total or subtotal (defined as attached area less than one quadrant) retinal detachment. The other two eyes had two-quadrant bullous retinal detachment. All eyes were macular off, and two eyes presented with grade C proliferative vitreoretinopathy. Three patients also received systemic steroids.

All the surgeries were done by three doctors (G.T.K., R.D.B., and D.A.L.). Pneumatic retinopexy was used as initial treatment for all patients. Two eyes (Cases 2 and 8) received cryotherapy at the same time of PR. C3F8 was used in 5 eyes and SF6 in 4 eyes. Intraocular pressure restored to normal or slightly higher than normal after the long-acting gas injection in all patients at 1 to 3 days. Few eyes may still have low intraocular pressures on the second day after injection. However, the intraocular pressures could continue to increase in the following few days. Choroidal detachment was rapidly and significantly improved after the gas bubble injection in all patients. Almost all choroidal detachments resolved within the first 1 to 3 days, and, if present, only limited localized choroidal detachment was left. The reattachment rate after PR alone was 33%. Four eyes (Cases 1, 3, 7, and 8) had complete reattachment of the retina after PR. Two eyes (Cases 1 and 3) underwent laser photocoagulation, and 1 eye (Case 7) underwent cryotherapy around the breaks. No recurrence of retinal detachment was noted in 2 eyes (Cases 3 and 7) after 6 and 14 months of follow-up, respectively. One eye (Case 8) developed late recurrent inferior retinal detachment at 3 months after PR. However, further surgery was refused because of the poor visual prognosis, multiple major systemic diseases, and elderly age (90 years). One eye (Case 1) had recurrence of retinal detachment with choroidal detachment after the intraocular gas bubble reabsorbed. This patient received combined vitrectomy and scleral buckle surgery at 4 weeks after PR. The extent of retinal detachment was decreased, but not completely resolved, after PR in five patients. Definitive retinal reattachment surgery was performed within 1 week after PR. Overall, primary vitrectomy combined with scleral buckle was performed in five eyes, and scleral buckle alone was performed in one eye. None of the eyes required drainage of choroidal detachment, and uveitis improved in all eyes before vitreoretinal

