Invited Review

Historical, Current and Future Approaches to Surgery for Rhegmatogenous Retinal Detachment

Hiroshi Kunikata,^{1,2} Toshiaki Abe³ and Toru Nakazawa^{1,2,4,5}

¹Department of Ophthalmology, Tohoku University Graduate School of Medicine, Sendai, Miyagi, Japan
²Department of Retinal Disease Control, Tohoku University Graduate School of Medicine, Sendai, Miyagi, Japan
³Division of Clinical Cell Therapy Center for Advanced Medical Research and Development, Tohoku University Graduate School of Medicine, Sendai, Miyagi, Japan

⁴Department of Advanced Ophthalmic Medicine, Tohoku University Graduate School of Medicine, Sendai, Miyagi, Japan

⁵Department of Ophthalmic Imaging and Information Analytics, Tohoku University Graduate School of Medicine, Sendai, Miyagi, Japan

Rhegmatogenous retinal detachment (RRD) is a serious condition that can cause blindness without surgical treatment. RRD occurs when a retinal tear or hole allows fluid to accumulate below the retinal surface, causing the retina to separate from the underlying layers. RRD is difficult to treat because each case is unique, varying with the location, size, and duration of the detachment, as well as patient age. The first successful methods to reattach the retina in RRD used thermocautery to repair the detachment. Many renowned ophthalmologists continued to study RRD and developed many new surgical approaches, notably: scleral buckling (SB), in which a silicone band is placed around the eye to reduce traction on the retina caused by the vitreous humor that fills the eye; pars plana vitrectomy (PPV), which eliminates traction on the retina by removing the vitreous; and pneumatic retinopexy (PR), in which the retina is reattached by pushing it back into place with an expanding gas bubble injected into the eye. However, no consensus has been reached on which approach is ideal. Furthermore, recent surgical and non-surgical breakthroughs, such as artificial vitreous substitutes and neuroprotective drugs, must also be considered. Thus, this review provides a guide for ocular specialists and non-specialists on the historical background of RRD, summarizes the three current main techniques (SB, PR and PPV) compares these three techniques, and provides an overview of new technologies that promise to greatly improve outcomes after RRD surgery.

Keywords: artificial vitreous; giant retinal tear; neuroprotection; pars plana vitrectomy; scleral buckling Tohoku J. Exp. Med., 2019 July, **248** (3), 159-168. © 2019 Tohoku University Medical Press

Introduction

Rhegmatogenous retinal detachment (RRD) is a serious, sight-threatening condition, with an incidence of 1 in 10,000 persons per year, which can cause blindness in the affected eye unless surgical treatment is received. RRD arises when the retina is torn, allowing fluid to accumulate in the subretinal space. This causes a split in the layers of the retina: the neurosensory layers separate from the underlying retinal pigment epithelium (Fig. 1).

RRD typically presents with the sudden appearance of spots in the visual field, flashes of light, blurred vision, or a curtain-like shadow over the visual field. The incidence of RRD peaks at two ages: the 20s and the 50s. Aging, myo-

pia, prior cataract surgery, trauma and a family history of RRD are known risk factors. RRD is an emergency requiring immediate treatment by an ophthalmologist, with outcomes significantly worsening after even a single day. However, successful treatment is difficult because each case of RRD is very different, varying with the location, size, and duration of the tear, and with patient age (Fig. 2). RRD also includes giant retinal tear (GRT) (Fig. 2D).

The history of RRD care starts with Gonin (1923), who observed that RRD could be caused by retinal tear, and was the first to successfully reattach a retina with Paquelin thermocautery (Gonin 1923; Rumpf 1976). Following this accomplishment, various new methods were introduced, three of which are still common today: scleral buckling

Received May 16, 2019; revised and accepted June 26, 2019. Published online July 13, 2019; doi: 10.1620/tjem.248.159.

Correspondence: Hiroshi Kunikata, M.D., Ph.D., Department of Ophthalmology, Tohoku University Graduate School of Medicine, 1-1 Seiryo-machi, Aoba-ku, Sendai, Miyagi 980-8574, Japan.

e-mail: kunikata@oph.med.tohoku.ac.jp

Dr. Hiroshi Kunikata is a recipient of the 2017 Gold Prize, Tohoku University School of Medicine.



Rhegmatogenous retinal detachment (RRD)

Fig. 1. Schema of RRD.

(A) Focal RRD due to atrophic holes. This condition is common in young patients.(B) Total RRD due to retinal tear. This condition is common in older patients.



Fig. 2. Fundus photographs of various types of RRD.

(A) RRD due to a retinal tear in the inferotemporal quadrant (arrow).

(B) Flat, focal RRD due to atrophic holes in the inferotemporal quadrant (arrow).

(C) Bullous RRD due to a retinal tear in the superotemporal quadrant (arrow). The optic disc cannot be seen due to the bullous RRD.

(D) RRD with a 120 degree GRT in the superotemporal quadrant (arrow).

(SB), in which a silicone band is placed around the eye (Schepens 1951; Custodis 1951), pars plana vitrectomy (PPV), in which the vitreous humor filling the eye is removed, (Machemer et al. 1971; Peyman et al. 1976;

Freeman and Castillejos 1981; Leaver et al. 1984; Escoffery et al. 1985), and pneumatic retinopexy (PR), in which expanding gas is used to push the retina back into place (Hilton and Grizzard 1986). These techniques have dra-

matically improved reattachment rates for RRD, an achievement that is due to the outstanding efforts of the researchers cited here.

Importantly, there is no single ideal strategy to treat RRD. SB, PPV, and PR each have distinct characteristics, including their effects on visual function, surgical success rates, and rates of complication. Furthermore, new surgical and non-surgical strategies are becoming or will likely soon become available, such as artificial substitutes for the vitreous and neuroprotective drugs. Thus, this review will serve as a guide for specialists and non-specialists to the historical background of RRD treatment, summarize current knowledge on the three main approaches, compare them, and provide an overview of recent discoveries and innovations that promise to improve RRD outcomes in the near future.

