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## Section 3 Special Adjuncts to Treatment

 Chapter
 Silicone Oil in Vitreoretinal Surgery

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#### INTRODUCTION

Since the US Federal Drug Administration approved the use of silicone oil as an intraocular tamponade in 1996, this agent has been used with increasing frequency in the USA and elsewhere as an adjunct in vitreoretinal surgery. Silicone oil has been used most commonly in the management of complex rhegmatogenous retinal detachments due to severe proliferative vitreoretinopathy (PVR), giant retinal tears, viral retinitis, trauma, and proliferative diabetic retinopathy (PDR). Additional applications now include idiopathic, myopic, and traumatic macular holes, colobomatous retinal detachments, and chronic uveitis with severe hypotony. In this chapter, we review the unique surgical techniques associated with silicone oil usage, the clinical settings in which silicone oil tamponade may be used, the advantages and disadvantages of silicone oil compared with other tamponades and the complications associated with its use.

# HISTORICAL PERSPECTIVE

Based on the experimental work of Stone<sup>1</sup> and Armaly,<sup>2</sup> Paul Cibis<sup>3-6</sup> introduced liquid silicone oil for use in retinal reattachment surgery in the early 1960s. This initial clinical application of silicone oil came before the advent of modern pars plana vitreous surgery.<sup>7</sup> Utilizing both its relatively high interfacial tension with water as well as its hydraulic capabilities, Cibis envisioned silicone oil both as an extended intraocular tamponade as well as a surgical instrument. Silicone was utilized as a tamponade for pushing back the retina against the force of preretinal membranes<sup>8</sup> and as an intrument to separate preretinal membranes. With these approaches, previously inoperable retinal detachments could be treated with significant anatomical and visual success.

Despite initial success and excitement with the use of liquid silicone oil, the combination of the untimely death of Cibis in 1965 and the increasing reports of complications associated with prolonged silicone tamponade<sup>9-17</sup> led to near abandonment of the use of silicone oil in retinal surgery. Only a few retinal surgeons, most notably John Scott in England,<sup>18-21</sup> continued to use liquid silicone oil, thus extending the work of Cibis and providing additional experience with silicone oil as a long-acting tamponade.

With the advent of modern vitreous microsurgery in the 1970s, several investigators, including Jean Haut in France,<sup>22-26</sup>

Relja Zivojnovic in the Netherlands,<sup>27–29</sup> and Peter Leaver in England,<sup>30–38</sup> successfully combined pars plana vitrectomy techniques with the use of silicone oil as an internal tamponade. As the use of silicone oil spread, other advances, such as the inferior peripheral iridectomy<sup>39,40</sup> and relaxing retinotomy<sup>41–43</sup> in selected cases reduced the complication rates and further increased the likelihood of successful retinal reattachment.<sup>44–69</sup>

While in Europe silicone oil was used with increasing frequency in the treatment of complex retinal detachments, retinal surgeons in the USA focused their attention on improving fluid–gas exchange techniques<sup>70–73</sup> and on the development of longer-acting gases<sup>74,75</sup> for extended intraocular tamponade (see Chapter 127 for review). By the mid-1980s, the relative safety and efficacy of these two tamponades had not been defined. Uncontrolled clinical studies suggested that the guaranteed and extended nature of the silicone oil tamponade might improve the anatomic results for complex cases, but that the ultimate visual results might be compromised by complications related to its use.<sup>76</sup> Thus was born the Silicone Study, organized by Stephen Ryan, which sought to compare the safety and efficacy of silicone oil to long-acting gas as a tamponade in the repair of complex rhegmatogenous retinal detachments with severe PVR.<sup>76,77</sup>

#### INDICATIONS FOR SILICONE OIL TAMPONADE

Silicone oil tamponade is now utilized in the management of a wide variety of vitreoretinal problems. Here we review some specific indications for the use of silicone oil.

# Retinal detachment complicated by severe proliferative vitreoretinopathy

The Silicone Study was a prospective, multicentered, randomized, controlled clinical trial comparing silicone oil and long-acting gases in the management of eyes with severe PVR.<sup>76</sup> In this study, eyes were divided into two groups: group 1 (eyes with no previous history of vitreous surgery) and group 2 (eyes with a previous history of at least one vitrectomy with gas for PVR). This study concluded that overall, silicone oil was superior to sulfur hexafluoride gas<sup>78</sup> and roughly equivalent to perfluoropropane ( $C_3F_8$ ) gas<sup>79,80</sup> in the management of retinal detachment with severe PVR. Despite their overall equivalence, however, certain subgroups of eyes appeared to do better with silicone oil

than with  $C_3F_8$ . Relative indications for the use of silicone oil include the need to travel by air or on land to higher elevations and anticipated difficulty with postoperative prone positioning (children, and those who are mentally or physically impaired).<sup>81,82</sup> Eyes with severe anterior PVR also did better with silicone oil than with C<sub>3</sub>F<sub>8</sub>.<sup>83</sup> In group 1, patients undergoing relaxing retinotomy, whose eyes were treated with silicone oil did better both anatomically and visually than eyes receiving C<sub>3</sub>F<sub>8</sub> gas.<sup>84</sup> Relative indications for the use of gas rather than silicone oil include: a high probability of corneal tamponade touch (such as when there is a poor iris diaphragm); the presence of superior retinal breaks on the posterior slope of a high scleral buckle (since gas conforms better than silicone to the slopes of the buckle); and the presence of a silicone intraocular lens with an open posterior capsule (see Complications, below).<sup>82</sup> An interesting cost-benefit analysis revealed that silicone oil was slightly more cost-effective than C<sub>3</sub>F<sub>8</sub> gas in eyes with PVR without previous vitrectomy, whereas C3F8 gas was more cost-effective than silicone oil with previous vitrectomy and PVR.85 The study also concluded that PVR surgery on eyes with either tamponade was cost-effective when compared with other widely accepted intravitreal therapies across diverse medical specialties.

# Complications of severe proliferative diabetic retinopathy

The use of silicone oil in the management of patients with severe PDR remains controversial. In Europe, silicone oil is often used during the initial vitrectomy for severe diabetic traction retinal detachment as well as for recurrent diabetic vitreous hemorrhage following previous vitrectomy surgery.<sup>86–89</sup> The rationale for silicone oil use in PDR is based on a potential reduction in postoperative hemorrhage, a more rapid recovery of visual function (for example, in one-eyed patients, in contrast with gas tamponade) and reduced postoperative positioning requirements.<sup>90–93</sup> A downside of the use of silicone oil in diabetic patients is the necessity for a second operation to remove it. Unlike in eyes with PVR, there has been no prospective, randomized clinical trial comparing silicone oil with extended gas tamponade in eyes with severe PDR.

Silicone oil may be of potential use in diabetic patients with severe anterior-segment neovascularization or anterior hyaloidal fibrovascular proliferation.94,95 A silicone oil tamponade may suppress anterior-segment neovascularization by impeding the movement of vasoproliferative factors from the posterior segment to the anterior segment or by increasing oxygen tension in the aqueous by preventing diffusion of oxygen-enriched aqueous to the posterior segment.96,97 In an uncontrolled series, we performed revision of vitrectomy and silicone oil injection in 18 eyes that developed advanced iris neovascularization or anterior hyaloidal fibrovascular proliferation complicated by retinal detachment or media opacity after vitrectomy for the complications of PDR.95 Stabilization or regression of the anterior ocular neovascular changes was noted in 83% of the eyes. Sustained retinal reattachment was achieved in 56% of eyes, with visual acuity improving to 20/400 or better in 28% of eyes. Posteriorsegment vascular or avascular reproliferation was the main cause

for anatomic failure, while generalized retinal vascular ischemia was felt to be the main cause for poor visual results despite retinal reattachment.

Douglas et al.<sup>98</sup>advocate the use of pars plana resection, vitrectomy, and silicone oil in eyes with severe PDR and combined traction/rhegmatogenous retinal detachment involving the macula. In a retrospective, noncomparative consecutive series of 22 eyes in 22 patients, the authors observed macular attachment in 91% of eyes at the final follow-up visit (average of 15 months). In the 64% of patients who underwent silicone oil removal, visual acuity of 20/400 or better was found in 93% of cases. In contrast, in those patients who did not undergo silicone oil removal, only one case (8.3%) achieved a visual acuity of 20/400.

We also advocate the use of silicone oil after failure of conventional vitreous surgery for PDR due to the development of severe PVR.<sup>99</sup> While these eyes have a very poor anatomical and visual prognosis, at least some could be salvaged by reoperation with a silicone oil tamponade. A randomized, controlled clinical trial would be required to assess the relative contribution of silicone oil to the success or failure in these complicated diabetic cases.

#### Selected cases of macular hole

Silicone oil tamponade has been used in the repair of macular holes in several settings: retinal detachment caused by macular holes, idiopathic macular holes, and traumatic macular holes. Macular holes causing retinal detachments usually occur in eves with pathologic myopia, often in patients of Asian or Middle Eastern descent. Modern pars plana vitrectomy techniques, accompanied by the use of a gas tamponade and prone positioning, have been of value in the management of these macular hole-detachment cases.<sup>100-102</sup> Silicone oil may be advantageous in patients for whom postoperative positioning is impaired by physical or psychological factors or in whom traveling at high altitudes is required. In addition, silicone oil remains a reasonable approach in eyes failing attempts with a gas tamponade.<sup>100,103</sup> Its principal disadvantage with respect to gas is the necessity for a second operation to remove the oil 4 to 8 weeks after the initial surgery.

