• Prospective •

Vitreous function and intervention of it with vitrectomy and other modalities

Yao Zong[1], *Qian-Ying Gao*[2], *Yan-Nian Hui*[3]

[1]Department of Ophthalmology, the Affiliated Hospital of Qingdao University, Qingdao 266003, Shandong Province, China
[2]Vesber Vitreous Institute, Guanghzou 510000, Guangdong Province, China
[3]Department of Ophthalmology, Eye Institute of PLA, Xijing Hospital, Fourth Military Medical University, Xi'an 710032, Shaanxi Province, China
Correspondence to: Qian-Ying Gao. Vesber Vitreous Institute, Guanghzou 510000, Guangdong Province, China. gaoqy@hotmail.com; Yan-Nian Hui. Department of Ophthalmology, Eye Institute of PLA, Xijing Hospital, Fourth Military Medical University, No.127 Changle West Road, Xi'an 710032, Shaanxi Province, China. ynlhui@163.com
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Abstract

● The vitreous body, the largest intraocular component, plays a key role in eye development, refraction, cell barrier function, oxygen metabolism and the pathogenesis of assorted diseases. Age, refraction and systemic diseases can cause vitreous metabolic abnormalities. With the continuous development of vitrectomy techniques and equipment, vitreous injections and vitrectomies have increased over the recent decades. However, the normal oxygen tension gradient in the vitreous helps to protect the lens and anterior chamber angle from oxidative stress damage, whereas the increased vitreous oxygen tension around lens and the trabecular meshwork after vitrectomy. It may lead to postoperative nuclear cataract and increase the risk for glaucoma. As a conventional procedure, scleral buckling holds several advantages over vitrectomy in selected cases. This review raises concerns regarding the function of the vitreous and encourages conducting vitreous interventions prudently if it is possible.

● **KEYWORDS:** vitreous; function; oxygen metabolism; vitrectomy; scleral buckling
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INTRODUCTION

The vitreous gel, which is mostly composed of water, is optically transparent, and has important roles in eye development, refraction, cellular barriers, and intraocular oxygen metabolism. The vitreous gel liquefies with aging. This liquefaction process is involved in many vitreoretinal diseases, including rhegmatogenous retinal detachment (RRD), retinal tear, vitreomacular traction syndrome, epiretinal membrane, and macular hole. RRD is caused by the formation of retinal tears, allowing vitreous fluid into the subretinal space, which results in the separation of the retinal neuroepithelial layer from the retinal pigment epithelium (RPE). The reported annual incidence of RRD is about 18.2 cases per 100 000 people in the Netherlands[1] and 13.3 per 100 000 people in Europe[2]. A study in Denmark found that the age- and sex-standardized incidence rate of RRD increased by more than 50% during 2000-2016[3]. In China, the annual incidence were 7.98 cases per 100 000 people based on data of Beijing[4], and 14.4 cases per 100 000 people based on data of Shanghai[5]. Scleral buckling (SB) is the traditional procedure for the treatment of RRD, and demonstrates favorable curative effect with few complications, such as refractive change, scleral laceration, globe ischemia, choroidal hemorrhage and detachments, macular fold and buckle exposure, which might be reduced by careful planning, appropriate patient selection, and good surgical technique[6]. However, with the continuous development of vitrectomy techniques and equipment, the use of SB is gradually declining and even facing the possibility of being eliminated. Some doctors choose intravitreal injection and pars plana vitrectomy (PPV) without the proper indications, because of inadequate knowledge of the vitreous body, leading to severe complications that could have been avoided, such as cataract, intraocular hypertension, preretinal fibrosis, corneal edema, oil migration and emulsification[7-8]. Studies show no significant difference in the achievement ratio of operations between PPV, SB or the combined procedures for the treatment of RRD[9]. Unlike PPV, SB retains the intact vitreous body and reduces the interference of intraocular metabolism to the lowest level, in order to reduce the possibility of serious complications due to vitreous metabolic disturbance. Hence, we have emphasized the importance of

recognizing the functions of the vitreous body and increasing the popularity of SB for treating suitable primary RRD, as well as advised caution in the use of more aggressive surgery such as PPV. Besides that, the traditional SB is also improved by several modifications, which reduce complications and surgical difficulty, and shorten the operation time, increases the popularity of SB for treating primary RRD and maintain SB as an option for appropriate patients in the future[10-11]. It is time to recognize the functions of the vitreous, and the necessity for following strict surgical indications and careful assessment for vitrectomy procedures.