Scleral Buckling

SB is used to create an inward indentation in the sclera and the choroid, reducing traction of the vitreous on the retina around the tear and allowing retinal reattachment. SB using artificial materials was introduced as an exoplant method in the 1950s (Schepens 1951; Custodis 1951), followed by an implant method (Schepens et al. 1957) and a modified exoplant method (Lincoff et al. 1965). Currently, many shapes and types of silicone buckle are available for the exoplant method, and allow an excellent reattachment rate. In all types of procedure, cryopexy is used to repair the tear by permanently attaching the retina, and a piece of silicone sponge is then sutured to the sclera just behind the tear or hole. The sutured sponge creates an inward indentation in the sclera and the choroid (Fig. 3A, B). In complicated cases, such as those with multiple tears in various quadrants, an encircling SB is placed around the entire circumference of the eye. Thus, SB is a good choice for RRD, at least for experienced surgeons. However, it is a difficult technique to master, and thus remains unpopular, particularly because of its reliance on binocular indirect ophthalmoscopy, the great variety of buckle types, and the use of cryoprobes, among other reasons. Recently, the simultaneous use of a non-contact wide-angle viewing system and 27-gauge light fiber illumination for fundus visualization has added the advantages of microsurgery and indirect ophthalmoscopy to SB (Caporossi et al. 2019). Though a high rate of primary retinal reattachment has been reported with this approach, surgeons must pay close attention to the risk



Fig. 3. Postoperative fundus photographs of SB and PPV.

(A) Early post-SB fundus photograph. Cryopexy scars are visible as white spots (shown by the arrow) on the inward indentation in the choroid in the superotemporal quadrant (arrow heads). The SB was successful and there is no remaining retinal detachment.

(B) Late post-SB fundus photograph. Atrophic holes (arrow) were successfully sealed by the inward indentation in the choroid in the inferotemporal quadrant (arrow heads).

(C) Post-27-gauge MIVS fundus photograph showing laser photocoagulation scars surrounding the repaired retinal tear in the inferotemporal quadrant (arrow), without RRD. There is 40% unabsorbed gas (arrow heads).

(D) Post-27-gauge MIVS fundus photograph showing laser photocoagulation scars surrounding multiple repaired retinal tears in the superonasal, superotemporal and inferotemporal quadrants (arrows), without RRD. There is 50% unabsorbed gas (arrow heads).

of postoperative infection caused by the creation of a scleral port into the vitreous cavity. The future introduction of techniques to illuminate the fundus without the need for a scleral port promises to simplify SB methods and improve outcomes.

Pars Plana Vitrectomy

In PPV, the vitreous is removed to eliminate the traction of the vitreous on the retina around the tear, allowing retinal reattachment. Closed PPV with 17-gauge instruments was introduced in the 1970s by Machemer et al. (1971), and gradual improvements to PPV enabled its use for RRD repair (Peyman et al. 1976; Escoffery et al. 1985). The later introduction of the fluid/air exchange technique allowed complete retinal attachment during surgery (Charles and Wang 1981), and PPV without SB became viable as a primary approach to RRD (Escoffery et al. 1985). With the introduction of 20-gauge PPV, vitrectomy became a popular choice among surgeons for RRD (Heimann et al. 2006, 2007; Von Fricken et al. 2009). All types of PPV need 3 scleral ports: one each for infusion, a light pipe and a vitreous cutter, located 3.5 mm posterior to the limbus. After creation of the ports, the vitreous is cut and aspirated with a high speed cutter, and balanced salt solution is infused to compensate for the lost volume of vitreous humor. After resection of the vitreous is complete, the intraocular cavity is filled with air and the subretinal fluid is simultaneously aspirated through the tear. Finally, laser photocoagulation is performed around the edge of the retinal tear, and expanding gas or silicone oil (SO) is injected to tamponade the retina (Fig. 3C, D). PPV based on microincision vitrectomy surgery (MIVS) was introduced in the 2000s (Fujii et al. 2002; Eckardt 2005), and subsequent reports described its usefulness for RRD repair (Lai et al. 2008; Tsang et al. 2008; Mura et al. 2009; Kunikata and Nishida 2010). Recently, 27-gauge MIVS, the smallest size yet used, has been introduced for RRD treatment, increasing surgical precision (Oshima et al. 2007; Romano et al. 2015) (Fig. 3C, D). Currently, 27-gauge MIVS can be used for almost every step of vitreous surgery, except the removal of SO. In our experience, although SO can be injected using a soft intravenous needle through a 27-gauge cannula, its removal from the vitreous cavity through a 27-gauge cannula is not currently practical. Thus, it is necessary to plan for SO removal with a 25-gauge cannula. Though PPV is now one of the main approaches to RRD repair, if the vitreous is removed and RRD then reoccurs, the eye can easily progress to total bullous RRD with proliferative vitreoretinopathy (PVR) (Shu et al. 2019) (Table 1). Thus, PPV should only be used for RRD after careful consideration and comparison with other methods.

Pneumatic Retinopexy

In PR, the surgeon uses the intravitreal injection of an expanding gas bubble as a tamponade to reattach the retina, without the need for an inward indentation in the sclera, i.e., SB, and without the need to remove the vitreous, i.e., PPV. Treatment of RRD with diathermy and injection of air into the vitreous was reported very early, in the 1930s, by Rosengren (1938). Only after a very long time had passed was PR re-introduced by Hilton (Hilton and Grizzard 1986), who pioneered the use of expanding gas in the 1980s and gave the procedure its current name (Kreissig et al. 1986; Tornambe 1988; Algvere et al. 1988; Freeman et al. 1988; Friberg and Eller 1988; Kamp Mortensen and Sjolie 1988). All types of PR use the injection of an expanding gas bubble, without PPV, combined with laser photocoagulation or cryopexy to seal the retinal tear. Traditionally, PR is used for cases of RRD with specific preoperative characteristics: uncomplicated RRD with retinal breaks in the superior region (i.e., around the 8 o'clock position) or multiple superior breaks confined to a single clockwise sector, with a clear vitreous (Tornambe et al. 1991; Gilca et al. 2014). Recently, PR for primary repair of RRD has been reported to result in successful anatomic outcomes in about 75% of cases, including cases with various preoperative characteristics (Jung et al. 2019). However, cases with preoperative pseudophakia have been reported to have worse

	Advantages	Disadvantages	Suggested use
Scleral buckling	High reattachment rate with greater VA improvement in phakic eyes.	Postoperative cataract progression.	Young RRD patients with preoperative phakia.
Pars plana vitrectomy	High reattachment rate in pseudophakic eyes.	Postoperative PVR and cataract progression.	Older RRD patients with retinal tears in various regions, including GRT and PVR. Should be combined with cataract surgery in older patients.
Pneumatic retinopexy	Better postoperative VA, less metamorphopsia, less cataract progression and significant cost savings.	Unsuitable in RRD cases with an inferior tear or with preoperative pseudophakia, due to lower reattachment rate.	RRD patients with preoperative phakia, with retinal breaks in the superior region, and with a clear vitreous.