In an initial study of silicone oil as a temporary tamponade in eves with idiopathic macular holes, results were promising.<sup>104</sup> In this retrospective consecutive series including 40 eves and employing autologous serum but no internal limiting membrane peeling, we found that 80% of the holes could be sealed with one operation and that the overall success rate increased to 92.5% with a second procedure. Visual acuity improved an average of 2.6 lines in all eyes. More recently, Lai et al. found a lower anatomic macular hole closure rate with silicone oil compared with gas.<sup>105</sup> The rate of hole closure with one operation was 65% with oil versus 91% with gas. The reoperation rate was also significantly higher with oil: 35% versus 4% with gas. The final closure rate with more than one operation was not statistically significant between the two groups: 90% with oil versus 96% with gas (P = 0.628). The final median visual acuity, however, was significantly better for gas than oil (20/50 versus 20/70, respectively. There were no differences in the prevelance of internal limiting membrane peeling or the use of indocyanine green dye between the two groups. Factors proposed to account for the greater success rate with gas versus oil include the greater buoyancy force with gas, the unproven possibility of silicone oil toxicity, and a glial response with gas which has not yet been evaluated for silicone oil. Other factors could include the higher surface tension of gas versus oil which may facilitate isolation of the hole from fluid currents as it heals, and the occurrence of emulsification with oil which may lead to droplets in the hole itself impeding hole closure.

While our enthusiasm for silicone oil has waned, we still consider the use of silicone oil for selected cases in the treatment of idiopathic macular holes when problems with postoperative positioning are anticipated, rapid return to normal function is required, air travel is necessary, or the patient is monocular.

The use of silicone oil in traumatic macular hole repair may also be considered. Again, the ability and willingness to maintain face-down postoperative positioning is of primary importance. Traumatic holes occur more often in young males and children in whom postoperative positioning may be less reliable. Overall, gas remains our tamponade of choice for nearly all cases of macular hole.

Silicone oil allows clear visualization of the macula and we have observed the time course and properties of macular hole closure utilizing optical coherence tomography.<sup>106</sup> By the first postoperative day, the macular hole was flat with resolution of parafoveal cysts. Complete hole closure was observed at 1 month in successful cases. Persistent retinal separation at 1 month was indicative of failure in all cases.

#### **Giant retinal tears**

Silicone oil may be used in the repair of giant retinal tears in two different ways: (1) as an instrument to facilitate unfolding and flattening of the retinal detachment and tear; and (2) as a long-term tamponade. The advent of liquid perfluorocarbons (PFCs) has allowed less traumatic flattening of retinal detachments caused by giant retinal tears and has led to PFCs largely replacing silicone oil techniques for intraoperative flattening of the retina.

The use of silicone oil in cases of giant retinal tear without PVR remains controversial. It is still widely used for this purpose in Europe, while extended intraocular tamponade with gas remains more popular in the USA. Reports of excellent anatomical and visual success with either technique are available,<sup>34,35,38,107–109</sup> but there are no randomized controlled studies directly comparing results with silicone to gas. We may select oil over gas when positioning is a concern, particularly when the tear extends to the 6 o'clock position.

# Retinal detachment associated with choroidal coloboma

A choroidal coloboma is a congenital lesion characterized by absence of the normal retina, retinal pigment epithelium, and choroids. These lesions are most commonly located in the inferonasal fundus and are associated with an incidence of retinal detachment of 23 to 42%.<sup>110,111</sup> Colobomatous retinal detachments are often caused by small, atrophic retinal breaks located

in or near the base of the coloboma. Scleral buckling techniques for the repair of these detachments result in low rates of success of 35 to 55%,<sup>110,111</sup> but it is still advocated for select patients by some authors.<sup>112</sup> Vitrectomy surgery has increased the success rate of repair of these rare and unusual detachments and is often used in combination with long-term silicone oil tamponade.<sup>113–115</sup> We achieved retinal reattachment in five of five eyes with choroidal colobomas utilizing silicone oil as an extended intraocular tamponade.<sup>114</sup> Adjunctive surgical techniques to vitrectomy included retinectomy in two eyes and cyanoacrylate retinopexy in one eye. In four of the five eyes, the silicone oil was removed after several months. Retinal redetachment was observed following silicone oil removal in one eye, suggesting the need for prolonged intraocular tamponade in at least some of these cases.

# Chronic uveitis with profound hypotony

Hypotony associated with chronic, intractable uveitis can be an important cause of severe vision loss in these patients. Vitreous surgery has been used to clear the ocular media, to remove inflammatory byproducts, and for diagnostic purposes.<sup>116–121</sup> We hypothesized that the space-occupying and compartmentalizing qualities of silicone oil might provide additional benefits in eyes with profound hypotony associated with scleral infolding and/or serous retinal detachment and reported on our use of vitrectomy with silicone oil tamponade in a series of five such eyes.<sup>122</sup> The silicone oil facilitated anatomic reattachment in three of five eyes, improved visual acuity in all five eyes, and increased intraocular pressure in four of five eyes at 6 months. At the final follow-up, the intraocular pressure was still improved or maintained in four eyes and the visual acuity, though poor, was improved over the baseline level in three eyes. Overall, the use of silicone oil appeared at least partially to benefit these extremely poor prognosis eyes.

#### Infectious retinitis

Silicone oil has been used with increasing frequency for the management of complex retinal detachments associated with infectious retinitis. The most common scenario is rhegmatogenous detachment associated with retinitis due to cytomegalovirus infection in immunologically compromised patients.<sup>107,123–129</sup> In these patients, the widespread and occult nature of the pathology, together with the potential for recurrence, make the use of a permanent silicone oil tamponade attractive.

Long-lasting ganciclovir implants, combined with silicone oil tamponade, have also been effective for some patients with cytomegalovirus-related retinal detachments (DF Martin, personal communication). In these cases, the implant is placed in a dependent quadrant to maximize access of the drug to the aqueous phase. A detailed review of the management of these detachments, with and without silicone oil, is provided in Chapter 156.

#### Trauma

Pars plana vitreous surgical techniques have increased the rate of successful repair of severely traumatized eyes. Silicone oil

Novartis Exhibit 2317.004 Regeneron v. Novartis, IPR2021-00816 has been used as an adjunct to vitreoretinal surgery in severe cases of penetrating ocular trauma, both as part of the initial vitrectomy and in later reoperations after initially unsuccessful surgery. Advocates of the use of silicone oil during the initial vitrectomy for severe penetrating ocular trauma believe that silicone oil helps to minimize intra- and postoperative hemorrhage, which are known risk factors for the development of PVR.<sup>130</sup> The extended nature of the silicone oil tamponade may also help to maintain retinal reattachment and avoid phthisis in such severely traumatized eyes.

In a recent retrospective case series, Spiegel and colleagues<sup>131</sup> reviewed the outcomes of severe ocular trauma managed with primary vitrectomy and silicone oil within 24 h of injury. Of 435 eyes with severe trauma, only 13 patients underwent immediate intervention with vitrectomy and silicone oil. This approach was restricted to eyes with extensive retinal lacerations greater than 4 disc diameters, retinal detachment, and/or substantial intraocular bleeding that had occurred during surgery. After a mean follow-up of 30 months, 11 eyes achieved a visual acuity ranging from 20/25 to 20/200. Silicone oil was removed in 11 of 13 eyes at an average of 6 months. Recurrent PVR developed in two eyes. While these results are encouraging and suggest that early vitrectomy with silicone oil may be of value in the recently injured eye, the study is uncontrolled. In addition, it is very hard to match eyes undergoing vitrectomy for trauma accurately because of the great degree of variability from case to case; consequently, assessing the actual benefits of silicone oil over modern gas techniques in primary trauma is extremely difficult.

When conventional vitreous surgery fails in cases of severe penetrating ocular trauma, repeat vitrectomy with long-term silicone oil tamponade may be used to improve the anatomic and visual outcomes.<sup>27,56,132-134</sup> Despite reasonable initial anatomic and functional success, ultimate visual and anatomic outcomes are often quite poor in these eyes. We utilized a silicone oil tamponade after failed primary vitreous surgery with intraocular gas in 42 cases of complicated retinal detachment following severe ocular trauma.<sup>132</sup> At 6-month follow-up, we achieved successful reattachment of the macula in 50% of cases and 28% of eyes had a visual acuity of 5/200 or better. By 2-year followup, however, only 33% were still completely attached posterior to the scleral buckle and only 12% were 5/200 or better. The high failure rate with long-term follow-up is often due to recurrent retinal detachment following silicone oil removal. We believe that the proliferative process associated with penetrating ocular trauma continues for a longer period of time than in eyes with nontraumatic retinal detachment. When conventional vitreous surgery has failed to rehabilitate these severely traumatized eyes, the ultimate prognosis is generally quite poor, even with reoperation and the use of silicone oil.

## **Complicated pediatric retinal detachment**

Silicone oil tamponade has been advocated for use in the repair of selected complicated retinal detachments in the pediatric population. The rationale for the choice of silicone as the intraocular tamponade includes the high incidence of trauma in these cases as well as the potential poorer compliance with positioning instructions. We reported the results of 48 consecutive cases of complex retinal detachments in children 16 years old or younger managed with pars plana vitrectomy and silicone oil tamponade.<sup>135</sup> Forty-two percent of patients had a history of trauma and 35 of the eyes had undergone at least one previous retinal surgery. Of the 48 cases, only eight (17%) were countfingers vision or better postoperatively and only two eyes achieved a visual acuity of 20/200 or better. Thirty-five percent were successfully reattached at long-term follow-up but significant complications included corneal opacification (62%) and hypotony (58%). In a recent series of patients with pediatric retinal detachments, Weinberg and colleagues<sup>136</sup> also observed poor outcome in those patients requiring silicone oil at the time of surgery. They also observed a high incidence of trauma and identified a "new" predictor of poor visual outcomes - the inability of the clinician to determine the preoperative visual acuity confidently.