COMPOSITION AND PHYSIOLOGY OF THE VITREOUS BODY

It was thought previously that the vitreous body had no well-substantiated physiological function, apart from giving the eye its shape and volume, so that the eye would not be adversely affected by vitreous gel removal[12]. However, the new studies about vitreous found that an intact vitreous gel is crucial for stable intraocular metabolism and function. The vitreous gel plays a major role in refraction, cellular barriers, participating in intraocular oxygen metabolism and the pathology of diseases. To understand the physiological function of the vitreous body, we must first understand its structure, components, development, and metabolism.

The transparent, gelatinous vitreous makes up 80% of the intraocular volume, adjacent to the retina, lens and ciliary body. The vitreous gel is composed of the vitreous membrane, cortex and nucleus. The vitreous membrane, composed of dense collagen fibers, is located in the peripheral part of the vitreous. The vitreous cortex is located between the vitreous membrane and nucleus. The vitreous nucleus occupies most of the space in the middle, and in the center is the Cloquet canal, degenerated from the vascular primary vitreous with aging. The vitreous is most closely connected with the retina at the vitreous base, macula and optic disc. The posterior vitreous boundary membrane and inner limiting membrane jointly constitute the vitreous-retina interface.

As the embryo develops, vitreous gel formation is a dynamic process in which the avascular transparent secondary vitreous gradually replaces the primary vitreous. The highly hydrated, almost acellular vitreous gel is composed mainly of collagen and hyaluronan, with water accounting for approximately 98%-99% of it. The vitreous gel consists of only 0.1% macromolecules, in which collagens might be the most important for the structure of the vitreous gel[13]. These macromolecules are composed of hyaluronan, versican, and type IX collagen arranged with collagen fibrils in a network[14]. They are responsible for the gel's viscoelastic properties[15] and structural stability. Collagen fibrils are composed of collagen types II, V/XI, and IX, of which type II collagen is transformed from a soluble precursor (type II procollagen) with an amino-propeptide terminus and a carboxy-propeptide terminus and is synthesized and excreted by cells[16]. This has been shown in adult bovine eyes[17-18].

The vitreous gel is important in the eye development, in maintaining its elasticity and in reducing the scattering of light. Furthermore, the matrix, glue-like state of the vitreous gel acts as a barrier to cell invasion: it affects cell proliferation, inflammatory responses and neovascularization. These actions may be related to the vital function of intraocular oxygen distribution and metabolism[19].

VITREOUS OXYGEN METABOLISM

Recently studies indicated the vitreous gel is important for the regulation and distribution of oxygen. Oxygen enters the eye largely by diffusion from the retinal and iris vessels, as well as through the cornea, and a decreasing oxygen gradient extends from the retina to the lens in the intact vitreous[20]. Eyes without previous surgery (cataract or vitrectomy) exhibit a gradient of oxygen tension in the anterior chamber (Table 1[21]). A decreasing gradient of oxygen exists in the aqueous humor from the inner surface of the corneal endothelium (24.2±0.9 mm Hg) to the anterior surface of the lens (2.8±0.3 mm Hg)[21]. Siegfried *et al*[21] also pointed out that the oxygen levels of the aqueous humor decrease close to the pars plicata of the ciliary body (posterior chamber: 3.5±0.4 mm Hg) and the trabecular meshwork (12.9±0.7 mm Hg). These oxygen gradients play an important role in protecting the lens and trabecular network from oxidative stress because they are normally living in hyperoxia environments[19].

In 1989, Sakaue *et al*[22] used a polarographic oxygen electrode to measure the vitreous oxygen tension in the human vitreous body during vitreous surgery and found mean oxygen tensions of 16.7±3.7 mm Hg for the anterior peripheral vitreous body, 15.9±2.8 mm Hg for the central vitreous body, and 19.9±4.8 mm Hg for the posterior vitreous body, whereas the preretinal oxygen tension of a detached retina was much higher (around 30.0±4.8 mm Hg; Table 1). They also found similar vitreous oxygen tensions in human and rabbit eyes, except over the detached retina. Barbazetto *et al*[23], who also measured the oxygen tension in rabbit eyes, found a shallow decrease in the oxygen gradient from the retinal surface (40-60 mm Hg) to the posterior surface of the lens (10.9±3.6 mm Hg) in the intact vitreous body (Table 1). Holekamp *et al*[24] suggested that the vitreous gel maintained an intraocular oxygen gradient (Table 1), and that excessive oxygen stress promoted nuclear cataract formation. Shui *et al*[25] confirmed the presence of intraocular oxygen gradients in rabbit eyes with the discovery of a gradient of decreasing oxygen levels from the central corneal endothelium (43±2 mm Hg) to anterior surface of the lens (17±2 mm Hg). Also, a gradient of decreasing oxygen