Table 1. Advantages and disadvantages of scleral buckling, pars plana vitrectomy and pneumatic retinope.

VA, visual acuity; RRD, rhegmatogenous retinal detachment; GRT, giant retinal tear; PVR, proliferative vitreoretinopathy.

visual outcomes and less anatomical success, possibly due to poor visibility of the peripheral retina and a greater likelihood of multiple breaks in pseudophakic eyes (Gupta et al. 2018; Jung et al. 2019). Nevertheless, PR has been reported to lead to less morbidity and better postoperative visual acuity (VA) than SB (Tornambe and Hilton 1989) or PPV (Hillier et al. 2019). Compared to SB or PPV, PR has also been reported to have a potential cost savings of about 60% (Jung et al. 2019). Thus, the increased use of PR might have important financial advantages in many countries (Goldman et al. 2014). From the point of view of costeffectiveness and postoperative visual functional outcomes, PR may be the most suitable option for treatment of phakic eyes with RRD with superior breaks, even though additional procedures are required in a moderate number of cases (about 25%) (Table 1).

Scleral Buckling vs. Pars Plana Vitrectomy

A prospective, randomized multicenter clinical trial found that SB and PPV were most suitable for phakic and pseudophakic eyes, respectively. SB led to greater VA improvement in phakic, but not pseudophakic eyes, while PPV led to a higher primary anatomical success rate only in pseudophakic eyes (Heimann et al. 2007) (Table 1). In Japan, SB and PPV are chosen with almost equal frequency for young patients with RRD (Shu et al. 2019). Though SB and PPV exhibit similar primary anatomical reattachment rates, PPV has higher incidences of PVR and cataract formation within one year postoperatively (Shu et al. 2019). Thus, combining PPV with cataract surgery (i.e., triple surgery) in patients over 45 years old has been suggested to be an effective strategy in vitreoretinal surgery, improving both surgical results and the patient's quality of life (Ogino and Kumagai 2001). Triple surgery is also covered by health insurance in Japan, and triple surgery is recommended in phakic RRD patients \geq 45 years old, while PPV is recommended in pseudophakic RRD patients (Table 1). SB is recommended as the primary procedure in young phakic patients with RRD, to avoid the need for cataract surgery and subsequent PVR formation (Table 1). Of course, those two methods can also coexist, and a combination approach might be most effective in difficult cases of RRD, such as those with PVR or multiple tears, particularly inferior tears (Abu Eleinen et al. 2018) (Fig. 4), despite the increase in



Fig. 4. Pre- and post-operative fundus photographs in difficult cases of RRD.

(A) RRD due to retinal tears in multiple quadrants, including the inferonasal quadrant, confirmed intraoperatively. These tears are not clearly visible in this photograph.

(B) Total RRD with PVR due to a retinal tear in the superonasal quadrant (arrow). There is a severe proliferative membrane covering the retina, including the peripheral region, causing fixed retinal folds.

(C) Postoperative fundus photograph of the same case as in A. Expanding gas was injected at the end of 27-gauge MIVS with encircling SB. There is no remaining RRD in the circumferential inward indentation in the choroid (arrow heads). There is 40% unabsorbed gas.

(D) Postoperative fundus photograph of the same case as in B. SO was injected at the end of 27-gauge MIVS with encircling SB. In this image, laser photocoagulation scars are visible surrounding the repaired retinal tear in the superonasal quadrant (arrow) and the eye is still filled with SO; there is no remaining RRD in the circumferential inward indentation in the choroid (arrow heads).

surgical invasiveness.

Scleral Buckling vs. Pneumatic Retinopexy

A prospective, randomized multicenter clinical trial followed 179 patients for two years, and found that there was no significant change in overall attachment rates after SB and PR, but that there were significant differences in the subsequent need for cataract surgery (18% vs. 4%) and in the proportion of patients with a good final VA outcome (i.e., VA $\ge 20/50$: 67% vs. 89%) (Tornambe et al. 1991). Moreover, in phakic eyes, PR was found to be associated with a significantly higher reoperation rate than SB, even though the final visual outcome and reattachment rate after reoperation was equivalent (Han et al. 1998). Thus, PR is recommended in phakic eyes with RRD and superior retinal tears, in order to obtain better postoperative VA without subsequent cataract progression, even though reoperation may be required in some cases (Table 1). SB is recommended in RRD patients with tears in various locations who desire to avoid reoperation as far as possible (Table 1). SB and PR can also be combined, and this approach might be most effective in relatively complicated RRD cases, such as those with inferior tears or with vitreous hemorrhage (Cheng et al. 2013; Zhou et al. 2018).

Pars Plana Vitrectomy vs. Pneumatic Retinopexy

A recent prospective, randomized trial suggested that PR might be considered a first-line treatment for RRD in patients fulfilling certain criteria (Hillier et al. 2019), i.e., RRD with breaks within 1 clockwise sector, located at the 8 and 4 o'clock meridians. That study found that PR resulted in superior VA, less vertical metamorphopsia, and reduced morbidity when compared with PPV. However, many reports have shown that the primary reattachment rate after PR is not very high (about 60-80%) (Han et al. 1998; Gilca et al. 2014; Goldman et al. 2014; Hillier et al. 2019; Jung et al. 2019), in contrast with high reattachment rates after PPV (more than 90%) (Han et al. 1998; Kunikata and Nishida 2010). Thus, PR is recommended in RRD patients with retinal tears in the superior region who desire to have the best possible visual function, even if additional procedures are needed, while PPV is recommended in patients with retinal tears in various regions who desire to avoid reoperations, regardless of the possible impact on visual functional recovery (Table 1).