## **Endophthalmitis**

There is increasing evidence that silicone oil can suppress bacterial growth. With this in mind, several investigators have treated severe cases of endophthalmitis, unresponsive to initial antibiotic therapy ("tap and inject") with vitrectomy and silicone oil tamponade.<sup>137-139</sup>

In a prospective randomized controlled study by Azad and colleagues<sup>138</sup> of posttraumatic endophthalmitis, only one of 12 patients who failed conventional tap-and-inject therapy achieved vision greater than 20/200 when treated with vitrectomy alone compared with seven of 12 (58%) when treated with vitrectomy and silicone oil. Immediate postoperative detachments occurred in 33% of vitrectomy-only patients versus 0% of those treated with silicone oil. Mechanisms by which silicone may be useful include increased concentration of intravitreal antibiotics, innate bactericidal properties of silicone oil, and stabilization of atrophic retina minimizing the occurrence of retinal detachment. Select cases of endophthalmitis may benefit from silicone oil tamponade and further studies will be required to determine the appropriate timing and cases for its use.

# **GENERAL SURGICAL TECHNIQUES**

While silicone oil has been used with some success as an instrument for actual membrane dissection,<sup>21</sup> it is now used primarily as an intraocular tamponade. The main physical properties of silicone oil that determine its clinical applications are its surface (interfacial) tension, specific gravity, and viscosity (Table 130-1). The two most commonly used silicone oils are classified based on their viscosity. The lower-viscosity (1000 cs) silicone oil was selected for use in the Silicone Oil Study while the higherviscosity (5000 cs) silicone oil was the first one approved by the Federal Drug Administration for use in the USA. Now both are commercially available worldwide. As reviewed in Chapter 129, higher-viscosity silicone oil has a lower tendency to emulsify, i.e., to break up into tiny bubbles postoperatively.<sup>140–143</sup> This may be advantageous, since some of the complications related to silicone oil use, reviewed later in this chapter, may relate to

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Substance	Molecular weight*	Viscosity (cs)	Surface tension† (dyn/cm)	Specific gravity
Silicone oil (1000)	25 000	1000	21.2	0.971
Silicone oil (5000)	50 000	5000	21.3	0.973
Perfluoropropane gas	188	NA	70	<0.0001
Sulfur hexafluoride gas	146	NA	70	<0.0001
Air	29	NA	70	<0.0001
Physiologic saline	NA	1.0	NA	1.0064
Water	18	1.0	NA	1.0000
Perfluo-n-octane‡	438	0.8	14	1.76

\*Molecular weights for silicone oil can vary significantly, as discussed in Chapter 129.

+Surface tension occurs at the interface of a liquid and another immiscible liquid (interfacial surface tension) or gas. The silicone oil surface tensions reported here are values measured in vitro (see Chapter 129). They are much lower than the theoretical value of ~50 due to impurities in the oil itself. A further lowering of surface tension has been reported in vivo due to the presence of proteins and surfactants within the eye.

 $\ddagger Perfluoron brand of perfluorocarbon liquid, chemical formula <math display="inline">C_8F_{18}$ 

NA, not applicable.

the degree of emulsification. Another determinant of oil emulsification, however, may be the presence of impurities in the oil, so maximally purified silicone oil is preferred for clinical use. The commercially available preparations of 1000 cs and 5000 cs silicone oil are of high-grade purity and a clinically significant difference in emulsification has not been reported. The main advantage of using the 1000 cs is quicker infusion and removal compared to 5000 cs oil.

Of note, clinical studies are currently underway in Europe evaluating "heavy silicone oil" as an internal tamponade for complicated retinal detachments. The silicone oil–RMN<sub>3</sub> mixture, for example, has a density of 1.03 and viscosity of 3800 cs. A recent prospective study of the silicone oil–RMN<sub>3</sub> mixture found that the oil was well tolerated.<sup>144</sup> We await the results of further studies to determine if heavy silicone oils or PFC liquids may be useful for postoperative tamponade agents.

The relationship between the viscosity of silicone oil and its surface tension remains a common cause of confusion in understanding how silicone oil works as an internal tamponade.<sup>145</sup> Despite marked viscosity differences, the 1000 cs and 5000 cs silicone oils have nearly identical surface tensions. Therefore, each silicone oil will have the same tendency to tamponade a retinal break (desired result) as well as to pass through holes in the retina under traction (unwanted result).<sup>146</sup> The surface tension of silicone oil relative to water is much less than that of gas relative to water (21 versus 70 dyn/cm: Table 130-1). Silicone will therefore pass through retinal breaks still under traction more readily than will gas.

Silicone oil has important physicochemical differences from long-acting gases, PFC liquids, air, and physiologic saline solutions. Both the 1000 cs and 5000 cs silicone oils have a specific gravity just less than 1.0 and are, therefore, "lighter than water." As shown in Table 130-1, the relative specific gravity for each of these tamponades is: air  $\sim$  gas << silicone oil > water  $\sim$  saline < PFC liquids. This is of primary importance in two similar but different surgical maneuvers: (1) when utilizing the tamponade for the purpose of retinal flattening; and (2) when a temporary tamponade is exchanged for silicone oil. In the sections that follow, we consider the technical aspects of infusing silicone oil into the eye, including exchanging silicone oil with various temporary tamponades.

#### Infusion of silicone oil

Due to the high viscosity of silicone oil, relatively high pressures are required to infuse silicone into the eye in comparison to other substances. Special methods have been developed to minimize the infusion pressure required.<sup>27,55,57,61</sup> The silicone oil is placed in a relatively large syringe (e.g., 20 ml syringe for 5 to 10 ml of silicone oil) which can handle the high pressures necessary for injection (plastic is preferable to glass for safety reasons). The injection pressures are highest near the siliconecontaining syringe, and it is important to be certain that reliable connections (Luer-lok) will prevent the lines from coming apart at this point. According to Poiseuille's law, the flow of a fluid in a tube is proportional to the fourth power of the radius of the tube and inversely proportional to the length of the tube. In order to decrease the resistance to injection of silicone oil, we have found it helpful to modify the infusion line by keeping it as short as possible, while at the same time increasing its diameter. It is also helpful to use a relatively nondistensible material for silicone infusion tubing, such as polyethylene, since the high pressures that are necessary for silicone oil injection cause the diameter of distensible tubing to enlarge. When the injection is stopped, undesired further injection can occur as the distended tubing returns to its normal diameter by forcing more silicone into the eye. A disposable infusion line is advantageous because of the difficulty of cleaning silicone from the tubing. If only tubing normally used for fluid infusion is available, it is best to reserve some of these lines to be used only in silicone cases in order to lessen the likelihood that small bubbles of residual silicone oil left in the lines will flow into eyes in which no silicone oil injection is planned.

A number of automated silicone pumps are available either integrated into modern vitrectomy systems or as free-standing units. Most of these injectors work as mechanical syringe drives that are controlled by the surgeon with a foot pedal. As they are volume-dependent rather than pressure-dependent, either underfilling or overfilling of the eye is a risk. Alternatively, various manual "screw-in" syringe systems have been described that are simpler, cheaper, and easier to maintain. While attractive for their simplicity, these systems do not provide quite as good surgeon control of the silicone oil injection process.

The connection of the infusion line to the eye wall may be made in several ways. A cannula system allows for the rapid exchange of the conventional infusion line with a line specifically designed for silicone oil infusion.<sup>147,148</sup> Alternate methods include using the conventional infusion line for silicone infusion, attaching the silicone tubing to the sutured-in infusion cannula, suturing in the silicone infusion line in place of the previous infusion line, or placing a 19- or 20-gauge needle or blunt cannula through an open sclerotomy through which the silicone oil is infused. Note that some silicone infusion lines are heavier than conventional saline lines and when these lines are employed, it is important to direct the infusion cannula towards the posterior pole during silicone infusion to prevent the silicone from being inadvertently injected directly into the anterior chamber.

#### Fluid-silicone exchange

One technique for infusing silicone oil into an eye is to exchange it directly with the fluid filling the eye after vitrectomy and elimination of retinal traction. At the same time that silicone is infused, the retina is flattened by internal drainage of subretinal fliud in a manner similar to a fluid-gas exchange. The specific gravity of silicone oil is just less than 1 and thus it is "lighter than water." As a result, the silicone oil settles above the physiologic saline as silicone is infused into the eye. When a fluid-silicone exchange is performed, an extrusion needle must be placed in the fluid phase both within the vitreous cavity as well as through a retinal break or drainage retinotomy to remove the displaced preretinal and subretinal fluid as the oil is infused. Either passive efflux or active aspiration may be used to remove the fluid. If active aspiration is used, there is the risk of generating a negative pressure at the extrusion needle tip since the rate of silicone infusion may lag behind the fluid aspiration, especially with the higher-viscosity oils. If this occurs, the eye wall may collapse or the retina may incarcerate into the extrusion needle tip (Fig. 130-1). It is important to monitor the intraocular pressure

closely during the fluid–silicone exchange, especially near the end of the procedure when silicone oil may plug the extrusion needle. In this situation, continued infusion of silicone oil can lead to marked intraocular pressure elevation and vascular compromise. Thus, it is critical to watch for pulsation or nonperfusion of the central retinal artery and optic nerve head while performing a silicone oil–fluid exchange. At the completion of the exchange, endolaser retinopexy can then be applied through the silicone oil to the now attached retina.