Table 1 Intraocualr oxygen tensions in the representative studies

Author, year	Species	Vitreous state	Oxygen tensions (mm Hg)			Oxygen gradient	Meansurement	Respiration
			Anterior segment	Vitreous body	Retinal surface			
Sakaue, 1989[22]j	Human	Intact or PVD		16.7±3.7 (APV- PL), 15.9±2.8 (CV), 19.9±4.8 (PV)	30.0±4.8 (DR)	NA	O_2 electrode (PO-100) and an amplifier (PO-2080, MRC)	Room air
	Rabbit	Intact		13.9±4.3 (APV-PL), 16.0±3.5(CV), 22.5±2.1 (PV)	4.3 (DR), 39.5±3.4 (AR)	NA		
Maeda and Tano, 1996[42]j	Human (PDR)	Pre-V		16.1±5.4 (PeriV-PL), 16.2±5.0 (CV)	17.1±4.0 (macula), 32.1±10.0[a] (NV), 31.4±10.1[a] (NVD)	+	O_2 electrode and an amplifier (PO-2080, MRC)	Ambient air
		Post-V		14.5±3.0 (PeriV-PL), 16.4±3.1 (CV)	15.9±2.9 (macula), 14.4±2.8 (NV), 17.2±2.5 (NVD)	-		
Barbazetto, 2004[23]j	Rabbit	Pre-V	28.7±6.1 (CAC), 10.4±3.0 (CL)	10.9±3.6 (PL), 12.0±3.2 (CV)	40-60	+	FOXY fiber optic oxygen sensor (Ocean Optics Inc., USA)	Not described
		Immediately Post-V		90-140 (CV)		-		
		30min Post-V		28.9±12.2 (CV)				
		2wk Post-V	15.4±1.4[b] (CL)	16.4±4.2[b] (CV)				
		8wk Post-V	13.83±0.02[b] (CL)	13.8±0.02[b] (CV)				
Holekamp, 2005[24]j	Human	Group1						
		Pre-V		8.7±0.6 (PL), 7.1±0.5[c] (CV)		+	Optical oxygen sensor (Oxford)	Inhaled oxygen (21-90)%
		Immediately Post-V		69.6±4.8[d] (PL), 75.6±4.1[d] (CV)		-		
		Group2						
		Control		10.3±0.6 (PL), 8.4±0.7[c] (CV)		+		
		3-20mo Post-V		12.9±0.5[e] (PL), 13.3±0.8[e] (CV)		-		
		All subjects						Inhaled oxygen (≥21%)
		Pre-V		11.1±0.6 (PL), 8.9±0.6 (CV)		+		
		Immediately Post-V		71.7±2.6[d] (PL), 77.2±2.2[d] (CV)		-		
Shui, 2006[25]j	Rabbit	Intact	43±2 (BC), 27±2 (CAC), 17±2 (AL), 27±3 (ACA), 21±1 (PC)	6±0 (PL), 13±2 (CV)	31±2	+	Optical oxygen sensor (Oxford)	Normoxic
Quiram, 2007[33]j	Cat	Intact		16±2 (CV)		NA	Platinum-based fluorophore O_2 sensor (Oxford)	Room air
		PVD		26±2[f] (CV)				
	Rat	Intact		23±2 (CV)				
		PVD		35±5[f] (CV)				
Siegfried, 2010[21]j	Human	Reference	24.2±0.9 (BC), 11.5±0.5 (CAC), 2.8±0.3 (AL), 12.9±0.7 (ACA), 3.5±0.4 (PC)	8.7±0.6 (PL)		+	30-gauge optical oxygen sensor (Oxylab)	Supplemental oxygen by nasal cannula
		Pre-V	23.2 ±1.4 (BC), 9.7±0.9 (CAC), 2.3±0.6 (AL), 15.1±1.2 (ACA), 8.5±0.9[g] (PC)	12.9±0.5[g] (PL)		NA		
		Pre-cataract surgery	20.7±1.8 (BC), 11.9±0.5 (CAC), 11.0±1.2[g] (AL), 14.9±1.3 (ACA), 6.7±0.7[g] (PC)	10.9 ±0.8[g] (PL)				
		Pre-both surgery	26.7±1.4 (BC), 15.6±0.6[g] (CAC), 11.3±1.6[g] (AL), 24.7±1.5[g] (ACA), 10.7±0.7[g] (PC)					
Lange, 2011[35]j	Human	PDR		5.6 ±1.03[h] (AV-PL), 6.03 ±1.08[h] (CV)	15.42±2.55[h]	+	Optical oxygen sensor (Oxford)	No supplementary oxygen
		Control		10.69±1.82 (AV-PL), 11.12±1.67 (CV)	9.78±0.64	-		