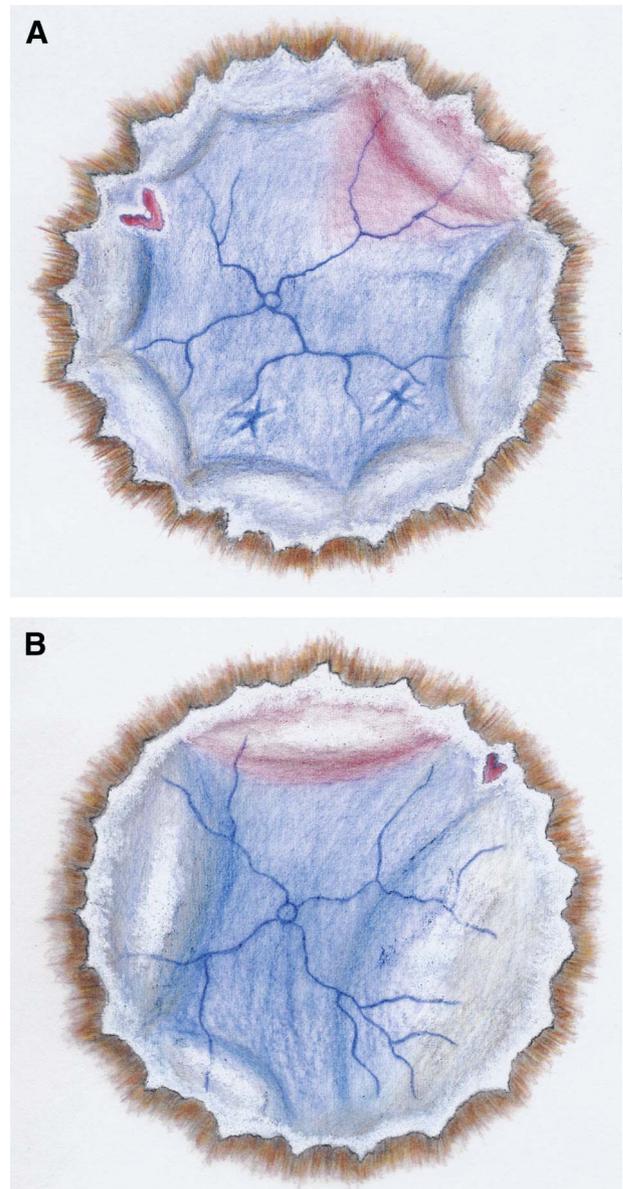


Fig. 1. Representative fundus illustrations of our patients. **A**, Case 6. A 69-year-old woman had progressive visual loss of her left eye. Fundus examination showed a superonasal retinal tear, subtotal retinal detachment, full-thickness retinal folds over inferior retina, and 360° choroidal detachment. The intraocular pressure was 0 mmHg. **B**, Case 8. A 90-year-old woman had intracapsular cataract extraction and anterior chamber intraocular lens implantation in both eyes 10 years ago. She had superotemporal retinal tear, subtotal retinal detachment, and near total choroidal detachment in her left eye. The intraocular pressure is 0 mmHg.

surgery. Silicone oil was used at the end of surgery in 1 patient (Case 5). All these patients had anatomical reattachment of retina after the operation. There were no major intraoperative or postoperative complications, such as recurrence of choroidal detachment, suprachoroidal hemorrhage, subretinal hemorrhage, or endophthalmitis, that were noted in this study. Improvement of visual acuity was noted in all

Table 1. The Clinical Manifestation and Treatment Course of Patients

| | Age and Gender | Eye | Lens Status | Extent of RD | Macula | Total Number and Location of Break(s) | | Grade C PVR | Initial IOP |
|---|----------------|-----|-------------|--------------|--------|---------------------------------------|--|-------------|-------------|
| | | | | | | | | | |
| 1 | 64 M | OD | PCIOL | 2 quadrants | Off | 2, superotemporal | | No | 1 |
| 2 | 58 M | OD | Phakic | Total | Off | 1, superior | | No | 9 |
| 3 | 62 M | OS | PCIOL | Total | Off | 1, superotemporal | | No | 7 |
| 4 | 58 M | OS | PCIOL | Total | Off | 3, nasal and superior | | No | 9 |
| 5 | 67 M | OD | Phakic | Total | Off | 2, superior | | Yes | 0 |
| 6 | 69 F | OS | Aphakic | Subtotal | Off | 1, superonasal | | Yes | 0 |
| 7 | 68 M | OS | Phakic | 2 quadrants | Off | 1, superotemporal | | No | 4 |
| 8 | 90 F | OS | ACIOL | Subtotal | Off | 1, superotemporal | | No | 0 |
| 9 | 67 F | OD | PCIOL | Total | Off | 1, superonasal | | No | 0 |

| | Oral Steroid | Gas for PR | IOP, Day 1 | VR Surgery | Follow-up | Visual Acuity | | Late Complications |
|---|--------------|------------|------------|------------|------------|---------------|--------|-------------------------|
| | | | | | | Initial | Final | |
| 1 | Yes | C3F8 | 7 | VT + SB | 13 years | HM | 20/400 | Thick ERM |
| 2 | No | SF6 | 27 | VT + SB | 1 month | 20/200 | 20/100 | — |
| 3 | No | C3F8 | 13 | No | 6 months | 20/200 | 20/70 | Fine ERM |
| 4 | No | SF6 | 10 | VT + SB | 2 months | HM | 20/400 | — |
| 5 | Yes | SF6 | 7 | VT + SB | 11 months | HM | 8/200 | — |
| 6 | No | SF6 | 1 | SB | 12 months | HM | 20/400 | Thick ERM |
| 7 | No | C3F8 | 23 | No | 14 months | 4/200 | 20/30 | — |
| 8 | No | C3F8 | | No | 3 months | HM | 20/100 | RD recurred at 3 months |
| 9 | Yes | C3F8 | | VT + SB | 1.5 months | HM | 3/200 | — |