# Air-silicone exchange

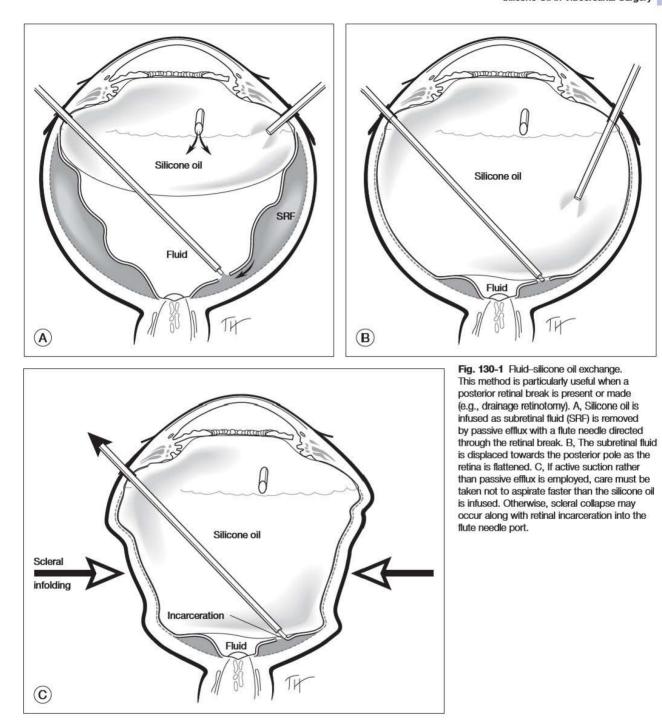
Fluid–air exchange with internal drainage of subretinal fluid followed by air–silicone exchange is another common maneuver when silicone oil is used as the long-term intraocular tamponade. With this approach, the retina is first flattened with the fluid–air exchange and internal drainage of subretinal fluid. Endolaser retinopexy, if desired, is applied through the air-filled eye. Finally, silicone oil is infused into the air-filled eye as air is allowed to vent through a loose sclerotomy (Fig. 130-2). Silicone injection is continued until the silicone in the eye rises to the level of the sclerotomies (phakic or pseudophakic eyes) or to the plane of the iris (aphakic eye). The intraocular pressure is left normal by allowing some silicone oil to escape through the sclerotomy if necessary.

## Perfluorocarbon liquid-silicone exchange

A more recent and increasingly popular method for dealing with complex retinal detachments in which a silicone oil tamponade is desired is first to flatten the retina with liquid PFC and then to exchange the PFC for silicone oil.<sup>149–152</sup>

The technique is similar to a fluid–silicone exchange except that the retina is already flat if there is an anterior break through which subretinal fluid can be expressed as the PFC is injected. Thus, the potentially hazardous removal of subretinal fluid with an extrusion needle during silicone infusion is obviated. At the end of the PFC–silicone exchange, it is important to check carefully to make sure all of the PFC has been removed. With this technique, endolaser retinopexy can be applied, through either the PFC or the silicone oil, depending on the surgeon's preference.

A variation of the above techniques is a "sandwich" method of subretinal fluid removal and silicone oil injection. This is particularly helpful when a retinal break is neither very posterior nor very anterior. With this approach, a combination of liquid PFC and air or silicone oil is used to "sandwich" a retinal break (Fig. 130-3). In the presence of a total retinal detachment associated with a moderately anterior retinal break, the PFC liquid is used first to flatten the posterior retina by expressing the posterior subretinal fluid through the retinal break (Fig. 130-3A). The PFC liquid is brought just to the posterior edge of the retinal break, but not over it. Subretinal fluid remains loculated beneath the anterior detached retina. A fluid-air or fluid-silicone exchange is then performed to flatten the anterior retina as an extrusion needle evacuates subretinal fluid through the same break (Fig. 130-3B). Once the retina is completely flat, the remaining physiologic saline and PFC liquid is removed as



completely as possible with the extrusion needle as air or silicone injection continues. Endolaser is then applied to surround the retinal break (Fig. 130-3C). If air is used initially, it is subsequently exchanged for silicone oil, as described in the section on air–silicone exchange, above.

Surgical maneuvers in the silicone oil-filled eye

While some vitreoretinal surgical maneuvers, such as membrane peeling, are now infrequently performed in a silicone oil-filled eye, there are several surgical techniques that are still commonly used in combination with the infusion of silicone oil. The main

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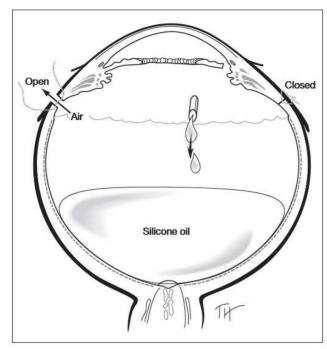


Fig. 130-2 Air-silicone oil exchange. Silicone oil is infused into the airfilled eyes as air is allowed to vent through a loose sclerotomy.

surgical adjunct to silicone infusion is manipulation of the retina when a large retinal tear or retinotomy is present in order to allow it to flatten smoothly as silicone injection continues.<sup>34,34,38,55</sup> With large retinotomies or giant retinal tears, it is not necessary to begin retinal unfolding until about 75% of the preretinal fluid has been replaced by the oil (Fig. 130-4A). At that point, the surgeon very gently strokes the traction-free retina into its desired position with a soft-tipped cannula while slowly continuing the fluid-silicone exchange (Fig. 130-4B). The enlarging silicone bubble will eventually help hold the retina in its final position. This part of the procedure is frequently lengthy as the surgeon must carefully search for pockets of residual preretinal and subretinal fluid until the retina is fully attached and the subretinal space is completely dry (Fig. 130-4C and D). The development of subretinal silicone oil during this maneuver generally indicates that insufficient traction has been released and that further retinal surgery for release of this traction is necessary (see Complications, below). The advent of liquid PFCs, which allow retinal unfolding and flattening without as much mechanical trauma, has largely replaced unfolding of the retina under silicone oil where these are available.

#### ANTERIOR-SEGMENT CONSIDERATIONS

# Management of the crystalline lens

The decision whether or not to remove a clear crystalline lens depends on the particular pathology present. In general, if extensive dissection within the vitreous base is required, we remove the lens in order to gain better surgical access. If the pathology is primarily posterior, then the lens is frequently retained. Most reports indicate that, when the lens is retained, late postoperative cataract is very likely.<sup>28,64,153,154</sup> Even if the oil is removed routinely at 6 weeks after injection, a high percentage of eyes will go on to develop cataract within 3 years.<sup>153</sup>

If it is elected to remove the crystalline lens during PVR surgery, a lensectomy can be performed, leaving the eye aphakic with or without preservation of the anterior lens capsule for later secondary posterior-chamber intraocular lens implantation. Retention of the anterior lens capsule can minimize intraoperative and postoperative complications of gas or oil, simplify future posterior-chamber intraocular lens placement, and maintain a normal iris appearance.<sup>155</sup>

More recently, there has been increasing interest in combining phacoemulsification, posterior-chamber intraocular lens implantation, and vitreous surgery for PVR.<sup>156</sup> A combined approach is attractive because cataract surgery has become more atraumatic with the use of phacoemulsification and self-sealing small incisions. The combined procedure has the advantages of creating good access to the anterior vitreous base region, avoiding a two-step procedure regarding lens management, and making quick optical rehabilitation possible.

#### Management of an intraocular lens

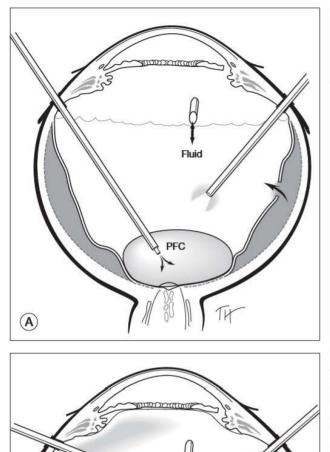
The approach to intraocular lenses present at the time of silicone surgery varies according to the lens type and degree of anatomical derangement of anterior-segment structures. Posterior-chamber intraocular lenses are generally, but not always, removed. Unless the posterior capsule is intact and tamponade of silicone is anticipated for only a short duration, we believe that silicone posterior-chamber intraocular lenses should be removed because of the intractable adhesion that develops when silicone oil contacts silicone intraocular lenses (see Complications, below).

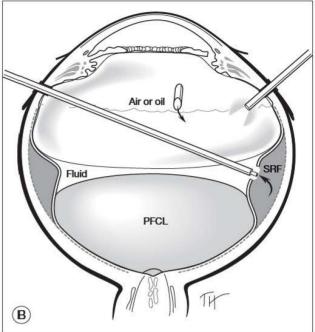
#### Inferior peripheral iridectomy

An inferior peripheral iridectomy is necessary in eyes where papillary block secondary to silicone oil is likely to occur.<sup>39,40,157</sup> As silicone oil has a specific gravity less than 1, it floats and therefore tends to occlude the pupil and any superior iridectomy. The inferior location of the peripheral iridectomy allows aqueous to pass under the silicone oil bubble and to enter the anterior chamber without causing pupillary block (Fig. 130-5). The inferior iridectomy should be basal and relatively large, as small iridectomies are more likely to close spontaneously postoperatively.

In general, aphakic eyes or pseudophakic eyes with anteriorchamber intraocular lenses require an inferior peripheral iridectomy. In addition, pseudophakic eyes with posterior-chamber intraocular lenses may require an inferior iridectomy if there is not adequate capsular or zonular support. Often it is possible to assess the adequacy of the intraocular lens–capsular–iris diaphragm preoperatively. In addition, the adequacy of the barrier to silicone oil movement into the anterior chamber may be evaluated intraoperatively during an air–fluid exchange or during silicone oil infusion. If air or oil enters the anterior chamber, then the

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**Fig. 130-3** Perfluorocarbon (PFC) liquid–silicone oil exchange: "sandwich" technique for subretinal fluid removal. A, Once adequate membrane peeling has been performed and the retina is mobile (free of traction), the "heavier-than-water" PFC liquid is slowly infused over the optic nerve head to flatten the posterior retina and drive subretinal fluid through the anterior retinal break. B, Subretinal fluid loculated anterior to the retinal break is then displaced posteriorly by silicone oil infusion and removed through the retinal break The remaining PFC liquid (PFCL) is then aspirated as silicone oil or air injection continues. C, After removing the PFCL and any residual fluid, endolaser may then be applied under either silicone oil or gas.

barrier to the anterior chamber is probably inadequate and an inferior peripheral iridectomy is recommended.

