·Perspective·

Vitreous substitutes: challenges and directions

Qian-Ying Gao[1], Yue Fu[1], Yan-Nian Hui[2]

[1]State Key Laboratory of Ophthalmology, Zhongshan Ophthalmic Center, Sun Yat-sen University, Guangzhou 510060, Guangdong Province, China
[2]Department of Ophthalmology, Xijing Hospital, the Fourth Military Medical University, Xi'an 710032, Shaanxi Province, China
Correspondence to: Qian-Ying Gao. State Key Laboratory of Ophthalmology, Zhongshan Ophthalmic Center, Sun Yat-sen University, Guangzhou 510060, Guangdong Province, China. gaoqy@mail.sysu.edu.cn
Received: 2014-01-19 Accepted: 2014-02-10

Abstract

• **The natural vitreous body has a fine structure and complex functions. The imitation of the natural vitreous body by vitreous substitutes is a challenging work for both researchers and ophthalmologists. Gases, silicone oil, heavy silicone oil and hydrogels, particularly the former two vitreous substitutes are clinically widely used with certain complications. Those, however, are not real artificial vitreous due to lack of structure and function like the natural vitreous body. This article reviews the situations, challenges, and future directions in the development of vitreous substitutes, particularly the experimental and clinical use of a new artificial foldable capsular vitreous body.**

• **KEYWORDS:** vitreous substitute; artificial vitreous; foldable capsular vitreous body; silicone oil
DOI:10.3980/j.issn.2222-3959.2015.03.01

Gao QY, Fu Y, Hui YN. Vitreous substitutes: challenges and directions. *Int J Ophthalmol* 2015;8(3):437-440

STRUCTURES AND FUNCTIONS OF THE VITREOUS BODY

The natural vitreous body is a transparent, gelatinoids structure occupying four-fifths of the volume of the eye. Its thin membrane-like structure corresponds to the vitreous cortex, which extends from the ora serrata to the posterior pole [1]. It is somewhat spherical but slightly flattened meridionally, and there is a cup-shaped depression in its anterior surface fitted with the posterior capsule of the lens. It consists of approximately 99% water by weight, collagen fibers (types II, V/XI, VI, and IX), hyaluronic acid, opticin, fibrillin, and hyaluronan, which can maintain a certain spatial relationship with dipolar water molecules, together with 90% hyalocytes and 10% fibroblasts near the vitreous cortex [1,2]. In adult humans, the vitreous body has an approximate weight of 4 g, a density of 1.0053-1.0089 g/cm^3, a refractive index of 1.3345-1.3348, and a pH range of 7.0-7.4. The physiological function of the vitreous body involves supporting adjacent posterior segment structures, providing an ocular refractive medium, transporting metabolites, such as oxygen, and acting as a cell barrier to inhibit cell migration from the retina to the vitreous cavity [3]. With age, the natural vitreous body gradually shrinks and collapses during the course of syneresis. This phenomenon may eventually lead to posterior vitreous detachment and can play a crucial role in the formation of retinal breaks, which result in rhegmatogenous retinal detachment and a various complications of vitreomacular traction syndrome[4].

CURRENT VITREOUS SUBSTITUTES

The vitreous body cannot regenerate, so the vitreous cavity must be filled with suitable vitreous substitutes that keep the retina in place and prevent insertion of prosthesis after enucleation of the eye. Vitreous substitutes are one of the most interesting and challenging topics of research in ophthalmology [2]. Although the several vitreous substitutes available include inert gas, silicone oil, heavy silicone oil, and hydrogels, to date, octafluoropropane (C3F8) and sulfur hexafluoride (SF6) are the most commonly used in clinics[2]. These gases are spontaneously absorbed in 6 to 80d and then are replaced by aqueous humor most possibly complicated with lens opacification and high intraocular pressure (IOP)[5]. Silicone oil is hydrophobic, viscous, transparent, and stable, with a specific gravity of 0.97 g/mL and a refractive index of 1.404. The viscosity of silicone oil is measured in centistokes, and it varies linearly in chain length and molecular weight. Varieties with 1000 and 5000 centistokes are commonly used in clinics. Their surface tension is approximately 40 mN/m. Introduced by Cibis *et al* [6] in 1962, silicone oil has been the most important adjunct for internal tamponade in the treatment of complicated retinal or choroidal detachment for the past five decades. It is commonly applied to treat superior retinal detachment through buoyancy force and high interfacial tension, and it is the only substance currently accepted as a long-term vitreous substitute. Silicone oil is the preferred choice in complex retinal detachments, such as long-standing rhegmatogenous retinal detachment, traction retinal detachment, giant retinal tears, proliferative diabetic retinopathy, and severe endophthalmitis involving the posterior segment.