Giant Retinal Tear

Effective treatment of GRT, i.e., a circumferential tear \geq 90 degrees, is very important for patients' visual quality of life and is a great challenge to ophthalmologists because of technical difficulties in treatment and the high risk of surgical complications. GRT is rare, comprising only 1% of RRD cases, with an annual incidence of about 1/1,000,000 (Ang et al. 2010; Shunmugam et al. 2014). Various treatments have been used for GRT, including SB (Holland and Smith 1977), PR (Kreissig et al. 1986; Irvine

and Lahey 1994), PPV with gas tamponade (Freeman and Castillejos 1981; Sirimongkolkasem et al. 1991), and PPV with SO tamponade (Leaver et al. 1984; Sirimongkolkasem et al. 1991). Historically, the postoperative reattachment rate for GRT was low and reattachment was unreliable. The introduction in the 1980s of intraoperative perfluorocarbon liquid (PFCL) by Chang et al. (1989) dramatically increased reattachment rates after GRT surgery (Lee et al. 2009). Other recent technical advancements, such as MIVS, wide viewing systems, and chandelier illumination, have also greatly improved GRT treatment (primary reattachment rate: more than 90%) (Kunikata et al. 2011) (Fig. 5). Some authors have reported success in GRT treatment with an adjunctive encircling SB (Al-Khairi et al. 2008; Goezinne et al. 2008), but we consider that initial MIVS for GRT does not need to be combined with an encircling SB (Kunikata et al. 2011; Kunikata 2014), a view reinforced by other investigators (Quezada-Ruiz and Cano-Hidalgo 2014; Hocaoglu et al. 2019). However, we recommend using a two-step technique in all cases, including, first, the application of PFCL and its immediate intraoperative replacement with SO tamponade (Fig. 5), and second, the removal of the tamponade after two or three weeks (Kunikata 2014). The first step flattens the rolled-up part of the retina and prevents retinal slippage, and the second step prevents SO-associated glaucoma, keratopathy and PVR. The follow-up SO removal procedure also provides an opportunity to treat minor complications, such as subretinal PFCL (Kunikata et al. 2011; Kunikata 2014). GRT is still difficult to treat successfully, even for experienced vitreous surgeons (Shunmugam et al. 2014). Therefore, the two-step technique based on MIVS is highly recommended for complete repair of GRTs at the current moment (Table 1), although the situation may change if artificial vitreous substitutes become available.

Artificial Vitreous

Expanding gas and SO tamponades are a very common feature of modern PPV to repair RRD, but these materials still have many problems to be overcome. Problems with expanding gas tamponades include: 1) the requirement for patients to maintain the same position (prone, side up or sitting); 2) difficulty in using them to reattach inferior tears; 3) difficulty in adjusting the volume of the expanding gas after surgery, leading to either a too-small volume (causing a risk of retinal re-detachment) or a too-high volume (causing a risk of glaucoma); and 4) the lack of visibility for patients through the gas. Problems facing SO tamponades include: 1) a risk of causing glaucoma, keratopathy and PVR, if the SO tamponade is long-standing; 2) the requirement for additional surgery to remove the SO; and 3) distorted vision for patients due to the difference in refractive index.

A material that could be used as an artificial vitreous might ameliorate problems with gas and SO tamponades and provide an internal tamponade effect through swelling



Fig. 5. Intraoperative photographs of 27-gauge MIVS for a case with GRT more than 300 degrees.
All photographs show successive steps of a single procedure in the same eye.
(A) PFCL is injected to gently push the inverted retina (arrows) back into place and reattach it.
(B) After the retina has been partially reattached using PFCL (arrow heads), multiple radial microretinotomies (arrows) (visible as the frilled edges of the retina) are created to prevent the edges from rolling up after re-attachment.
(C) Laser photocoagulation is performed in double lines on the edges of the retinal tear after complete reattachment (arrow).

(D) After laser photocoagulation on the edges of the tear, the PFCL (arrow heads) is exchanged with SO directly through a 27-gauge cannula.

pressure. Such a material would need the appropriate viscosity, have good biocompatibility, optical clarity, a suitable refractive index, and suitable rheological properties, while being non-toxic to the retina (Mariacher and Szurman 2015). Among the wide variety of materials proposed or tested as vitreous substitutes, synthetic polymers have been most often considered in the past (Chirila et al. 1994). Recently, new alternatives have been examined, including materials such as cross-linked synthetic polymers and hyaluronate hydrogels (Schramm et al. 2012; Hayashi et al. 2017; Schnichels et al. 2017; Januschowski et al. 2019). The properties of hydrogels make them promising candidate biomaterials for a permanent artificial vitreous in the treatment of RRD. The discovery of suitable materials for use as an artificial vitreous in PPV for RRD, particularly when treating GRT or PVR, promises to eliminate the need for follow-up surgery to remove the SO tamponade, as well as patient discomfort caused by SO or gas tamponades.

Neuroprotection

Even after successful reattachment, degeneration of the photoreceptors in the detached area of the retina often prevents complete recovery of visual function (Wakabayashi et al. 2009; Kunikata et al. 2011; Shunmugam et al. 2014).

The cause of photoreceptor cell death in RRD is mainly thought to be insufficient oxygen and nutritional support to the detached retina from the underlying retinal pigment epithelial cells. Many animal models of RRD have been developed to investigate this phenomenon and to elucidate the pathogenic mechanisms underlying retinal cell death (Cook et al. 1995; Hisatomi et al. 2002; Nakazawa et al. 2006, 2007a, b). The expression of monocyte chemoattractant protein-1 (MCP-1) and tumor necrosis factor-alpha (TNF α), and subsequent movement of the macrophages and microglia, are considered critical parts of retinal detachment-induced photoreceptor apoptosis (Nakazawa et al. 2007a, 2011; Okunuki et al. 2018). There is also accumulating evidence that not only apoptotic, but also autophagic and necrotic signaling are involved in photoreceptor cell death (Murakami et al. 2013).

Many potential neuroprotective agents have been tested in animal RRD models to determine their ability to prevent retinal cell death. Agents examined thus far include dexamethasone (Nakazawa et al. 2011), tauroursodeoxy-cholic acid (TUDCA) (Mantopoulos et al. 2011), exogenous erythropoietin (EPO) (Xie et al. 2012), lutein (Woo et al. 2013), macrophage migration inhibitory factor (MIF) inhibitors (Kim et al. 2017), and α -adrenoceptors (Li et al. 2019).