 $(\mathbf{C})$ 

Air or oil

Endolase

If the need for an inferior iridectomy is anticipated, it is best performed while physiologic saline is still present in the eye. With air in the eye, an air lock may occur and with silicone oil in the eye, the oil may clog the cutter line or become displaced into the anterior chamber. The vitreous cutter, set on suction only, is placed through the pars plana incision, behind the iris. Aspiration alone is used to identify the optimal position of the peripheral iridectomy before the iris is cut. A lower cutting rate of 100 to 300 is used to facilitate creation of the iridectomy. Ideally, the peripheral iridectomy should be placed at 6 o'clock as peripherally as possible, without cutting the ciliary processes. If the pupil is widely dilated, a smaller iridectomy should be

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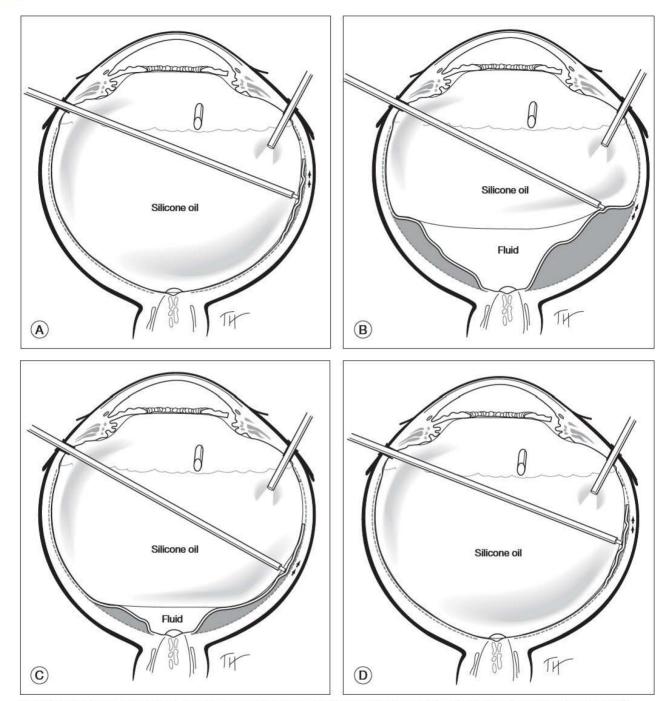


Fig. 130-4 Surgical maneuver under silicone oil: flattening of giant retinal tear or large retinotomy. A, Retinal unfolding is initiated after about 75% of the preretinal fluid has been replaced by the oil. With the eye soft, the retinal edge is engaged with a soft-tipped cannula and then gently tucked under the peripheral edge of the silicone bubble. B, Fluid-silicone exchange is slowly continued as the surgeon gently strokes the retina back towards its normal position. C and D, Residual subretinal fluid is aspirated from the edge of the break or retinotomy until the retina is fully attached.

made and care should be taken not to cut the iris near the papillary margin. Forceps manipulation of the iris edge through the other sclerotomy may facilitate creation of the inferior iridectomy in eyes with a widely dilated pupil. If iris retractors

are used, the iridectomy should be made before the pupil is widely dilated.

In some cases, there is inadequate iris tissue to support an inferior peripheral iridectomy. Complete or partial aniridia is

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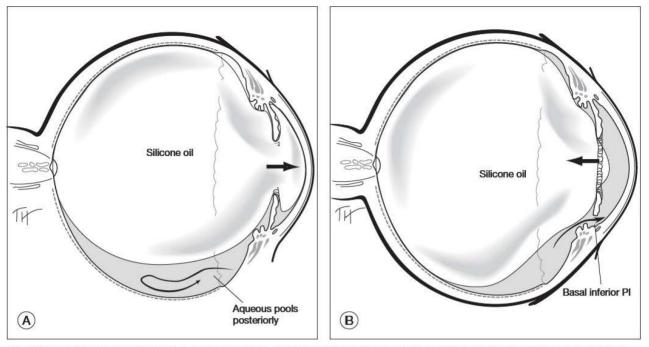


Fig. 130-5 Inferior peripheral iridectomy. A, In the aphakic eye, the silicone bubble can occlude the pupil or a superior iridectomy, creating pupillary block with aqueous misdirection into the posterior segment (arrow). B, An inferior peripheral iridectomy (PI) allows the aqueous fluid to continue its normal route into the anterior chamber, preventing (or relieving) pupillary block. (Modified with permission from Ando D. Intraocular hypertension resulting from pupillary block by silicone oil. Am J Ophthalmol 1985; 99:87–88.<sup>30</sup>)

most common in severely traumatized eyes. For these cases, Thumann and colleagues<sup>158</sup> have developed an artificial iris diaphragm to prevent papillary block and silicone–corneal contact. In a series of 41 eyes, a "closed" artificial iris diaphragm was utilized in hypotonous eyes to prevent keratopathy. The oil remained behind the diaphragm in 25 (61%) of cases.

Recently, we have observed cases of pupillary block glaucoma in phakic eyes. These patients may have had a relative overfill, which may occur in the setting of a scleral buckle where postoperative choroidal edema may reduce posteriorsegment volume. In addition, weakened zonules from previous trauma or surgical manipulation may also be risk factors. We managed such cases with a laser iridectomy and face-down positioning. All cases ultimately required a surgical inferior iridectomy with or without wash-out of the anterior-chamber oil droplet.<sup>159</sup>

#### COMPLICATIONS

A variety of complications are associated with the use of silicone oil in vitreoretinal surgery for complex retinal problems. These complications may be divided into intraoperative complications, early postoperative complications, and late postoperative complications. Some of these complications may be unique to the use of silicone oil but others may be more related to the underlying pathology and other aspects of surgical intervention. Here we review the major complications associated with the use of silicone oil and discuss strategies for their prevention and management when they do occur.

# Suprachoroidal silicone oil

Suprachoroidal silicone oil injection is a rare but devastating complication that occurs with incomplete penetration of the choroids with the silicone infusion line. This may occur when exchanging infusion cannulas or when the original cannula rotates and slips out of position. This complication is more common when the choroid is already thickened by a number of mechanisms, including hypotony, inflammation, and hemorrhage. Thus, eyes with chronic retinal detachments, uveitis, and trauma may be at increased risk of suprachoroidal injection of silicone oil. To minimize the risk of this complication, visually confirm the position of the silicone oil cannula before injection and use an extra-long (6 mm) infusion cannula if necessary. If suprachoroidal silicone oil injection does occur, it is very difficult to treat successfully, particularly with the higher-viscosity oils. We have tried to increase the infusion pressure through another sclerotomy site while enlarging the size of the original infusion sclerotomy. Despite all efforts, however, some silicone oil frequently remains in the suprachoroidal space. This may appear during the postoperative period as a localized choroidal detachment that persists indefinitely with the same configuration.

# 2222 Section 3 Special Adjuncts to Treatment

#### Subretinal silicone oil

Subretinal silicone oil injection occurs because of unrelieved traction on the retina or because of excess manipulation of the retina under silicone oil. This complication will always occur if the retina cannot be flattened under air (air-fluid exchange). It may still occur despite flattening of the retina under air, since the surface tension of air with respect to water is greater than that of silicone oil (Table 130-1). The risk of subretinal oil migration can be minimized by maximum release of retinal traction through preretinal membrane removal prior to silicone oil injection. If this is still insufficient to flatten the retina under air, or if the retinal mobility remains poor, then a relaxing retinotomy with removal of subretinal traction (if present) may be required. Subretinal silicone oil is recognized by a failure of the retina to flatten, frequently associated with enlargement of retinal breaks and a glistening subretinal reflex. A visible oil-water interface in the subretinal space is also frequently present. If inadequate traction relief is the cause of subretinal silicone migration, then the preretinal and subretinal silicone oil is removed and retinal traction is relieved by preretinal membrane removal, relaxing retinotomy, and/or subretinal membrane removal.

Sometimes, subretinal movement of silicone oil is caused by excessive manipulation of the retina rather than by unrelieved traction. In this case, usually only a small amount of subretinal oil is present and it can be removed without removing all of the preretinal silicone. A small amount of infusion fluid is injected over the optic disc and subretinal silicone is aspirated through a retinal break or retinotomy (Fig. 130-6). PFC liquid can also be used to assist with this maneuver. The fluid–silicone exchange is then completed with internal drainage of subretinal fluid through the retinal break or retinotomy site.

#### Intraocular bleeding

Intraoperative bleeding in the silicone oil-filled eye may occur from a relaxing retinotomy edge, a sclerotomy site, or from manipulations of the retina under silicone oil. This complication may be prevented by assiduous attention to hemostasis during the procedure. Management depends on the amount and location of the hemorrhage. Small preretinal hemorrhages can be managed by transient elevation of the infusion pressure, gentle aspiration of the blood from the surface of the retina or retinal pigment epithelium, and judicious diathermy at the bleeding site. Large preretinal or subretinal hemorrhages are best handled by removing the silicone oil, controlling the hemorrhage, and removing the blood as completely as possible, followed by reinjection of silicone oil. It is imperative to removal all hemorrhage as completely as possible because of the adverse affect of retained intraocular blood on reproliferation.<sup>160</sup>

Even with meticulous attention to intraoperative hemostasis, thick hemorrhage layered on the retinal surface is occasionally seen on the first postoperative day, especially in association with large relaxing retinotomies. Such hemorrhage increases the risk of reproliferation and retinal redetachment postoperatively.<sup>41–43</sup> When this complication occurs, we generally reoperate within several days. At reoperation, the silicone oil is first removed, followed by removal of the blood, and finally by reinjection of silicone.