APV: Anterior peripheral vitreous; AV: Anterior vitreous; CV: Central vitreous; PV: Posterior vitreous; PeriV: Peripheral vitreous; DR: Detached retina; AR: Attached retina; NV: Neovascularization; NVD: Neovascularization of optic disc; CAC: Center of anterior chamber; BC: Beneath the cornea; ACA: Anterior chamber angle; PC: Posterior chamber; CL: Central lens; PL: Posterior surface of the lens; AL: Anterior surface of the lens; RS: Retinal surface; Pre-V: Pre-vitrectomy; Post-V: Post-vitrectomy; MRC: Mitsubishi-rayon, Tokyo, Japan; Oxford: Oxford Optronix, Oxford, UK. +: There is an intraocular oxygen gradient; -: No intraocular oxygen gradient; NA: Not assessed. [i]mean±SD, [j]mean±SEM; [a]P<0.01 difference between NV and the other values in the pre-vitrectomy group (one-way ANOVA); [b]P<0.02 difference between pre- and post-operative values (t-test); [c]P<0.05 difference between the lens and the vitreous (paired t-test); [d]P<0.0001 difference between pre- and post-vitrectomy; [e]P<0.02 difference between the first vitrectomy and second or third vitrectomy; [f]P<0.001 difference between the PVD eyes induced by injection of microplasmin and the contralateral eyes; [g]P<0.05 difference between the eyes with previous ocular surgery and reference eyes; [h]P<0.05 difference between the diabetic subjects and control subjects.

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Tel: 8629-82245172 8629-82210956 Email: ijopress@163.com

levels from the surface of retina (31±2 mm Hg) to the posterior surface of the lens (6±0 mm Hg; Table 1). Based on the human and rabbit *in vivo* data, Filas *et al*[26] developed a computational model to reproduce the oxygen distributions in human vitreous under physiological and environmentally perturbed conditions. Further study showed that the vitreous oxygen consumption might maintain a lower oxygen tension near the lens because the vitreous gel preserves ascorbate levels to sustain oxygen consumption[27]. The effect of oxygen consumption by the lens on the intraocular gradient of oxygen tension remains unclear because of a lack of direct data regarding oxygen consumption in the intact human lens. By contrast, eyes with previous cataract surgery showed significantly increased oxygen tension in front of the intraocular lens and the posterior chamber[21], suggesting that oxygen consumption by the lens may also contribute to the hypoxic environment of the lens. Research in rabbits has shown an oxygen consumption by the posterior half of the lens of 0.21 μL/h under normoxic conditions[25]. Due to much smaller lenses in humans, the oxygen consumption would be much weaker than the rabbits.

In addition to oxygen, all molecules, including vascular epithelial growth factor (VEGF), are transported relatively slowly from the retina and through the viscous vitreous humor in the intact eye[28]. The unique oxygen concentration gradient in vitreous gel results from the ratio of oxygen supply and consumption in different parts of the vitreous gel. The maintenance of vitreous oxygen tension is mainly related to vitreous ascorbate (vitamin C). In intact vitreous gel, the average vitamin C content is close to 2 mmol/L[29], whereas in the blood it is approximately 50 μmol/L[30]. In addition to the high oxygen demand and rich blood circulation of the retina, active vitamin C transporters of the retina and ciliary body pigment epithelium actively transport vitamin C by a temperature-sensitive and energy-dependent kinetic mechanism[31], so the normal vitreous has a high amount of vitamin C and low vitreous oxygen tension. The retina has the ability to regulate its own blood flow, and this self-regulation is largely controlled by retinal chemical conditions, especially oxygen tension. The variation in vitreous oxygen tension may relate to some intraocular diseases[27].

LIQUEFACTION, THE AGE-RELATED VITREOUS DEGENERATION

The vitreous gel is a homogeneous jelly inside the infant's eyes. The vitreous body condenses and degrades in a slow process, and collagenous condensation and liquefied cavities gradually form[13]. Vitreous gel liquefaction might be the initial factor in many vitreoretinal diseases. However, its pathogenesis is not well understood.

Aging vitreous collagen fibrils degrade, which may underlie vitreous liquefaction and the ensuing posterior vitreous detachment (PVD). Changes, with aging, in the collagen fibrils on the vitreous surface include a loss of type IX collagen and a fourfold increase in the exposure of type II collagen; these changes predispose the vitreous collagen fibrils to fusion, fusion and weakening of the vitreoretinal adhesion[32]. In PVD, the cortical vitreous pulls away from the retina. This can result in the formation of retinal tears, epiretinal membranes, and macular holes and the development of RRD, vitreomacular traction syndrome, and macular edema. Although vitreous liquefaction plays a major role in many vitreoretinal diseases, little is known about its pathogenesis. Advanced glycation end products, proteoglycan, hyaluronic acid, and other macromolecules, might gradually liquefy the vitreous, destroy the balance of oxygen distribution and disturb the regulation of oxygen.