ACIOL, anterior chamber intraocular lens implant; ERM, epiretinal membrane; F, female; HM, hand motion; M, male; IOP, intraocular pressure; IOP, Day 1, intraocular pressure at post-injection Day 1; PCIOL, posterior chamber intraocular lens implant; PVR, proliferative vitreoretinopathy; RD, retinal detachment; SB, scleral buckle; VR, vitreoretinal; VT, vitrectomy.

patients. The median visual acuity improved to 20/100 (range: 3/200–20/30) at final follow-up. Late complications included epiretinal membrane in 3 eyes between 3 months and 1 year after operation. One eye (Case 1) underwent vitrectomy and membrane peeling to remove the thick epiretinal membrane. One eye (Case 5) had silicone oil removal at 4 months without recurrent detachment.

Two patients (Cases 5 and 6) developed high intraocular pressures without pain after PR. In Case 5, intraocular pressure was increased to 40 mmHg 1 week after injection; whereas in Case 6, intraocular pressure was 42 mmHg 2 days after injection. In both patients, the elevated intraocular pressure had improved within 2 days under topical and oral antiglaucoma agent treatments.

Discussion

The syndrome of choroidal detachment, hypotony, and vitritis associated with retinal detachment is uncommon, difficult to repair, and has a poor visual prognosis.^{1–3} These eyes are at high risk for proliferative vitreoretinopathy, which accounts for most cases of recurrent retinal detachment and poor visual outcome.^{1,3,7,10} Although the exact mechanism of this

syndrome is not fully understood, hypotony produced by acute retinal detachment was believed to be one of the most important factors.^{1,3,7,10} Hypotony may precipitate choroidal detachment by arteriolar dilation and ciliary body swelling and detachment. This leads to breakdown of the blood–retinal barrier and transudation of excessive serum-containing fibronectin and platelet-derived growth factor. These components lead to migration of retinal pigment epithelium and the beginning of the proliferative vitreoretinopathy process.¹¹ Early restoration of intraocular pressure and resolution of choroidal detachment is a reasonable approach to optimize the final outcome and was successfully accomplished by the intraocular injection of a gas bubble in this series of eyes.

In most previous reports, preoperative systemic steroid was given for several days to several weeks in an attempt to resolve choroidal detachment, reduce inflammation, and increase intraocular pressure before the major vitreoretinal operation.^{4–7} However, the effect is still controversial.^{4–7} Sharma et al⁵ showed that patients treated with preoperative oral steroid for one week had a trend of better single operation success rate (81.8% versus 66.7%). However, patients receiving vitreoretinal surgery immediately had a better chance of increased visual acuity by 2 lines

or more (89% versus 73%). Sharma explained that this might be because of a longer time of macular detachment in those patients taking steroids for 1 week before surgery. Although neither of the above results were statistically significant, this study leaves the role of systemic steroid as uncertain in improving retinal reattachment or visual outcome for this syndrome.