Administration of neuroprotective agents in human subjects with RRD is still rare. However, the adjunctive use of steroids has been reported to be a promising tool for the prevention of PVR formation in eyes treated with vitreoretinal surgery (Gagliano et al. 2015; Shi et al. 2015). Furthermore, the preoperative intravitreal injection of triamcinolone acetonide has been reported to suppress elevated levels of intraocular chemokines, including MCP-1, in eyes with RRD (Kunikata et al. 2013). After macula-off RRD surgery, increased cone density has been confirmed with adaptive optics, suggesting postoperative regeneration of the photoreceptor outer segment (Ra et al. 2017). To reinforce protection or regeneration of the photoreceptor cells, we hope to combine RRD surgery with adjunct drug administration during the perioperative period as a neuroprotective strategy in the near future.

Conclusion

Though the ideal approach to RRD repair has not yet been established, exemplary work by previous generations of ophthalmologists has provided us with multiple effective options: SB, PR, and PPV. All three approaches can ensure reattachment, preserve visual function, and avoid complications, but each has characteristic advantages in certain patients. Making the most suitable choice can be difficult, but the reports summarized here provide a great deal of information to help surgical decision making and enable individualized treatment for patients with RRD. Furthermore, recent findings on new surgical and non-surgical techniques and materials, such as artificial vitreous substitutes and neuroprotective treatments, are also important. This review summarizes current knowledge on the treatment of RRD, discusses characteristics of the current three main approaches, i.e., SB, PPV and PR, provides historical context and comparisons, and provides an overview of recent findings that promise to improve postoperative outcomes for RRD, leading to the establishment of the best possible treatment for RRD.

Acknowledgments

This paper was supported by JST grants from JSPS KAKENHI Grants-in-Aid for Scientific Research (C) (H.K. No. 17K11445). The funders had no role in the design or conduct of the study; collection, management, analysis, or interpretation of the data; preparation, review, or approval of the manuscript; or the decision to submit the manuscript for publication.

Conflict of Interest

The authors declare no conflict of interest.

References

Abu Eleinen, K.G., Mohalhal, A.A., Ghalwash, D.A., Abdel-Kader, A.A., Ghalwash, A.A., Mohalhal, I.A. & Abdullatif, A.M. (2018) Vitrectomy with scleral buckling versus with inferior retinectomy in treating primary rhegmatogenous retinal detachment with PVR and inferior breaks. *Eye (Lond.)*, **32**, 1839-1844.

- Al-Khairi, A.M., Al-Kahtani, E., Kangave, D. & Abu El-Asrar, A.M. (2008) Prognostic factors associated with outcomes after giant retinal tear management using perfluorocarbon liquids. *Eur. J. Ophthalmol.*, 18, 270-277.
- Algvere, P., Hallnas, K. & Palmqvist, B.M. (1988) Success and complications of pneumatic retinopexy. Am. J. Ophthalmol., 106, 400-404.
- Ang, G.S., Townend, J. & Lois, N. (2010) Epidemiology of giant retinal tears in the United Kingdom: the British Giant Retinal Tear Epidemiology Eye Study (BGEES). *Invest. Ophthalmol. Vis. Sci.*, **51**, 4781-4787.
- Caporossi, T., Finocchio, L., Barca, F., Franco, F., Tartaro, R. & Rizzo, S. (2019) Scleral buckling for primary rhegmatogenous retinal detachment using a noncontact wide-angle viewing system with a cannula-based 27-G chandelier endoilluminator. *Retina*, doi: 10.1097/IAE.000000000001891. [Epub ahead of print]
- Chang, S., Lincoff, H., Zimmerman, N.J. & Fuchs, W. (1989) Giant retinal tears. Surgical techniques and results using perfluorocarbon liquids. Arch. Ophthalmol., 107, 761-766.
- Charles, S. & Wang, C. (1981) A motorized gas injector for vitreous surgery. *Arch. Ophthalmol.*, **99**, 1398.
- Cheng, H.C., Lee, S.M., Lee, F.L., Liu, J.H., Kuan, C.H. & Lin, P.K. (2013) Short-term external buckling with pneumatic retinopexy for retinal detachment with inferior retinal breaks. *Am. J. Ophthalmol.*, **155**, 750-756, 756 e751.
- Chirila, T.V., Tahija, S., Hong, Y., Vijayasekaran, S. & Constable, I.J. (1994) Synthetic polymers as materials for artificial vitreous body: review and recent advances. *J. Biomater. Appl.*, 9, 121-137.
- Cook, B., Lewis, G.P., Fisher, S.K. & Adler, R. (1995) Apoptotic photoreceptor degeneration in experimental retinal detachment. *Invest. Ophthalmol. Vis. Sci.*, 36, 990-996.
- Custodis, E. (1951) Beobachtungen bei der diathermischen Behandlung der Netxhautablosug und ein Hinweis zur Therapie der Amotio retinae. Ber Dtsch. Opthalmol. Ges., 57, 227-230.
- Eckardt, C. (2005) Transconjunctival sutureless 23-gauge vitrectomy. *Retina*, 25, 208-211.
- Escoffery, R.F., Olk, R.J., Grand, M.G. & Boniuk, I. (1985) Vitrectomy without scleral buckling for primary rhegmatogenous retinal detachment. *Am. J. Ophthalmol.*, **99**, 275-281.
- Freeman, H.M. & Castillejos, M.E. (1981) Current management of giant retinal breaks: results with vitrectomy and total air fluid exchange in 95 cases. *Trans. Am. Ophthalmol. Soc.*, 79, 89-102.
- Freeman, W.R., Lipson, B.K., Morgan, C.M. & Liggett, P.E. (1988) New posteriorly located retinal breaks after pneumatic retinopexy. *Ophthalmology*, 95, 14-18.
- Friberg, T.R. & Eller, A.W. (1988) Pneumatic repair of primary and secondary retinal detachments using a binocular indirect ophthalmoscope laser delivery system. *Ophthalmology*, 95, 187-193.
- Fujii, G.Y., De Juan, E. Jr., Humayun, M.S., Pieramici, D.J., Chang, T.S., Awh, C., Ng, E., Barnes, A., Wu, S.L. & Sommerville, D.N. (2002) A new 25-gauge instrument system for transconjunctival sutureless vitrectomy surgery. *Ophthalmology*, **109**, 1807-1812; discussion 1813.
- Gagliano, C., Toro, M.D., Avitabile, T., Stella, S. & Uva, M.G. (2015) Intravitreal steroids for the prevention of PVR after surgery for retinal detachment. *Curr. Pharm. Des.*, **21**, 4698-4702.
- Gilca, M., Duval, R., Goodyear, E., Olivier, S. & Cordahi, G. (2014) Factors associated with outcomes of pneumatic retinopexy for rhegmatogenous retinal detachments: a retrospective review of 422 cases. *Retina*, 34, 693-699.
- Goezinne, F., LA Heiji, E.C., Berendschot, T.T., Gast, S.T., Liem, A.T., Lundqvist, I.L. & Hendrikse, F. (2008) Low redetachment rate due to encircling scleral buckle in giant retinal tears treated with vitrectomy and silicone oil. *Retina*, 28, 485-492.