Vitreal-matrix status is also affected the ascorbate content. The concentration of ascorbate in the liquified vitreous of individuals is decreased, compared with the gel vitreous, and the oxygen consumption of the vitreous also decreases once liquified, indirectly increasing the oxygen tension of the vitreous[27]. Quiram *et al*[33] found that PVD induced in rats and cats by intravitreal injection of microplasmin increased the oxygen tension of the vitreous (Table 1) and the rate of oxygen exchange. This, in turn, could cause oxygen stress to increase, but on the other side, could also be beneficial against ischemic retinal diseases. The viscosity of the vitreous gel essentially disappears after vitreous liquefaction or vitrectomy, the liquified vitreous body facilitates the diffusion of many substances, including oxygen[33] and nutrients[28]. The oxygen tension increases in the liquefied vitreous, exposing the posterior of the lens to increased oxygen and causing nuclear sclerotic cataracts[20].

Unlike PVD, incomplete PVD is a risk factor for many retinal diseases, the probable reason may be the attachment and traction of the vitreous cortex to the macula can induce chronic low-grade inflammation, which may also develop into wet age-related macular degeneration (AMD)[34]. The adherent posterior vitreous interferes with oxygenation and nutrition of the macula and binds VEGF to the collagen fibers at the retinal vitreous interface, resulting in exacerbation of the retinal exposure to these cytokines, and promoting the formation of neovascularization. Inducing complete PVD might protect against wet AMD. In a previous study, oxygen tension in the central part of the vitreous was 46% lower in diabetic retinopathy patients than in healthy controls, whereas oxygen tension anterior to the retina was 37% higher[35] (Table 1). The preretinal oxygen level was closely related to the vitreous VEGF concentration; for instance, retinal hypoxia or chronic inflammatory stimulus might increase the vitreous VEGF concentration in proliferative diabetic retinopathy (PDR)[35]. The

concentrations of both VEGF and hypoxia-inducible factor-1α (HIF-1α) are increased in the vitreous body in PDR and closely correlate with disease activity[36]. Substantial evidence suggests that VEGF plays a key role in the pathogenesis of neovascularization[37-38], which is the primary cause of vision loss in PDR[39-40]. Neovascularization is the formation of new microvascular networks from existing blood vessels[41], and is characterized by vasodilation, microvascular leakage, and abnormal proliferation of vascular endothelial cells. Successful vitrectomy for PDR stabilizes the oxygen levels, maintains the balance of oxygenation, and inhibits neovascularization[42] (Table 1).

TRENDS IN VITREORETINAL PROCEDURES FOR RHEGMATOGENOUS RETINAL DETACHMENT

RRD is a common, potentially blinding eye disease, caused by vitreous degenerations and retinal tears[9]. Historically, SB surgery was the operation chosen as the treatment for RRD. Over the past decade, the PPV technique has developed rapidly and advanced in numerous ways. Studies of United States Medicare Part B Fee-for-Service data have shown that vitreoretinal procedures increased six-fold from 2000 to 2014; vitrectomy use for RRD increased from 13 814 to 19 288 surgeries, whereas SB sharply declined from 6502 to 1260 procedures. The percentages of different types of operations for retinal detachment repair were 83% vitrectomy, 5% SB and 12% pneumatic retinopexy in 2014[43]. A study analyzed data between 1997 and 2007, and found that vitrectomies for RRD increased 72%, and the quantity of intravitreal injections was more than doubling every year, whereas SBs performed without vitrectomy decreased 69% across the 10-year interval[44]. PPV was more common (49%) than SB (11%), especially in the pseudophakic patients and patients with vitreous hemorrhage[45]. During 2003-2016, PPV became the most commonly performed procedure, whereas the proportion of SB procedures continued to decline to levels below 10%. Vitreous surgery is now considered by American retinal surgeons to be the first choice for the treatment of RRD[46]. A study in South Korea reported that no obvious trend was observed in the surgical approaches from 2007 to 2011[47]. These results suggest that vitrectomy and intravitreal injection have been considered the mainstay of therapy instead of SB. Therefore, one could ask whether SB surgery has been replaced by vitrectomy. At least, the possible replacement of SB surgery by vitreous surgery is now a relevant question.