However, the use of silicone oil has not always been successful. An anatomic success rate of around 70% was reported, with complications that include cataract, keratopathy, anterior chamber oil emulsification, and glaucoma. Several reports demonstrated the migration of silicone oil droplets into the retina and the optic nerve. Others showed the widespread loss of myelinated optic nerve fibers caused by the oil's free-fluid characteristics within the eye[7,8].

Heavy silicone oil (HSO), which is a solution of perfluorohexyloctane and silicone oil prepared as an internal tamponade, has recently been used in retinal detachment surgery. However, it causes complications, such as emulsification and inflammatory reactions[9]. The preliminary results of a recent multicentric randomized trial failed to demonstrate the real superiority of HSO in comparison with standard silicone oil in eyes with proliferative vitreoretinopathy of the lower retina[10].

Hydrogels and smart hydrogels seem the best candidates as long-term vitreous substitutes because they show excellent transparency and good biocompatibility. They can act as viscoelastic shock-absorbing materials, thereby closely mimicking the behavior of natural vitreous body. Because hydrogels are networks of polymer chains that contain 99.9% water, they are hydrophilic and not flowable. Recently, several cross-linked polymeric hydrogels have been proposed, such as poly (vinyl alcohol) (PVA), poly (1-vinyl-2-pyrrolidone), poly (acrylamide) (PAA), and poly (ethylene glycol) (PEG) [2,11-13]. They showed excellent biocompatibility, are biodegradable, and mimic closely the physico-mechanical properties of natural vitreous body [2]. However, many issues, such as retinal toxicity, increased IOP, and the formation of opacities still need to be addressed. Fragmentation and changes in viscoelastic properties and resiliency after injection through a small-gauge needle have also been found in some types of hydrogels. Smart hydrogels are a relatively new class of stimuli-sensitive hydrogels. They possess the common properties of conventional hydrogels, and they can respond to a variety of signals, including PH, temperature, light, pressure, electric fields, and chemicals [14]. Generally, smart hydrogels appear promising, but research on their use is still at an early experimental stage, and their effects of long-term toxicity are unknown[5].

CHALLENGES TOWARDS VITREOUS SUBSTITUTES

In order to mimic perfectly the natural vitreous body, current research on vitreous substitutes aims to develop ideal materials that are nontoxic and inert and transparent, with good water and oxygen permeability, high compatibility, and good elasticity [15-20]. The materials must be hydrophilic and capable of forming a gel within the vitreous cavity. Therefore, although research over the past 50y has sought to replace the natural vitreous body of the eye, an ideal and permanent vitreous substitute has yet to be found [15]. When the natural vitreous body is speculated from its normal position, it contacts very tender tissues, such as the retina, ciliary body, and lens. Therefore, the vitreous substitute must have specific eye-related compatibility. Speculated from normal functions of the natural vitreous body, the vitreous substitute must have a transparent and vitreous-closed refractive index in order to see clearly, transport metabolites, such as oxygen, and act as a cell barrier to inhibit cell migration. The vitreous substitute should also be injectable such that it easily passes through small incisions. More importantly, bio-reactions between vitreous substitutes and the eye should be seriously considered and evaluated after the vitreous substitute is injected into the vitreous cavity. Even though silicone oil is inert *in vitro*, subsequent bio-degradation is inevitable. In fact, current injected vitreous substitutes, such as silicone oil, heavy oil, and hydrogels, cannot form solid structures, and they are biodegraded by ocular humor over time. In addition, they cannot transport metabolites, such as oxygen.