- Goldman, D.R., Shah, C.P. & Heier, J.S. (2014) Expanded criteria for pneumatic retinopexy and potential cost savings. *Ophthalmology*, **121**, 318-326.
- Gonin, J. (1923) Guérison opératoires de décollements rétiniens. *Rev. Gén. Ophtalmol.*, 37, 337-340.
- Gupta, D., Ching, J. & Tornambe, P.E. (2018) Clinically undetected retinal breaks causing retinal detachment: a review of options for management. Surv. Ophthalmol., 63, 579-588.
- Han, D.P., Mohsin, N.C., Guse, C.E., Hartz, A. & Tarkanian, C.N. (1998) Comparison of pneumatic retinopexy and scleral buckling in the management of primary rhegmatogenous retinal detachment. Southern Wisconsin Pneumatic Retinopexy Study Group. Am. J. Ophthalmol., 126, 658-668.
- Hayashi, K., Okamoto, F., Hoshi, S., Katashima, T., Zujur, D., Li, X., Shibayama, M., Gilbert, E., Chung, U., Ohba, S., Oshika, T. & Sakai, T. (2017) Fast-forming hydrogel with ultralow polymeric content as an artificial vitreous body. *Nat. Biomed. Eng.*, 1, 0044.
- Heimann, H., Bartz-Schmidt, K.U., Bornfeld, N., Weiss, C., Hilgers, R.D. & Foerster, M.H.; Scleral Buckling versus Primary Vitrectomy in Rhegmatogenous Retinal Detachment Study Group (2007) Scleral buckling versus primary vitrectomy in rhegmatogenous retinal detachment: a prospective randomized multicenter clinical study. *Ophthalmology*, **114**, 2142-2154.
- Heimann, H., Zou, X., Jandeck, C., Kellner, U., Bechrakis, N.E., Kreusel, K.M., Helbig, H., Krause, L., Schuler, A., Bornfeld, N. & Foerster, M.H. (2006) Primary vitrectomy for rhegmatogenous retinal detachment: an analysis of 512 cases. *Graefes Arch. Clin. Exp. Ophthalmol.*, 244, 69-78.
- Hillier, R.J., Felfeli, T., Berger, A.R., Wong, D.T., Altomare, F., Dai, D., Giavedoni, L.R., Kertes, P.J., Kohly, R.P. & Muni, R.H. (2019) The pneumatic retinopexy versus vitrectomy for the management of primary rhegmatogenous retinal detachment outcomes randomized trial (PIVOT). *Ophthalmology*, **126**, 531-539.
- Hilton, G.F. & Grizzard, W.S. (1986) Pneumatic retinopexy. A two-step outpatient operation without conjunctival incision. *Ophthalmology*, 93, 626-641.
- Hisatomi, T., Sakamoto, T., Goto, Y., Yamanaka, I., Oshima, Y., Hata, Y., Ishibashi, T., Inomata, H., Susin, S.A. & Kroemer, G. (2002) Critical role of photoreceptor apoptosis in functional damage after retinal detachment. *Curr. Eye Res.*, 24, 161-172.
- Hocaoglu, M., Karacorlu, M., Ersoz, M.G., Sayman Muslubas, I. & Arf, S. (2019) Vitrectomy with silicone oil tamponade for retinal detachment associated with giant retinal tears: favourable outcomes without adjuvant scleral buckling. *Acta Ophthalmol.*, 97, e271-e276.
- Holland, P.M. & Smith, T.R. (1977) Broad scleral buckle in the management of retinal detachments with giant tears. Am. J. Ophthalmol., 83, 518-525.
- Irvine, A.R. & Lahey, J.M. (1994) Pneumatic retinopexy for giant retinal tears. *Ophthalmology*, **101**, 524-528.
- Januschowski, K., Schnichels, S., Hurst, J., Hohenadl, C., Reither, C., Rickmann, A., Pohl, L., Bartz-Schmidt, K.U. & Spitzer, M.S. (2019) Ex vivo biophysical characterization of a hydrogel-based artificial vitreous substitute. *PLoS One*, 14, e0209217.
- Jung, J.J., Cheng, J., Pan, J.Y., Brinton, D.A. & Hoang, Q.V. (2019) Anatomic, visual, and financial outcomes for traditional and nontraditional primary pneumatic retinopexy for retinal detachment. Am. J. Ophthalmol., 200, 187-200.
- Kamp Mortensen, K. & Sjolie, A.K. (1988) Retinal detachment treated by pneumatic retinopexy. *Acta Ophthalmol. (Copenh.)*, 66, 187-189.
- Kim, B., Kusibati, R., Heisler-Taylor, T., Mantopoulos, D., Ding, J., Abdel-Rahman, M.H., Satoskar, A.R., Godbout, J.P., Bhattacharya, S.K. & Cebulla, C.M. (2017) MIF inhibitor ISO-1 protects photoreceptors and reduces gliosis in experi-

mental retinal detachment. Sci. Rep., 7, 14336.