The main reasons why surgeons are reluctant to perform SB surgery are that the disrupted view of indirect ophthalmoscopy hampered by poor pupillary dilation and media opacities[48-49], the serious complications during the discharge of fluid from the suprachoroidal cavity[50-51], and the steep learning curve and poor ergonomics of the operative techniques[50]. To solve such problems, novel techniques for SB have been developed, including sutureless buckling and suprachoroidal buckling, reshaping the silicone segment, modified needle drainage, laser choroidotomy, infusion-assisted drainage[50], and chandelier-assistance SB[11]. These new techniques make the learning process easier and safer. No matter how exquisite the PPV surgical skill is, PPV will inevitably lead to damage in the vitreous structure and the intraocular environment. Therefore, we advocate that the ophthalmologists enhance their knowledge of SB surgery.

The surgeons should select the proper surgery for RRD based on the patient status. PPV was more likely to be performed on older patients, or those with pseudophakia and vitreous hemorrhage; young patients tended to undergo SB[45-47]. In older patients and those with pseudophakia and vitreous hemorrhage, RRD is usually caused by retinal tears, vitreoretinal traction induced by PVD, and extensive vitreous liquefaction. Vitreoretinal traction and extensive liquefaction reduce the reattachment rate of SB. In young patients without obvious PVD or extensive vitreous liquefaction, RRD is characterized by small atrophic holes, shallow detachment, and slow progression, which can usually be cured with SB alone[52]. SB remains the first-choice surgical procedure in young phakic patients, as it retains the vitreous body intact and does not interfere with intraocular metabolism. Therefore, SB still has its unquestionable indications, such as in young patients, or patients with an old retinal detachment or inferior retinal detachment caused by an atrophic hole.

COMPARISON OF OUTCOMES BETWEEN VITRECTOMY AND SCLERAL BUCKLING SURGERY

Studies have shown no significant differences in the achievement ratio of operation between PPV, SB and the combined surgery, with primary anatomical success rates of 89.0%, 87.0%, and 85.7%, and final anatomical success rates at 6-month of 98.1%, 100%, and 99.4%, respectively[9]. Another study, focused on pneumatic retinopexy performed for RRD at six academic centers in the United States, found that the single-procedure anatomic success rate was 66.8%[53].

The relative efficacy of PPV and SB surgeries remains controversial, and there may be no differences in primary success rates, visual acuity improvement, final anatomical reattachment, and incidence rates of repeated retinal detachment between PPV and SB in treating primary RRD. In terms of complications, a previous study found that cataract progression and iatrogenic tears were more common after PPV, whereas choroidal detachment was more common after SB[54]. The rate of cataract occurrence in young patients after PPV is as high as 60% and is closely related to intraocular gas[55]. The single-surgery anatomic success rates of SB and PPV/SB have been found to be higher than that of PPV, and SB has been

shown to have better visual outcomes than PPV or PPV/SB, even after cataract extraction[56]. A large randomized clinical trial showed that the mean best-corrected visual acuity (BCVA) change was significantly greater after SB of phakic patients, and the difference in re-detachment rates of SB and PPV in the phakic patients was not statistically significant[57]. The refractive error induced by the vitreous-gel substitutes causes the vision decline temporarily. For example, the refractive state of the eyes with silicone oil injection is a hyperopic shift of +4.0 to 7.0 D[58]. SB induces only a small refractive error (-1.38 D) and is beneficial to visual rehabilitation in the early postoperative period[59]. Thus, although the anatomic success rates of PPV and SB are similar, SB is superior to PPV for RRD in many respects, including early recovery of visual acuity and prevention of cataract progression[52].

Proliferative vitreoretinopathy (PVR) occurs in 5%-10% of RRD cases and is the leading cause of surgical failure[60-62]. PVR is initiated by fibroblasts derived from RPE cells that are transformed into mesenchymal cells and begin the deposition of collagen and the extracellular matrix, arranged by disordered inflammatory chemokines and growth factors that induce excessive inflammation in the positions of retinal tears and detachment[60,63].

The development of PVR might be closely associated with pre-existing PVR, extensive retinal detachment, vitreous hemorrhage, huge retinal breaks, pseudophakia, and surgical factors[64-66]. Hooymans *et al*[61] reviewed the rate of postoperative PVR of 186 consecutive patients with primary RRD repaired with SB combined with cryotherapy, and found that in 6% of the eyes with PVR, some of the PVR had presented preoperatively, and that pseudophakia may also be a risk factor. Therefore, careful preoperative physical examination and timely diagnosis of pre-existing PVR are effective ways to prevent PVR. Some studies have found several predictive biomarkers for determining the probability of PVR, which might be beneficial in choosing suitable operation techniques[60].