NEW CONCEPT OF ARTIFICIAL VITREOUS

Silicone oil, heavy oil, and hydrogels are called vitreous substitutes instead of artificial vitreous. Similar to the artificial lens, they are solid in shape and have a refractive function. Our new concept of artificial vitreous includes these qualities. Inspired by the structure of the natural vitreous body, we postulate a novel foldable capsular vitreous body (FCVB) to restore the shape and function of the natural vitreous body [21]. FCVB is a globally innovative product developed by the State Key Laboratory of Ophthalmology, Zhongshan Ophthalmic Center, Sun Yat-sen University and jointly produced by Guangzhou Vesber Biotechnology Co., Ltd. FCVB can be regarded as an artificial vitreous and consists of a thin vitreous-shaped capsule, a drain tube, and a valve. After foldable implantation into the eye, an injectable medium, such as a balanced salt solution (BSS), silicone oil, or hydrogels, is then injected into the capsule which inflated to support the retina. The capsular material of FCVB is silicone rubber. The capsule was fabricated *via* a computer simulation of the human and rabbit vitreous cavities. The control of the IOP is achieved with adjusting the amount of injected medium through the tube-valve system [21]. Too much will lead to anterior segment ischemia and neovascularization. After the medium was injected into the capsule through the tube-valve system, the valve was subsequently fixed onto the sclera surface similar to the glaucoma valve (Figure 1).

In our experiments with animal models, FCVB was found to mimic closely the morphology of the natural vitreous body and to restore its physiological functions, including

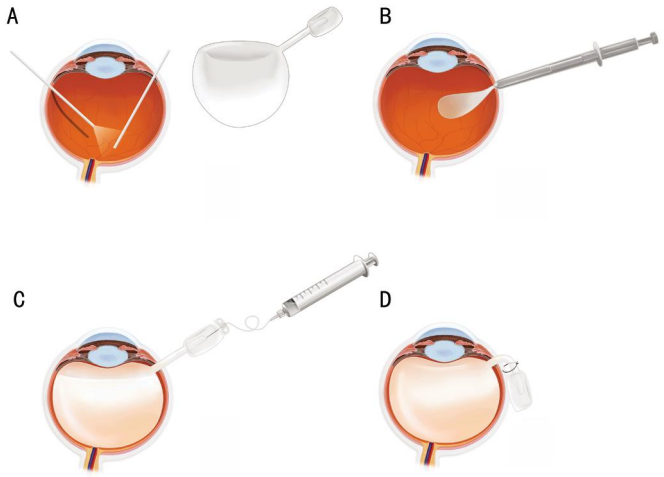

Figure 1 Implantation of the FCVB into the vitreous cavity A: Pars planar vitrectomy and fluid air exchange; B: The capsule was folded and implanted into the vitreous cavity; C: Silicone oil was injected into the capsule through a silicone tube-valve system to support the retina; D: The valve was subsequently fixed onto the sclera surface.

360-degree full-filled support, refraction, and cellular physical barriers, without obvious oxygen changes. In contrast, the silicone-oil control group showed obvious partial-filled support for the retina [22-27]. Reports by the State Food and Drug Administration in China showed that the FCVB has good mechanical, optical, and biocompatibility properties [28]. Its optical characteristics indicate that FCVB has high light transmission and laser irradiation stability.

We have conducted a pilot study on the treatment of severe retinal detachment at Zhongshan Ophthalmic Center of China. A standard three-port pars plana vitrectomy was performed, and FCVB was triple folded and sent into the vitreous cavity of three eyes; then silicone oil was injected into the capsule to support the retina. The treated eyes were examined using Goldmann applanation tonometry, fundus photography, optical coherence tomography, noncontact specular microscopy, and ultrasound biomicroscopy during a 12mo follow-up appointment. The results showed good flexibility, safety, and efficacy of FCVB in severe retinal detachment which helped avoid complications induced by silicone oil, such as silicone oil emulsification and migration within the eye, during a 12mo implantation period[29-32]. Based on this result, a much bigger multi-center clinical trial of 122 cases in nine hospitals was conducted in China to ascertain the safety and efficacy of FCVB as an artificial vitreous. The observation periods ranged from 2.5 to 5y and the preliminary results are encouraging. No silicone emulsification was found in these patients at one-year follow-up period. The long-term effects are still under observation.