# Intraoperative optical problems

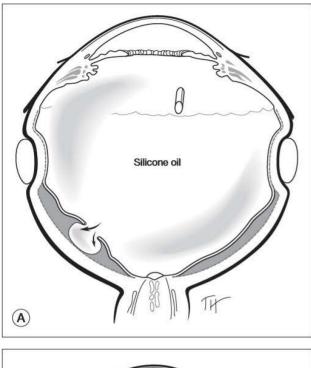
A variety of intraoperative optical problems can be encountered in association with the use of silicone oil. Pupillary miosis in the aphakic eye, in addition to reducing stereopsis and the view of the periphery, can make visualization difficult in an eye with silicone oil. The small pupil causes the oil to have a convex protrusion through the pupil and, because of its different refractive index, considerable distortion can be produced (Fig. 130-7). If this occurs, the anterior chamber may be temporarily filled with silicone oil, eliminating its strong plus lens effect. When surgical manipulations of the retina are completed, oil is removed from the anterior chamber, as discussed below.

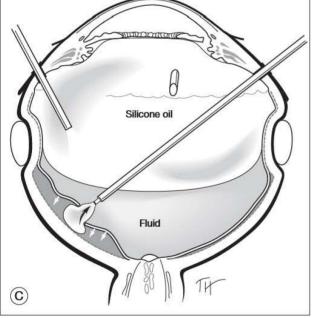
A more serious optical problem may occur when silicone oil droplets adhere to the posterior surface of silicone intraocular lenses (Fig. 130-8). These droplets are seen during reoperations when silicone oil is removed and only occur if the posterior capsule is open, allowing contact of the oil with the intraocular lens. There is currently no proven method to eliminate the oil droplets completely other than to remove the intraocular lens with or without intraocular lens exchange.<sup>161</sup> We consider the presence of a silicone intraocular lens with an open posterior capsule a relative contraindication to the use of silicone oil as an extended intraocular tamponade. We should note, however, that in Europe, a PFC liquid, fluorohexymeneoctane ( $F_6H_8$ ), has been utilized to dissolve oil droplets adherent to silicone lens implant.<sup>162</sup> Intraoperatively, PFC liquids and silicone oil seem immiscible, but a recent study documented the solubility of silicone oil in PFC liquids, which could account for the ability of PFC liquids to remove oil droplets from the back of silicone implants.<sup>163</sup>

#### Anterior-chamber silicone oil

When forward migration of silicone oil occurs during the course of silicone surgery in aphakic eves, it is usually not a major problem. While some surgeons are content to leave the silicone in the anterior chamber at the end of surgery, with the anticipation that it will retract in the early postoperative period, we prefer to remove it from the anterior chamber at the end of the procedure. The sclerotomies are closed and the infusion line is removed (Fig. 130-9A). With the eye soft, a thin cannula or needle attached to a syringe containing infusion fluid (or acetylcholine) is directed through the infusion sclerotomy and the inferior iridectomy into the periphery of the anterior chamber (Fig. 130-9B). Slow injection into the anterior-chamber angle then results in the silicone oil returning to the posterior segment. If the eye is firm while this maneuver is attempted, the infusion fluid will run posteriorly and silicone oil will remain in the anterior chamber.

If silicone oil migrates into the anterior chamber during surgery in phakic or pseudophakic eyes, management is more complex. It is usually easiest and most efficient first to remove all of the silicone oil from the posterior segment. The anterior-chamber silicone oil is then removed while simultaneously injecting a viscoelastic. An inferior peripheral iridectomy should be made in pseudophakic patients, if not already present. The silicone oil injection is then repeated, following which the viscoelastic is replaced with physiologic infusion fluid.





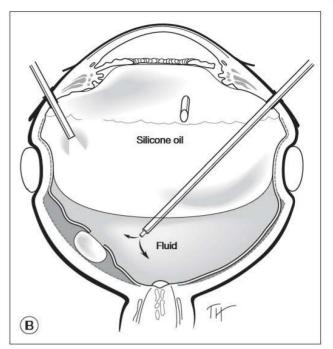


Fig. 130-6 Removal of small silicone bubble behind the retina. A, A small amount of silicone oil is displaced into the subretinal space by excessive manipulation of the retina. B, A small amount of infusion fluid is injected over the optic disc. C, Subretinal silicone is aspirated through a retinal break or retinotomy.

Postoperative silicone oil migration into the anterior chamber is an important complication. In the early postoperative period, it is most frequently due to blockage of the inferior peripheral iridectomy or an inadequate lens or intraocular lens–iris diaphragm. If silicone oil is allowed to remain in the anterior chamber, optical problems along with corneal endothelial damage may be anticipated. A pronounced fibrin reaction is the most common cause of a blocked inferior peripheral iridectomy in the early postoperative period. A YAG laser iridotomy can occasionally open an iridectomy blocked by fibrin, but usually the small opening created closes off again. Postoperative fibrin occluding the inferior iridectomy can be more effectively managed by an anterior-chamber injection of tissue plasminogen activator (tPA). A published series used 25  $\mu$ g in 0.1 ml of tPA to clear fibrin

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Surgical Retina Section 3 Special Adjuncts to Treatment

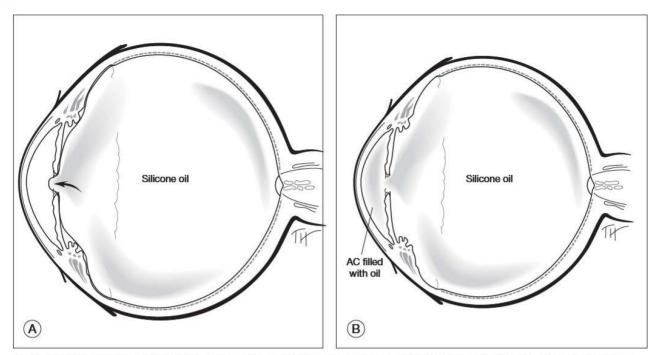


Fig. 130-7 Pupillary miosis in the aphakic eye filled with silicone oil. A, The convex protrusion of silicone oil through the small pupil produces a highplus lens effect, with poor visualization of the periphery, poor stereopsis, and significant optical distortion. B, To facilitate visualization of the retina, the anterior chamber may be temporarily filled with silicone oil, eliminating the strong plus lens effect. This is done by injecting silicone oil through the pars plana while fluid is aspirated from the anterior chamber using a soft-tipped cannula positioned frm a sclerotomy through the pupil or the inferior peripheral iridectomy. When surgical manipulations of the retina are completed, oil is removed from the anterior chamber, as shown in Figure 130-9.

from the anterior chamber.<sup>164</sup> In practice, we have found that  $6.25 \ \mu g$  of tPA in 0.05 ml is effective within 20 min or less and involves a smaller volume of material injected into the anterior chamber. The main risks of tPA injection are severe hyphema

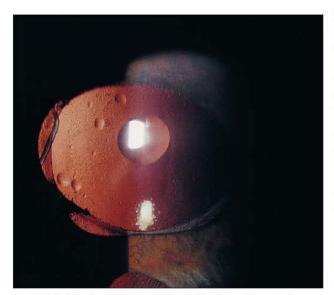


Fig. 130-8 Adhesion of silicone oil droplets to silicone intraocular lens after silicone oil removal.

and vitreous hemorrhage, but these are infrequent.164-166 Late closure of the inferior iridectomy, frequently associated with iris retraction and forward movement of silicone oil, is also a potential problem. Overall, we noted that 33% of inferior peripheral iridectomies closed postoperatively.<sup>167</sup> Eyes undergoing silicone oil surgery for diabetic retinopathy and penetrating ocular trauma were more likely than eyes with rhegmatogenous retinal detachment and PVR to develop closure of the inferior iridectomy. We believe that postoperative fibrin is an important risk factor for iridectomy closure. We were able to reduce the rate of inferior iridectomy closure by treating eyes manifesting a fibrin reaction in the early postoperative period with tPA.<sup>166</sup> Fibrin formation is usually maximal at 3 to 5 days postoperatively, so if significant anterior-chamber inflammation is observed on the first postoperative day, a revisit between postoperative days 3 and 5 may be in order.<sup>164,165,168</sup> This later visit is also the optimal time for tPA injection since fibrin formation has not vet reached its peak earlier in the postoperative course.<sup>165</sup> If fibrin recurs, repeat tPA injections may be necessary.

Late forward movement of silicone oil into the anterior chamber is frequently caused by recurrent retinal detachment or hypotony. With recurrent retinal detachment the effective vitreous volume is reduced. As the silicone oil volume remains constant, silicone oil must go either into the anterior chamber or into the subretinal space. Treatment involves prompt reoperation with retinal reattachment.

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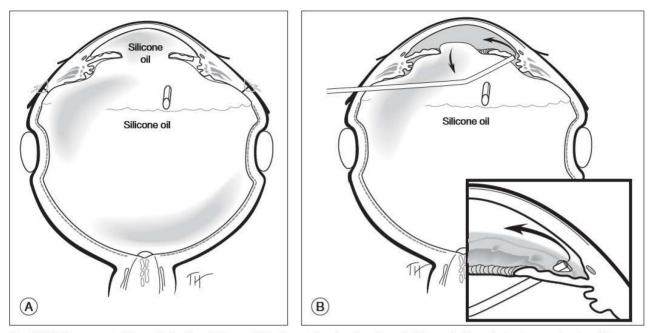


Fig. 130-9 Management of forward migration of silicone oil into the anterior chamber of an aphakic eye. A, The sclerotomies are closed and the infusion line is removed. B, With the eye soft, a thin cannula or needle attached to a syringe containing infusion fluid is directed through the infusion sclerotomy and the inferior indectomy into the periphery of the anterior chamber. Slow injection into the anterior-chamber angle then results in the silicone oil returning to the posterior segment.