Surgical factors include extensive laser retinopexy and cryopexy, unclosed retinal tears, scleral perforation, and vitreous hemorrhage in the perioperative period[65,67]. Cryotherapy causes the chorioretinal trauma, leads to alterations in the protein matrix, and results in the release of RPE cells throughout the ocular fluid, and imprecise cryotherapy can result in increased risk of PVR[68-71]. Location of the break with a cryoprobe, adjuvant photocoagulation, and drainage of the subretinal fluids (SRF) followed by cryopexy ensures precise retinopexy and less release of RPE[50].

Nevertheless, SB surgery can cause several complications during the discharge of fluid from the suprachoroidal cavity. The traditional SRF drainage through the incision may cause incomplete drainage, dry tap, choroidal hemorrhage, retinal incarceration, and retinal tears. Sudden hypotony due to copious drainage can cause choroidal detachment[50].

To prevent such problems, novel techniques for SB have been introduced. First, the modified needle drainage is performed through a sclera puncture with a 26-gauge needle, which provides adequate drainage with a much lower complication rate (15%) than the traditional method (32.5%)[51]. In addition, an endolaser probe was applied to perform the choroidotomy after scleral cut-down in order to hemostasis by coagulating the choroidal vessels and prevent iatrogenic retinal break. Laser choroidotomy reduces the incidence of retinal perforation and bleeding at the time of drainage[72-73]. Infusion-assisted drainage can be placed to combat sudden hypotony due to copious drainage and to maintain intraocular pressure during drainage[50].

Lincoff *et al*[74] highlighted benefits of non-drainage of SRF, which remains relevant in RRD repair today. The operation includes three main procedures: occluding retinal hiatus by cryotherapy, placing a silicone sponge for each retinal break, and non-drainage of SRF. Minimal segmental buckling without drainage is an effective technique for repair of RRD with a single break or a few breaks within a few clock hours, and may result in less postoperative pain[75]. This technique of SB surgery simplifies the operative procedures, reduces the operation difficulty, shortens the operation time, and decreases the surgical trauma[76].

Although, for those more complicated RRD cases, such as huge retinal tears, multiple breaks, PDR and PVR, PPV are much safer and more effective. However, SB remains a relevant surgery for the right cases, with better results and fewer complications.

COMPLICATIONS AND VITREOUS METABOLIC DISTURBANCES OF PARS PLANA VITRECTOMY

PPV removes of most natural vitreous, resulting in metabolic disturbance of the vitreous, which leads to a high risk of complications[19]. Some adverse events appear to be more common in association with PPV than with SB, such as nuclear cataracts and new iatrogenic breaks[54]. The preretinal fibrosis, recurrent traction retinal detachments, oil migration to the anterior chamber, corneal edema and oil emulsification are also frequent complications for PPV[7]. Although there are many reasons for these complications, disturbance of oxygen metabolism in the natural vitreous may be one of the important factors that were ignored by the surgeons.

The incidence of cataract, glaucoma or retinal disease is elevated after PPV, which may be related to vitreous oxygen distribution in patients. In a clinical study, Holekamp *et al*[24] compared the preoperative and postoperative vitreous oxygen tension (Table 1). There was a low vitreous oxygen tension

adjacent to the lens (8.7±0.6 mm Hg) and in the middle vitreous (7.1±0.5 mm Hg) with an intraocular oxygen gradient at the baseline (before starting the surgery). The oxygen tension sharply increased adjacent to the lens (69.6±4.8 mm Hg) and in the middle vitreous (75.6±4.1 mm Hg) immediately after vitrectomy and loss of an oxygen gradient. Patients who had undergone the previous vitrectomy for 3-20-month maintained a high vitreous oxygen tension without an oxygen gradient[24]. Similarly, Barbazetto *et al*[23] reported that a significantly elevated oxygen tension in the lens and vitreous for at least 8-week without an oxygen gradient in rabbit eyes post-vitrectomy. These findings suggested that excessive oxygen stress may contribute to cataract formation following surgery (Table 1).

In a group of RRD patients after PPV, 56.5% had an increase in intraocular pressure (IOP) during the follow-up period[77]. The possible risk of open-angle glaucoma increases after PPV, and this is associated with increased oxygen stress that can potentially damage the trabecular-meshwork cells[21,78]. Siegfried *et al*[21] suggested that vitrectomy increased the oxygen tension in the anterior chamber angle from 12.9± 0.7 to 15.1±1.2 mm Hg, although this difference was not statistically significant (Table 1).