FCVB prevents silicone oil emulsification in the eye, is a long-term intraocular tamponade, and obviates the need for ocular prosthesis implantation in some severely damaged eyes. However, because it requires a relatively bigger incision and fails to reconstruct completely the oxygen transportation function of the natural vitreous body, FCVB is recommended as an intermediate product for use between silicone oil and ocular prosthesis. Nonetheless, it shows obvious advantages compared to ocular prosthesis. FCVB is patented in 21 countries including China, the United States, Russia, Australia, and Japan. In 2012, FCVB was rated one of four advances in retinal detachment surgery worldwide[33]. In 2013, it was rated one of the ten advances in ocular injury in China.

In addition, due to the tiny apertures in the capsule of FCVB, it can slowly release various drugs, such as dexamethasone sodium phosphate, protein kinase Cα, levofloxacin, and so on. Therefore, FCVB can also be used as an intravitreal and episcleral drug delivery system[34-40].

DIRECTIONS IN VITREOUS SUBSTITUTES

With the exceptions of silicone oil and heavy silicone oil, FCVB is the only artificial vitreous presently undergoing clinical trial. Although the problems of silicone oil emulsification and migration have been solved, and the vitreous cavity is fully filled by FCVB, many tough issues, such as maintaining the function of oxygen and metabolism transportation, need to be resolved. Therefore, much research remains to be done. Future research on vitreous substitute and artificial vitreous should focus on the following topics: solid structure and fully filling, uneasy to biodegradation by aqueous humor in the preceding 6mo, reconstructing the function of oxygen transportation and the metabolism to mimic the natural vitreous body, as well as the previously mentioned refraction, injectability, and biocompatibility.

ACKNOWLEDGEMENTS

Foundations: Supported by the "Twelfth Five-Year" Plan for Science & Technology Support Grant (No. 2012BAI08B02); the National 863 Project (No. 2009AA02Z404); the Guangdong Provincial Industry University Research Cooperation Plan (No. 2010A090200074)

Conflicts of Interest: Gao QY, None; **Fu Y,** None; **Hui YN,** None.

REFERENCES

1 Green WR SJ. Vitreoretinal interface. In: Ryan SJ, (ed.): *Retina* Philadelphia: Elsevier Mosby; 2006:1921-1989

2 Baino F. Towards an ideal biomaterial for vitreous replacement: historical overview and future trends. *Acta Biomater* 2011;7:921-935

3 Le Goff MM, Bishop PN. Adult vitreous structure and postnatal changes. *Eye (Lond)* 2008;22:1214-1222

4 Shao L, Wei W. Vitreomacular traction syndrome. *Chin Med J (Engl)* 2014;127:1566-1571

5 Kleinberg TT, Tzekov RT, Stein L, Ravi N, Kaushal S. Vitreous substitutes: a comprehensive review. *Surv Ophthalmol* 2011;56 (4): 300-323

6 Cibis PA, Becker B, Okun E, Canaan S. The use of liquid silicone in retinal detachment surgery. *Arch Ophthalmol* 1962;68:590-599

7 Ichhpujani P, Jindal A, Jay Katz L. Silicone oil induced glaucoma: A review. *Graefes Arch Clin Exp Ophthalmol* 2009;247(12):1585-1593

8 la Cour M, Lux A, Heegaard S. Visual loss under silicone oil. *Klin Monbl Augenheilkd* 2010;227(3):181-184

9 Morescalchi F, Costagliola C, Duse S, Gambicorti E, Parolini B, Arcidiacono B, Romano MR, Semeraro F. Heavy silicone oil and intraocular inflammation. *Biomed Res Int* 2014;2014:574825

10 Joussen AM, Rizzo S, Kirchhof B, Schrage N, Li X, Lente C, Hilgers RD; HSO-Study Group. Heavy silicone oil versus standard silicone oil in as vitreous tamponade in inferior PVR (HSO study): Interim analysis. *Acta Ophthalmol* 2011;89:e483-489