- Kreissig, I., Stanowsky, A., Lincoff, H. & Richard, G. (1986) The treatment of difficult retinal detachments with an expanding gas bubble without vitrectomy. *Graefes Arch. Clin. Exp. Ophthalmol.*, **224**, 51-54.
- Kunikata, H. (2014) Management of giant retinal tears using microincision vitrectomy surgery. Dev. Ophthalmol., 54, 182-187.
- Kunikata, H., Abe, T. & Nishida, K. (2011) Successful outcomes of 25- and 23-gauge vitrectomies for giant retinal tear detachments. *Ophthalmic Surg. Lasers Imaging*, 42, 487-492.
- Kunikata, H. & Nishida, K. (2010) Visual outcome and complications of 25-gauge vitrectomy for rhegmatogenous retinal detachment; 84 consecutive cases. *Eye (Lond.)*, 24, 1071-1077.
- Kunikata, H., Yasuda, M., Aizawa, N., Tanaka, Y., Abe, T. & Nakazawa, T. (2013) Intraocular concentrations of cytokines and chemokines in rhegmatogenous retinal detachment and the effect of intravitreal triamcinolone acetonide. *Am. J. Ophthalmol.*, **155**, 1028-1037 e1021.
- Lai, M.M., Ruby, A.J., Sarrafizadeh, R., Urban, K.E., Hassan, T.S., Drenser, K.A. & Garretson, B.R. (2008) Repair of primary rhegmatogenous retinal detachment using 25-gauge transconjunctival sutureless vitrectomy. *Retina*, 28, 729-734.
- Leaver, P.K., Cooling, R.J., Feretis, E.B., Lean, J.S. & McLeod, D. (1984) Vitrectomy and fluid/silicone-oil exchange for giant retinal tears: results at six months. *Br. J. Ophthalmol.*, 68, 432-438.
- Lee, S.Y., Ong, S.G., Wong, D.W. & Ang, C.L. (2009) Giant retinal tear management: an Asian experience. *Eye (Lond.)*, 23, 601-605.
- Li, T., Yang, S., She, X., Yan, Q., Zhang, P., Zhu, H., Wang, F., Luo, X. & Sun, X. (2019) Modulation of alpha-adrenoceptor signalling protects photoreceptors after retinal detachment by inhibiting oxidative stress and inflammation. *Br. J. Pharmacol.*, **176**, 801-813.
- Lincoff, H.A., Baras, I. & McLean, J. (1965) Modifications to the custodis procedure for retinal detachment. *Arch. Ophthalmol.*, 73, 160-163.
- Machemer, R., Buettner, H., Norton, E.W. & Parel, J.M. (1971) Vitrectomy: a pars plana approach. Trans. Am. Acad. Ophthalmol. Otolaryngol., 75, 813-820.
- Mantopoulos, D., Murakami, Y., Comander, J., Thanos, A., Roh, M., Miller, J.W. & Vavvas, D.G. (2011) Tauroursodeoxycholic acid (TUDCA) protects photoreceptors from cell death after experimental retinal detachment. *PLoS One*, 6, e24245.
- Mariacher, S. & Szurman, P. (2015) Artificial vitreous body: strategies for vitreous body substitutes. *Ophthalmologe*, **112**, 572-579.
- Mura, M., Tan, S.H. & De Smet, M.D. (2009) Use of 25-gauge vitrectomy in the management of primary rhegmatogenous retinal detachment. *Retina*, **29**, 1299-1304.
- Murakami, Y., Notomi, S., Hisatomi, T., Nakazawa, T., Ishibashi, T., Miller, J.W. & Vavvas, D.G. (2013) Photoreceptor cell death and rescue in retinal detachment and degenerations. *Prog. Retin. Eye Res.*, **37**, 114-140.
- Nakazawa, T., Hisatomi, T., Nakazawa, C., Noda, K., Maruyama, K., She, H., Matsubara, A., Miyahara, S., Nakao, S., Yin, Y., Benowitz, L., Hafezi-Moghadam, A. & Miller, J.W. (2007a) Monocyte chemoattractant protein 1 mediates retinal detachment-induced photoreceptor apoptosis. *Proc. Natl. Acad. Sci.* USA, 104, 2425-2430.
- Nakazawa, T., Kayama, M., Ryu, M., Kunikata, H., Watanabe, R., Yasuda, M., Kinugawa, J., Vavvas, D. & Miller, J.W. (2011) Tumor necrosis factor-alpha mediates photoreceptor death in a rodent model of retinal detachment. *Invest. Ophthalmol. Vis. Sci.*, **52**, 1384-1391.
- Nakazawa, T., Matsubara, A., Noda, K., Hisatomi, T., She, H., Skondra, D., Miyahara, S., Sobrin, L., Thomas, K.L., Chen,

D.F., Grosskreutz, C.L., Hafezi-Moghadam, A. & Miller, J.W. (2006) Characterization of cytokine responses to retinal detachment in rats. *Mol. Vis.*, **12**, 867-878.