The rationales for using PR in this particular syndrome are 1) rapid increase in intraocular pressure to resolve choroidal detachment; 2) potential tamponade of retinal break to enhance subretinal fluid absorption; and 3) quicker resolution of inflammation. In this present study, we measured the intraocular pressure between 1 and 3 days after PR. All patients had increased intraocular pressure and resolution of most of the choroidal detachments. Sometimes, it may take more than 1 day for restoring the normal intraocular pressure. A possible reason may be that it takes time for adequate aqueous secretion to fill the vitreous cavity volume that was released as a result of the resolution of choroidal detachment. There may be two mechanisms that improved hypotony, and hence choroidal detachment, in these patients. First, injection of gas itself can increase intraocular pressure. Abe et al¹² showed that the average intraocular pressure immediately after SF6 injection in 22 eyes was 46.5 ± 19.6 mmHg. In this retrospective study, surgeons individually decided on SF6 or C3F8 for use in those eyes. Second, tamponade of the retinal breaks by the gas bubble prevents further inflow of fluid from vitreous cavity into the subretinal space and may potentially even allow retinal reattachment in selected cases with the gas bubble alone. This is the mechanism of how PR could be used as a less invasive alternative treatment for uncomplicated retinal detachment when the breaks are located in superior quadrants.⁸ In this present study, the reduction in the extent of retinal detachment in all patients at 1 to 3 days after PR supports that fluid flow from vitreous cavity to the subretinal space was decreased by the gas bubble tamponade. In fact, we were not able to localize all retinal breaks in all eyes during the initial fundus examination because of severe choroidal detachment and vitritis. Subsequently, on examination of the fundus after resolution of choroidal detachments, inferior breaks were not present in these eyes. Based on this study, the use of PR in this situation is uncertain if an inferior retinal break is present. Although the gas bubble may not be able to tamponade the inferior retinal break, theoretically, it may still be able to decrease choroidal detachment and vitritis by immediate elevation of intraocular pressure. The promising result of this study shows that intravitreal injection of a long-acting gas bubble is an effective and safe

technique in rapid restoration of intraocular pressure and resolution of choroidal detachment, thus facilitating subsequent definite retinal detachment repair.

The retinal reattachment rate of PR alone was 33% in this series, which is quite promising considering the poor prognosis and low retinal reattachment associated with this particular syndrome. However, 66.7% patients still required further reattachment surgery as a definitive procedure. The most significant benefit of the pneumatic procedure is facilitation of the more definitive procedure by resolution of the choroidal detachment and decreasing inflammation and extent of retinal detachment. None of the patients in this series required drainage of choroidal detachment at the time of scleral buckle and vitrectomy surgery. Primary vitrectomy was reported to have encouraging outcomes in the recent reports.⁴⁻⁷ It can reduce the inflammatory factors and retinal pigment epithelium cells in the vitreous cavity. Combined scleral buckle surgery was also performed in most of our patients in consideration of the high risk of proliferative vitreoretinopathy in previous reports.^{1-3,7} One patient (Case 6) received scleral buckle only. This eye was aphakic and presented with a superonasal retinal tear, subtotal retinal detachment, and grade C proliferative vitreoretinopathy with fixed folds in the inferior retina (Figure 1A). After resolution of choroidal detachment by PR, the residual retinal detachment could be successfully repaired by scleral buckle alone. There was no recurrence after 12 months of follow-up. The single operation reattachment rate of scleral buckle was only 35% to 52% in previous series.¹⁻³ The successful retina reattachment in this patient might be because of early resolution of hypotony and choroidal detachment, which would theoretically improve the success of retinal detachment surgery. In fact, all our patients had successful repair of their retinal detachment after PR with or without subsequent vitreoretinal surgery. Only 1 patient had recurrent retinal detachment at 3 months after PR alone, and because of her elderly age and systemic illness, she refused further major vitreoretinal surgery. However, PR allowed this patient to have a relative noninvasive and outpatient procedure, which provided her a chance of retinal detachment repair even with poor systemic health.

There are some other potential advantages of early restoration of intraocular pressure and rapid resolution of choroidal detachment: 1) decreased inflammation; 2) better identification of retinal breaks; 3) ability to apply cryotherapy to the tear without choroidal detachment; 4) lack of need for drainage of supra-choroidal fluid through sclerotomy; 5) facilitation of infusion cannula placement during vitrectomy; and 6) reduction of the risk of lens touch by the infusion

cannula or other instruments during vitrectomy when the vitreous cavity is compressed by high choroidal detachments.