11 Maruoka S, Matsuura T, Kawasaki K, Okamoto M, Yoshiaki H, Kodama M, Sugiyama M, Annaka M. Biocompatibility of polyvinylalcohol gel as a vitreous substitute. *Curr Eye Res* 2006;31:599-606

12 Pritchard CD, Crafoord S, Andreasson S, Arner KM, O'Shea TM, Langer R, Ghosh FK. Evaluation of viscoelastic poly (ethylene glycol) sols as vitreous substitutes in an experimental vitrectomy model in rabbits. *Acta Biomater* 2011;7(3):936-943

13 Paul D. Hamilton, Hyder A. Aliyar, Nathan Ravi. Biocompatibility of thiol-containing polyacrylamide polymers suitable for ophthalmic applications. *6 th International Biorelated Polymers Symposium. Pennsylvania Convention Center: Division of Polymer Chemistry* 2004; 495-496. http://oasys2.confex.com/acs/228nm/techprogram/P779129.HTM

14 Chaterji S, Kwon IK, Park K. Smart polymeric gels: Redefining the limits of biomedical devices. *Prog Polym Sci* 2007;32(8-9):1083-1122

15 Steijns D, Stilma JS. Vitrectomy: in search of the ideal vitreous replacement. *Ned Tijdschr Geneeskd* 2009;153:A433

16 Donati S, Caprani SM, Airaghi G, Vinciguerra R, Bartalena L, Testa F, Mariotti C, Porta G, Simonelli F, Azzolini C. Vitreous substitutes: the present and the future. *Biomed Res Int* 2014;2014:351804

17 Isakova K, Pralits JO, Repetto R, Romano MR. Mechanical models of the dynamics of vitreous substitutes. *Biomed Res Int* 2014;2014:672926

18 Tao Y, Tong X, Zhang Y, Lai J, Huang Y, Jiang YR, Guo BH. Evaluation of an *in situ* chemically crosslinked hydrogel as a long-term vitreous substitute material. *Acta Biomater* 2013;9:5022-5030

19 Zenoni S, Comi N, Fontana P, Romano MR. The combined use of heavy and light silicone oil in the treatment of complicated retinal detachment with 360° masculine retinal breaks: Tamponade effect or filling effect? *Ann Acad Med Singapore* 2012;41(10):440-443

20 Strotmann F, Wolf I, Galla HJ. The biocompatibility of a polyelectrolyte vitreous body substitute on a high resistance in vitro model of the blood-retinal barrier. *J Biomater Appl* 2013;28(3):334-342

21 Gao Q, Mou S, Ge J, To CH, Hui Y, Liu A, Wang Z, Long C, Tan J. A new strategy to replace the natural vitreous by a novel capsular artificial vitreous body with pressure-control valve. *Eye (Lond)* 2008;22(3):461-468

22 Chen J, Gao Q, Liu Y, Ge J, Cao X, Luo Y, Huang D, Zhou G, Lin S, Lin J, To CH, Siu AW. Clinical device-related article evaluation of morphology and functions of a foldable capsular vitreous body in the rabbit eye. *J Biomed Mater Res B Appl Biomater* 2011;97(2):396-404

23 Gao Q, Chen X, Ge J, Liu Y, Jiang Z, Lin Z, Liu Y. Refractive shifts in four selected artificial vitreous substitutes based on gullstrand-emsley and liou-brennan schematic eyes. *Invest Ophthalmol Vis Sci* 2009;50 (7): 3529-3534

24 Wang P, Gao Q, Jiang Z, Lin J, Liu Y, Chen J, Zhou L, Li H, Yang Q, Wang T. Biocompatibility and retinal support of a foldable capsular vitreous body injected with saline or silicone oil implanted in rabbit eyes. *Clin Experiment Ophthalmol* 2012;40(1):e67-75

25 Feng S, Chen H, Liu Y, Huang Z, Sun X, Zhou L, Lu X, Gao Q. A novel vitreous substitute of using a foldable capsular vitreous body injected with polyvinylalcohol hydrogel. *Sci Rep* 2013;3:1838

26 Chen H, Feng S, Liu Y, Huang Z, Sun X, Zhou L, Lu X, Gao Q. Functional evaluation of a novel vitreous substitute using polyethylene glycol sols injected into a foldable capsular vitreous body. *J Biomed Mater Res A* 2013;101(9):2538-2547