The mechanism by which surgical excision of vitreous gel can increase oxygen tension is as follows. First, the concentration of ascorbate is reduced in a sodium-free medium after PPV, and the oxygen consumption of the vitreous also decreases, which indirectly increases the oxygen tension of the vitreous[27,29]. Second, the liquified vitreous body, which lacks the viscosity of the gel, shows an increased rate of oxygen exchange within the vitreous cavity, thereby inducing increases in vitreal oxygen tension[28,33]. In vitrectomized eyes, the risk of retinal neovascularization decreases due to the increased oxygen diffusion and faster clearance of VEGF, but the risk of iris neovascularization increases due to the presence of less oxygen and more VEGF in the anterior segment[28].

Vitreous is non-renewable, and therefore vitreous replacements must be used after a PPV for RRD. Gases, silicone oil, heavy silicone oil and hydrogels, of which the gases and silicone oil are widely used clinically as vitreous substitutes. However, none of the current substitutes can completely replace the natural vitreous, as the substitutes lack the structure and function of the natural vitreous gel[79]. Intraocular gases have the frequent complications including IOP elevation, cataract, anterior chamber and subconjunctival gas displacement, and the rare complications such as the subretinal and cranial gas migration[8]. Intraocular silicone oil is associated with many complications, such as temporary high IOP, inflammation, cataract, emulsification, glaucoma, ocular hypotension, keratopathy and PVR[80]. There is often (5/53) unexplained atrophy of the optic nerve after silicone-oil filling[81]. Silicone oil, as a foreign substance, was shown to aggravate chronic inflammation in eyes with chronic uveitis and phthisis bulbi that were enucleated from patients after vitrectomy with silicone-oil tamponade[82].

COMPLICATIONS AND VITREOUS METABOLIC DISTURBANCES WITH LASER VAPORIZATION AND INTRAVITREAL DRUG INJECTION

In addition to vitrectomy, vitreous interventions include laser photocoagulation and intravitreal injections. Neodymium-doped yttrium aluminum garnet high-energy pulsed-laser ablation (Nd:YAG laser vitreolysis) has recently been applied to relieve vitreous floaters, whose prevalence may increase with a dramatically increased incidence of myopia[83]. In 1987, Hrisomalos *et al*[84] first reported Nd:YAG laser vaporization on six patients with floaters and transection of bands. Nd:YAG laser disrupts tissues through the formation of ionized gas that causes a shock wave to relieve vitreous floaters but may damage the adjacent lens[85]. There has not been sufficient evidence to prove that Nd:YAG laser vitreolysis is a safe and effective therapy, although the incidence of complications has thus far been low. Moreover, Lim[86] suggested that there was only fragmentary evidence to support the visual improvement after Nd:YAG laser vitreolysis. A clinical study on 32 eyes reported that the laser produced significant improvement in near visual function and the visual disturbance rate, but not in distance visual function at 6-month follow-up[87]. A sham-controlled, randomized clinical trial found that the BCVA changed by -0.2 letters in the laser group, which was not significantly different from the result in the sham group[88]. The resolution of floaters by Nd:YAG laser ranges between 0% and 100%, but for young patients (<30 years old) with floaters, the chances of significant improvement of symptoms are not high[89]. A research study on rabbits, focused on the possible hazardous side effects of treating floaters with Nd:YAG laser, suggested that Nd:YAG laser treatment should be restricted to the anterior portion of the vitreous to avoid disturbing the state of the vitreous gel, as laser treatment in the middle and posterior vitreous can increase the protein content, refractive index, and viscosity[90].

Intravitreal injections were the primary driving force for the growth of vitreous interventions[43]; the annual number of intravitreal injections has more than doubled[44]. Intravitreal drug injection is the main treatment for many retinal diseases. Repeated injections lead to increased risk of retinal detachment, retinal tear, increased IOP, cataracts, and endophthalmitis[91-95]. There are also some rare complications, identified in recent years, such as RPE tear[96], mycobacterium abscessus scleritis[97], and corneal subepithelial infiltrates that are associated with the intravitreous injection of bevacizumab,

because of an immune response to bevacizumab[98]. Eight of seventy-one eyes of patients with PDR developed ghost cell glaucoma after they underwent intravitreous injection of ranibizumab[99].

CONCLUSION

Vitreous gel plays a key role in ocular metabolism and in the pathological mechanisms of ocular diseases. It is necessary to pay attention to vitreous metabolic function and conduct vitreous intervention prudently to better maintain the metabolic balance and visual function of the eye. SB surgery remains the preferred therapy in young phakic patients without PVD, particularly in maintaining the integrity of the vitreous gel, thus avoiding the complications of PPV. As we do not fully understand the function of vitreous gel, we should perform vitreous surgical intervention only after careful assessment.

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