In most of the previous reports, the size and extent of choroidal detachment were not clearly documented. In the series of Sharma et al,⁶ only 6 of 21 patients (29%) belong to the severe choroidal detachment group. However, all patients in our present study had a total 360° or near total choroidal detachments. The result of our present study is quite encouraging in consideration of the severity of this complicated retinal detachment with associated choroidal detachment and vitritis. The limitations of our study include the small number of cases and the relatively short follow-up time. However, the results were encouraging for the use of pneumatic resolution of choroidal detachment for this particular syndrome. In our study, the visual outcome was poor even after anatomic reattachment of the retina. The causes contributing to the poor visual outcome include chronic total or subtotal retinal detachment with macular involvement in all patients, development of epiretinal membrane, and recurrent retinal detachment. Further studies are warranted to determine the overall success rate, the optimal time to proceed to definitive vitreoretinal surgeries, visual outcome, and incidence of long-term complications such as proliferative vitreoretinopathy and macular pucker using this strategy beginning with the use of intraocular gas. Its efficacy in eyes with inferior breaks is also needed to be determined.

Pneumatic retinopexy is a feasible modality in the initial management of patients with rhegmatogenous retinal detachment associated with hypotony, severe choroidal detachment, and vitritis. By rapidly restoring intraocular pressure and resolving choroidal detachments, the gas bubble can facilitate subsequent vitreoretinal surgery. In addition, complete initial retinal reattachment with PR alone may be possible in 33% of these eyes.

Key words: pneumatic retinopexy, retinal detachment, vitreoretinal surgery.

References

1. Seelenfreund MH, Kraushar MF, Schepens CL, et al. Choroidal detachment associated with primary retinal detachment. *Arch Ophthalmol* 1974;91:254–258.
2. Gottlieb F. Combined choroidal and retinal detachment. *Arch Ophthalmol* 1972;88:481–486.
3. Rahman N, Harris GS. Choroidal detachment associated with retinal detachment as a presenting finding. *Can J Ophthalmol* 1992;27:245–248.
4. Yang CM. Pars plana vitrectomy in the treatment of combined rhegmatogenous retinal detachment and choroidal detachment in aphakic or pseudophakic patients. *Ophthalmic Surg Lasers* 1997; 28:288–293.
5. Sharma T, Gopal L, Reddy RK, et al. Primary vitrectomy for combined rhegmatogenous retinal detachment and choroidal detachment with or without oral corticosteroids: a pilot study. *Retina* 2005;25:152–157.
6. Sharma T, Gopal L, Badrinath SS. Primary vitrectomy for rhegmatogenous retinal detachment associated with choroidal detachment. *Ophthalmology* 1998;105:2282–2285.
7. Ghoraba HH. Primary vitrectomy for the management of rhegmatogenous retinal detachment associated with choroidal detachment. *Graefes Arch Clin Exp Ophthalmol* 2001;239: 733–736.
8. Saw SM, Gazzard G, Wagle AM, et al. An evidence-based analysis of surgical interventions for uncomplicated rhegmatogenous retinal detachment. *Acta Ophthalmol Scand* 2006;84: 606–612.
9. Tornambe PE, Poliner LS, Hilton GF, et al. Comparison of pneumatic retinopexy and scleral buckling in the management of primary rhegmatogenous retinal detachment. *Am J Ophthalmol* 1999;127:741–743.
10. Swan KC, Christensen L, Weisel JT. Choroidal detachment in the surgical treatment of retinal separation. *AMA Arch Ophthalmol* 1956;55:240–245.
11. Campochiaro PA, Jerdan JA, Glaser BM. Serum contains chemoattractants for human retinal pigment epithelial cells. *Arch Ophthalmol* 1984;102:1830–1833.
12. Abe T, Nakajima A, Nakamura H, et al. Intraocular pressure during pneumatic retinopexy. *Ophthalmic Surg Lasers* 1998; 29:391–396.