27 Yang W, Yuan Y, Zong Y, Huang Z, Mai S, Li Y, Qian X, Liu Y, Gao Q. Preliminary study on retinal vascular and oxygen-related changes after long-term silicone oil and foldable capsular vitreous body tamponade. *Sci Rep* 2014;4:5272

28 Liu Y, Jiang Z, Gao Q, Ge J, Chen J, Cao X, Shen Q, Ma P. Technical standards of a foldable capsular vitreous body in terms of mechanical, optical, and biocompatible properties. *Artif Organs*2010;34(10):836-845

29 Lin X, Ge J, Gao Q, Wang Z, Long C, He L, Liu Y, Jiang Z. Evaluation of the flexibility, efficacy, and safety of a foldable capsular vitreous body in the treatment of severe retinal detachment. *Invest Ophthalmol Vis Sci* 2011;52(1):374-381

30 Wang P, Gao Q, Lin X, Zhang S, Hu J, Liu Y, Xu N, Ge J. Comprehensive analysis of inflammatory immune mediators of the intraocular fluid aspirated from the foldable capsular vitreous body filled-eyes. *PLoS One* 2012;7(10):e46384

31 Zhang R, Wang T, Xie C, Lin X, Jiang Z, Wang Z, Liu Y, Luo Y, Long C, He L, Wang P, Gao Q. Evaluation of supporting role of a foldable capsular vitreous body with magnetic resonance imaging in the treatment of severe retinal detachment in human eyes. *Eye (Lond)* 2011;25(6):794-802

32 Lin X, Wang Z, Jiang Z, Long C, Liu Y, Wang P, Jin C, Yi C, Gao Q. Preliminary efficacy and safety of a silicone oil-filled foldable capsular vitreous body in the treatment of severe retinal detachment. *Retina* 2012; 32(4):729-741

33 Schwartz SG, Flynn HW, Jr., Mieler WF. Update on retinal detachment surgery. *Curr Opin Ophthalmol* 2013;24(3):255-261

34 Liu Y, Ke Q, Chen J, Wang Z, Xie Z, Jiang Z, Ge J, Gao Q. Sustained mechanical release of dexamethasone sodium phosphate from a foldable capsular vitreous body. *Invest Ophthalmol Vis Sci* 2010;51(3):1636-1642

35 Chen X, Liu Y, Jiang Z, Zhou L, Ge J, Gao Q. Protein kinase calpha downregulation via sirna-pkcalpha released from foldable capsular vitreous body in cultured human retinal pigment epithelium cells. *Int J Nanomedicine* 2011;6:1303-1311

36 Jiang Z, Wang T, Pan B, Xie Z, Wang P, Liu Y, Gao Q. Evaluation of the levofloxacin release characters from a rabbit foldable capsular vitreous body. *Int J Nanomedicine* 2012;7:1-10

37 Jiang Z, Wang P, Pan B, Xie Z, Li D, Wang T, Liu Y, Yuan Z, Gao Q. Evaluation of levofloxacin release characteristics from a human foldable capsular vitreous body *in vitro*. *J Ocul Pharmacol Ther* 2012;28(1):33-40

38 Wang T, Huang X, Gao Q, Feng L, Xie Z, Jiang Z, Liu Y, Li Y, Lin X, Lin J. A preliminary study to treat severe endophthalmitis via a foldable capsular vitreous body with sustained levofloxacin release in rabbits. *Invest Ophthalmol Vis Sci* 2013;54(1):804-812

39 Huang Z, Yang W, Zong Y, Qiu S, Chen X, Sun X, Zhou Y, Xie Z, Gao Q. A study of the dexamethasone sodium phosphate release properties from a periocular capsular drug delivery system. *Drug Deliv* 2014:1-9

40 Mai S, Lin L, Yang W, Deng X, Xie Z, Zong Y, Li Y, Gao Q. *In vitro*and *in vivo* release characteristics of Tacrolimus (FK506) from an episcleral drug-delivery implant. *J Ocul Pharmacol Ther* 2014;30(8):670-680