When chronic hypotony develops, the ocular volume decreases as the eye begins to shrink. With the volume of silicone oil remaining constant, silicone has nowhere to go but into the anterior chamber. Attempted partial removal of silicone oil usually just allows further shrinkage of the globe with recurrent forward movement of the silicone oil bubble. Complete removal of the oil in this situation risks the development of phthisis. Thus, we usually leave the silicone oil in place, realizing that corneal opacification may ultimately occur. If the development of hypotony is recent, then reoperation with dissection of membranes from the ciliary processes has been reported to improve the intraocular pressure and should be considered.<sup>169</sup>

#### **Recurrent retinal detachment**

In the Silicone Study, approximately 50% of patients with retinal detachments complicated by severe PVR developed a recurrent retinal detachment in the early or late postoperative period. This incidence was roughly the same whether long-acting  $C_3F_8$  gas tamponade or silicone oil is used,<sup>79,82</sup> thus the underlying mechanism is not specifically related to the use of silicone oil. Retinal detachment occurring within the first several weeks of surgery is probably due to persistent retinal traction not adequately relieved while late retinal redetachment is more likely due to reproliferation. Preventive measures include meticulous removal of epiretinal membranes to relieve retinal traction, assiduous vitreous base dissection when anterior PVR is present, and pharmacologic inhibition of reproliferation (see Chapter 142 for

pharmacologic strategies against reproliferation). When retinal redetachment occurs but the macula remains attached, the presence of silicone intraocular tamponade sometimes allows delaying reoperation to allow "maturation" of the proliferative process. If posterior or macular threatening detachment occurs, however, aggressive reoperation, including relaxing retinotomy, if necessary, is generally indicated. With reoperation, the Silicone Study reported successful posterior retinal reattachment in 71% of eyes.<sup>176</sup> About 40% of these patients achieved 5/200 vision or better. Eyes reattached with one operation alone have significantly better visual outcomes (5/200 or better in 70% of cases) than eyes requiring two more operations to achieve anatomic success (P = 0.02).<sup>79</sup>

Some authors have argued that silicone oil itself may contribute to the development of reproliferation. There is evidence that silicone oil may increase inflammation in the eye and Betis and colleagues have even reported on the development of preretinal silicone granulomas in a series of patients.<sup>170</sup> In 9% of these eyes, recurrent detachment occurred following silicone oil removal. A recent retrospective study from India<sup>171</sup> supports the results of the Silicone Study. In 118 eyes undergoing surgery for recent retinal detachment in silicone oil-filled eyes, 65% were successfully reattached. Silicone oil was subsequently removed in 60% of these patients. One case of postoperative sympathetic ophthalmia was attributed to silicone oil granuloma formation.<sup>172</sup> These controversial findings remain to be confirmed.

#### Keratopathy

Corneal abnormalities are a relatively frequent complication associated with both silicone oil and extended gas tamponades. In younger patients, corneal damage is frequently manifested as band keratopathy, while in the older age groups, diffuse bullous keratopathy is more common. In the Silicone Study, 27% of both silicone oil eyes and of  $C_3F_8$  gas eyes developed keratopathy in the first 24 months of follow-up.<sup>173</sup> Similar results were observed in eyes that were successfully reattached at 3 years and that were followed for up to 6 years.<sup>82</sup>

The Silicone Study determined that preoperative aphakia or pseudophakia, preoperative iris neovascularization, postoperative aqueous flare, and the need for reoperation were factors increasing the likelihood of postoperative corneal abnormalities in eyes following surgery for severe PVR.<sup>173</sup> Management strategies for minimizing the incidence of postoperative keratopathy include maintaining a patent inferior peripheral iridectomy and early removal of silicone oil, particularly when there is silicone–corneal contact. When silicone–corneal contact has been prolonged, however, marked corneal endothelial damage occurs.<sup>12,174–176</sup> The cornea may appear clear in this situation because of the lack of contact of aqueous with the posterior corneal surface.<sup>175,177</sup> If silicone is subsequently removed, immediate corneal opacification may occur, as the damaged corneal endothelium is again exposed to aqueous.

Corneal chelation is sometimes helpful for patients with band keratopathy. When severe keratopathy has developed, penetrating keratoplasty with or without silicone oil removal may be considered. The frequency of graft failure is much lower when silicone oil has previously been removed or is removed at the time of penetrating keratoplasty (25%) compared to when silicone oil is retained (67%).<sup>178</sup> A recent study also found that a history of trauma or a preoperative visual acuity of less than hand motion correlated with increased risk of graft failure.<sup>179</sup>

#### Glaucoma

There are several forms of glaucoma that may be directly related to the use of silicone oil.<sup>160</sup> While pupillary block glaucoma may occur at any time, it usually presents during the early postoperative period (days to several weeks).<sup>39,180-182</sup> Pupillary block glaucoma can occur in an aphakic eye and, less commonly, in pseudophakic eyes. In either case, the underlying mechanism is occlusion of the pupillary space by silicone oil in the absence of a functioning inferior peripheral iridectomy. Aqueous misdirection occurs as the flow of aqueous from the posterior to the anterior chamber is blocked and the anterior chamber is subsequently shallowed. Treatment involves creation of a patent inferior peripheral iridectomy.<sup>39,40,183</sup> Even if an inferior peripheral iridectomy is created at surgery, it may still be nonfunctional because of blockage by fibrin, blood, or residual posterior capsule. This situation is best treated by anterior-chamber tPA injection, as described above.

Another form of acute glaucoma occurring in the early postoperative period results from an overfill of silicone oil. Signs include shallowing of the anterior chamber with or without displacement of silicone oil into the anterior chamber. In some cases, a relative overfill of silicone oil is produced by choroidal swelling from extensive laser or cryotherapy, frequently in combination with lensectomy and scleral buckling. Medical management is preferred as this form of elevation intraocular pressure usually resolves as tissue swelling decreases. When an actual overfill of silicone oil is present, however, surgical intervention with partial removal of silicone oil is necessary. B-scan ultrasonography, while difficult in the silicone-filled eye, may help confirm the presence of an overfill. If a fluid level if present in the posterior segment in the supine patient, then an overfill is unlikely. Overfills are prevented by making sure that the intraocular pressure is left low or normal at the end of the procedure and that the silicone oil remains posterior to the iris or intraocular lens, if present.

The Silicone Study found a low incidence of chronic elevated intraocular pressure.<sup>184</sup> At 36 months, an elevated intraocular pressure did occur more frequently in silicone eyes than in C<sub>3</sub>F<sub>8</sub> gas eyes (8% versus 2%, P < 0.05). Prevention of late glaucoma should be directed at early silicone oil removal, since no eves with silicone oil removed exhibited chronic elevation of intraocular pressure at 36 months. While the underlying mechanisms of chronic intraocular pressure elevation in silicone oil eyes are unclear, emulsification of silicone oil affecting the filtering meshwork is considered to be a probable contributor (Fig. 130-10).<sup>50,174</sup> The emulsified droplets may block the trabecular meshwork directly or cause an inflammatory trabeculitis.141,185 If mild anterior-chamber reaction is present and prolonged silicone oil tamponade is required, we often treat patients with topical or periocular steroids to minimize theoretical inflammatory trabeculitis. The risk of steroid-induced glaucoma should always be considered. When persistent pressure problems occur, a glaucoma valve may be the treatment of choice. Oil migrating through valves has been reported even when the valve is placed in an inferior location. This is a rare complication.<sup>186,187</sup> Since silicone oil removal alone does not usually relieve the chronic elevation of intraocular pressure once it is established, a permanent scarring of the trabecular meshwork is likely. Initially, medical management of chronic elevation of the intraocular pressure can be effective but ultimately, glaucoma surgery may be required.

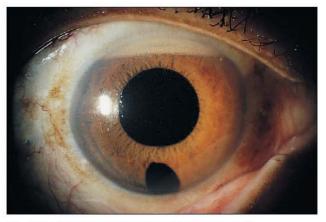


Fig. 130-10 Emulsified silicone oil in the anterior chamber.

# Hypotony

Chronic hypotony is a serious late postoperative complication following vitreous surgery with an extended intraocular tamponade for complicated retinal detachment. In the Silicone Study, the prevalence of hypotony (an intraocular pressure of 5 mmHg or less) at 36 months was lower for silicone-filled eyes than in C<sub>3</sub>F<sub>8</sub> gas-filled eyes (18% versus 31%, respectively).<sup>184</sup> Of the eyes with macular attachment at 36 months, only 3% of silicone oil-filled eyes were hypotonous with up to 6 years' follow-up, compared to 15% of  $C_3F_8$  gas-filled eyes (P < 0.001).<sup>82</sup> Prognostic factors for the development of hypotony included diffuse contraction of the retina anterior to the equator and postoperative retinal detachment. The causes of postoperative hypotony are not completely understood but are probably multifactorial. Hyposecretion of aqueous occurs in most instances, but increased uveoscleral outflow, particularly with large retinotomies, may also be a factor. Decreased aqueous production may be a function of multiple vitreoretinal procedures with damage to the aqueous production mechanisms, as hypotony is more common in eyes requiring reoperations. Gonvers<sup>153</sup> has suggested that hypotony occurs because of overcoagulation of the retina during retinal laser or cryo treatment. We feel that continuation of the proliferative process affecting the ciliary processes and resulting in decreased production of aqueous and/or increased outflow is important in the development of hypotony in at least some cases.64,184

The effective management of postoperative hypotony is problematic. If hypotony develops fairly early postoperatively, revision of vitrectomy with peeling of membranes from the ciliary processes may be of value.<sup>169</sup> In addition, subconjunctival injections of long-acting (depot) steroid may be given (anterior subconjunctival injections as opposed to posterior subtenon injections are more likely to produce an elevation (normalization) of intraocular pressure). Once hypotony is well established, no treatment is currently effective in reversing it. We consider chronic hypotony a contraindication to silicone oil removal because of the risk of precipitating phthisis. As we have seen, eyes with silicone oil in place and borderline intraocular pressures (5 to 10 mmHg) become hypotonous when silicone is removed; we now consider the overall ocular situation very carefully before recommending silicone oil removal in this situation.