- Nakazawa, T., Takeda, M., Lewis, G.P., Cho, K.S., Jiao, J., Wilhelmsson, U., Fisher, S.K., Pekny, M., Chen, D.F. & Miller, J.W. (2007b) Attenuated glial reactions and photoreceptor degeneration after retinal detachment in mice deficient in glial fibrillary acidic protein and vimentin. *Invest. Ophthalmol. Vis. Sci.*, 48, 2760-2768.
- Ogino, N. & Kumagai, K. (2001) Advantage of combined procedure in vitreous surgery. *Semin. Ophthalmol.*, 16, 137-138.
- Okunuki, Y., Mukai, R., Pearsall, E.A., Klokman, G., Husain, D., Park, D.H., Korobkina, E., Weiner, H.L., Butovsky, O., Ksander, B.R., Miller, J.W. & Connor, K.M. (2018) Microglia inhibit photoreceptor cell death and regulate immune cell infiltration in response to retinal detachment. *Proc. Natl. Acad. Sci. USA*, **115**, E6264-E6273.
- Oshima, Y., Awh, C.C. & Tano, Y. (2007) Self-retaining 27-gauge transconjunctival chandelier endoillumination for panoramic viewing during vitreous surgery. Am. J. Ophthalmol., 143, 166-167.
- Peyman, G.A., Huamonte, F.U. & Goldberg, M.F. (1976) One hundred consecutive pars plana vitrectomies using the vitrophage. Am. J. Ophthalmol., 81, 263-271.
- Quezada-Ruiz, C. & Cano-Hidalgo, R.A. (2014) Giant retinal tears treated with lens sparing, bimanual 23 g vitrectomy without scleral buckle. *Cir. Cir.*, **82**, 245-251.
- Ra, E., Ito, Y., Kawano, K., Iwase, T., Kaneko, H., Ueno, S., Yasuda, S., Kataoka, K. & Terasaki, H. (2017) Regeneration of photoreceptor outer segments after scleral buckling surgery for rhegmatogenous retinal detachment. *Am. J. Ophthalmol.*, 177, 17-26.
- Romano, M.R., Scotti, F. & Vinciguerra, P. (2015) 27-gauge vitrectomy for primary rhegmatogenous retinal detachment: is it feasible? Ann. Acad. Med. Singapore, 44, 185-187.
- Rosengren, B. (1938) Results of treatment of detachment of the retina with diathermy and injection of air into the vitreous. *Acta Ophthalmol.*, 16, 573-579.
- Rumpf, J. (1976) Jules gonin. Inventor of the surgical treatment for retinal detachment. *Surv. Ophthalmol.*, **21**, 276-284.
- Schepens, C.L. (1951) Progress in detachment surgery. Trans. Am. Acad. Ophthalmol. Otolaryngol., 55, 607-615.
- Schepens, C.L., Okamura, I.D. & Brockhurst, R.J. (1957) The scleral buckling procedures. I. Surgical techniques and management. AMA Arch. Ophthalmol., 58, 797-811.
- Schnichels, S., Schneider, N., Hohenadl, C., Hurst, J., Schatz, A., Januschowski, K. & Spitzer, M.S. (2017) Efficacy of two different thiol-modified crosslinked hyaluronate formulations as vitreous replacement compared to silicone oil in a model of retinal detachment. *PLoS One*, **12**, e0172895.
- Schramm, C., Spitzer, M.S., Henke-Fahle, S., Steinmetz, G., Januschowski, K., Heiduschka, P., Geis-Gerstorfer, J., Biedermann, T., Bartz-Schmidt, K.U. & Szurman, P. (2012) The cross-linked biopolymer hyaluronic acid as an artificial vitreous substitute. *Invest. Ophthalmol. Vis. Sci.*, 53, 613-621.
- Shi, H., Guo, T., Liu, P.C., Wang, Q.Y., Du, Y.R., Liu, Q.Y., He, M.M., Liu, J.L. & Yu, J. (2015) Steroids as an adjunct for reducing the incidence of proliferative vitreoretinopathy after

rhegmatogenous retinal detachment surgery: a systematic review and meta-analysis. *Drug Des. Devel. Ther.*, **9**, 1393-1400.

- Shu, I., Ishikawa, H., Nishikawa, H., Morikawa, S., Okamoto, F., Sakamoto, T., Sugimoto, M., Kondo, M., Iwasaki, M., Kinoshita, T., Toibana, T., Mitamura, Y., Takamura, Y., Motohashi, R., Shimura, M., et al. (2019) Scleral buckling versus vitrectomy for young japanese patients with rhegmatogenous retinal detachment in the era of microincision surgery: real-world evidence from a multicentre study in Japan. Acta Ophthalmol., doi: 10.1111/aos.14050 [Epub ahead of print].
- Shunmugam, M., Ang, G.S. & Lois, N. (2014) Giant retinal tears. Surv. Ophthalmol., 59, 192-216.
- Sirimongkolkasem, A., Samaiporn, S., Praweenwongwuth, K., Chongmankongcheep, L. & Lawtiantong, T. (1991) Surgical management of giant retinal tears. J. Med. Assoc. Thai., 74, 647-652.
- Tornambe, P.E. (1988) Pneumatic retinopexy. Surv. Ophthalmol., 32, 270-281.
- Tornambe, P.E. & Hilton, G.F. (1989) Pneumatic retinopexy. A multicenter randomized controlled clinical trial comparing pneumatic retinopexy with scleral buckling. The Retinal Detachment Study Group. *Ophthalmology*, **96**, 772-783; discussion 784.
- Tornambe, P.E., Hilton, G.F., Brinton, D.A., Flood, T.P., Green, S., Grizzard, W.S., Hammer, M.E., Leff, S.R., Masciulli, L., Morgan, C.M., et al. (1991) Pneumatic retinopexy. A two-year follow-up study of the multicenter clinical trial comparing pneumatic retinopexy with scleral buckling. *Ophthalmology*, 98, 1115-1123.
- Tsang, C.W., Cheung, B.T., Lam, R.F., Lee, G.K., Yuen, C.Y., Lai, T.Y. & Lam, D.S. (2008) Primary 23-gauge transconjunctival sutureless vitrectomy for rhegmatogenous retinal detachment. *Retina*, 28, 1075-1081.
- Von Fricken, M.A., Kunjukunju, N., Weber, C. & Ko, G. (2009) 25-gauge sutureless vitrectomy versus 20-gauge vitrectomy for the repair of primary rhegmatogenous retinal detachment. *Retina*, 29, 444-450.
- Wakabayashi, T., Oshima, Y., Fujimoto, H., Murakami, Y., Sakaguchi, H., Kusaka, S. & Tano, Y. (2009) Foveal microstructure and visual acuity after retinal detachment repair: imaging analysis by Fourier-domain optical coherence tomography. *Ophthalmology*, **116**, 519-528.
- Woo, T.T., Li, S.Y., Lai, W.W., Wong, D. & Lo, A.C. (2013) Neuroprotective effects of lutein in a rat model of retinal detachment. *Graefes Arch. Clin. Exp. Ophthalmol.*, 251, 41-51.
- Xie, Z., Chen, F., Wu, X., Zhuang, C., Zhu, J., Wang, J., Ji, H., Wang, Y. & Hua, X. (2012) Safety and efficacy of intravitreal injection of recombinant erythropoietin for protection of photoreceptor cells in a rat model of retinal detachment. *Eye* (*Lond.*), 26, 144-152.
- Zhou, C., Lin, Q., Wang, Y. & Qiu, Q. (2018) Pneumatic retinopexy combined with scleral buckling in the management of relatively complicated cases of rhegmatogenous retinal detachment: a multicenter, retrospective, observational consecutive case series. J. Int. Med. Res., 46, 316-325.