### Macular epiretinal membranes

Macular epiretinal membranes are a relatively late complication of PVR surgery, occurring in both silicone oil and  $C_3F_8$  eyes at about the same rate.<sup>188</sup> Overall, 15% of eyes in the Silicone Study developed a macular epiretinal membrane. The prevalence of macular epiretinal membrane was three times greater in aphakic or pseudophakic eyes compared to phakic eyes (P = 0.02) and there was also a correlation with large retinal breaks (>2 disc diameters, P = 0.04). Postoperative visual acuity was significantly better in eyes without a macular epiretinal membrane (P = 0.01). Conventional plars plana vitrectomy techniques with membrane peeling may be used to remove visually significant macular puckers. Silicone oil tamponade changes the refraction of the eye due to its higher index of refraction compared with vitreous.<sup>189</sup> The refractive shift created by silicone oil depends on the status of the lens (Fig. 130-11). In the normal phakic eye (Fig. 130-11A), the silicone oil forms a concave surface behind the lens. This acts as a minus lens inside the eye and therefore makes the eye more hyperopic. Geometrical optics based on Gullstrand's schematic eye lead to the prediction of an 8 D increase in hyperopia for the silicone-filled phakic eyes. In practice, this shift ranges from nearly no change (associated with an underfill) to a +10 D change. On average, the silicone-filled phakic eye will produce a 6 D hyperopic shift.<sup>189,190</sup>

In the aphakic eye, silicone oil produces a convex surface as it bulges through the pupillary aperture (Fig. 130-11B). This, in effect, creates a plus lens inside the eye and a myopic refractive shift. The degree of silicone convexity varies with the pupillary diameter and can account for variable refractions and fluctuating vision postoperatively. Calculations using the schematic eye indicate a refractive shift from +12.5 to +5.6 D when the aphakic eye is filled with silicone oil.<sup>189,190</sup> The 6.9 D theoretical difference is close to the 7.4 D average shift observed clinically by Stefansson and colleagues.<sup>189</sup> Fortunately, silicone tamponade with vitreous surgery is generally used on a temporary basis so the accompanying changes in refractive error are not usually permanent. When more prolonged or permanent tamponade is required, contact lens wear in suitable patients may be used to minimize the anisoconia associated with the anisometropia. In eyes with silicone oil, the presence of an intraocular lens with a plano posterior surface is advantageous because the refractive changes induced by silicone oil are minimized.

#### Cataract

Silicone oil as a direct cause of cataract is a controversial issue that is difficult to evaluate.<sup>132,191-193</sup> There are confounding factors, including vitrectomy itself, that occur with the use of silicone oil that make the date difficult to interpret. In some patients, feathering of the posterior capsule or posterior subcapsular vacuoles may be seen (similar to observations with a gas tamponade) in the early postoperative period. As with a gas tamponade, the feathering and vacuoles often clear within the first postoperative week. This is often followed, however, by later development of posterior subcapsular and/or nuclear sclerotic cataract.

A majority of clinical studies suggest that long-term silicone oil tamponade is associated with cataract formation.<sup>13,14,22,25,27-29,30,34-36,45,54,50,60,65,66,128,153,194,195,196</sup> One likely mechanism is impaired metabolic exchange across the posterior lens capsule. Another possible mechanism is direct toxicity of the oil itself. Histologic studies do not show evidence for intralenticular silicone oil, even in cases of advanced cataract formation.<sup>35</sup> In some patients, oil droplets can adhere directly to the posterior lens capsule following silicone oil removal. As these droplets are reabsorbed or displaced, a focal area of posterior capsule opacification may be seen, supporting the view that impaired metabolic exchange across the posterior lens capsule, as a result of silicone oil contact, may be an important factor in the development of late

Novartis Exhibit 2317.0018 Regeneron v. Novartis, IPR2021-00816

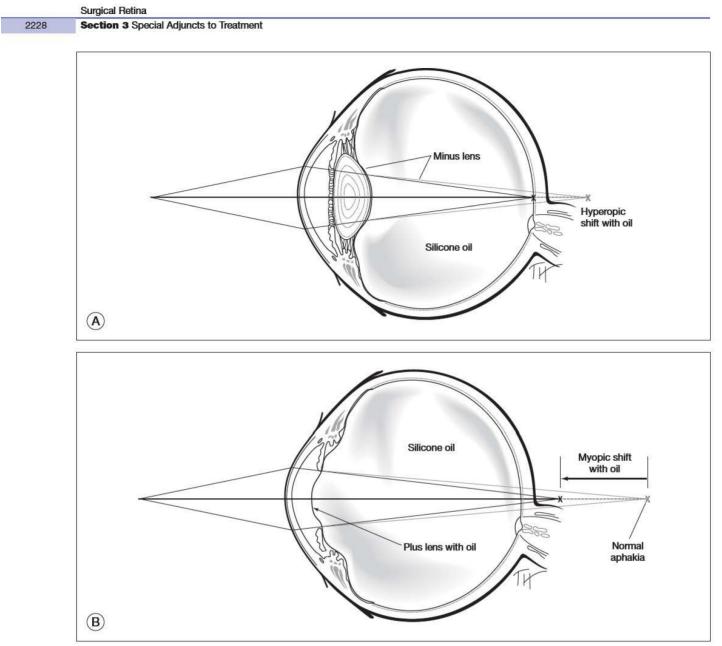


Fig. 130-11 Refractive shifts created by silicone oil. A, In the phakic eye, silicone oil forms a concave surface behind the lens. This acts as a minus lens inside the eye and therefore makes the eye more hyperopic. B, In the aphakic eye, silicone oil produces a convex surface as it bulges through the pupillary aperture. This, in effect, creates a plus lens inside the eye and a myopic refractive shift. The degree of silicone convexity varies with the pupillary diameter and can account for variable refractions and fluctuating vision postoperatively.

cataract. A recent histologic study identified increased posterior migration of lens epithelium and deposition of collagen contributing to cataract formation in silicone oil-filled eyes.<sup>197</sup> The authors coined the term "posterior fibrous pseudoanetphasia" to describe the lens changes observed.

In recent years, efforts have focused on removing silicone oil as early as possible to minimize the complications associated with long-term tamponade. Most reports to date suggest that even very early silicone oil removal (within 6 weeks of injection) is associated with a high incidence of late cataract.  $^{153}$ 

When a visually significant cataract in a silicone oil-filled eye with visual potential does occur, cataract surgery may be indicated. Ideally, the silicone oil either has been removed or can be removed at the time of the cataract surgery. If the silicone oil must be retained, the risk of silicone migration into the anterior chamber either during or following the cataract surgery is

Novartis Exhibit 2317.0019 Regeneron v. Novartis, IPR2021-00816 significant. In general, phacoemulsification is a good technique to use because of the small incision involved and the absence of anterior vitreous support.<sup>198</sup> If silicone oil does enter the anterior chamber during cataract surgery, we generally recommend removal of all of the silicone oil followed by completion of the cataract surgery, placement of an inferior iridectomy, and reinjection of silicone oil by one of the previously described techniques.

The choice of intraocular lens is important in eyes that either require a silicone oil tamponade or are at high risk of needing silicone oil in the future. Posterior-chamber intraocular lenses are preferred, especially if silicone oil is to remain in the eye. Because of the intractable adhesion of silicone oil to the surface of silicone intraocular lenses, these lenses are relatively contraindicated in such cases.<sup>161</sup> We believe that a large-diameter polymethylmethacrylate intraocular lens with no positioning holes and a plano posterior surface is ideal for this purpose.<sup>63,199</sup> The large diameter gives the retinal surgeon the best view of the fundus if any additional retinal surgery is required, no positioning holes prevent iris incarceration into the positioning holes, and a plano posterior lens surface minimizes the refractive changes induced by silicone oil.<sup>200</sup> Alternatively, acrylic posterior-chamber intraocular lenses may be considered if a foldable intraocular lens is chosen.161

The presence of a silicone oil tamponade will profoundly affect the axial length calculations used when selecting an intraocular lens implant. In the phakic eye, separate measurements are made of the anterior chamber depth (ACD), lens thickness (L), and the posterior-segment depth (PSD) (Fig. 130-12).<sup>201</sup> The PSD must then be corrected for the different speed of sound in silicone oil (986 m/s) versus vitreous fluid (1552 m/s).<sup>201,202</sup> The correction factor is therefore 986/1552. Thus, a typical eye with ACD of 2.5 mm, L of 5 mm, and PSD of 17 mm will have an apparent axial length of 34.3 mm with silicone oil tamponade and a true axial length of 24.5 mm. Without correction, the measured axial length is 40% longer than the true value.

When the eye is filled with silicone oil, it is important to measure the axial length with the patient in the upright position. In the supine position, there is an additional preretinal aqueous-oil interface which must be taken into account when making the lens calculation. Axial length measurement with the patient in the supine position is sometimes necessary, for example, when combining silicone oil removal with lens implantation in the pediatric patient under general anesthesia. When this is done, the additional length of the aqueous phase is added to the total axial length.

Another strategy for estimating the axial length in patients with silicone oil in a phakic eye is to use a fixed ratio. Murray and colleagues utilized a ratio of 0.71 in phakic eyes in their series and observed that a mean difference between the actual and predicted refractive error was 0.74 D when the intraocular lens was placed in the bag and 1.3 D when placed in the sulcus.<sup>203</sup>

When silicone oil removal is combined with cataract surgery, biometry readings may be obtained following silicone oil removal and before lens implantation in the operating room. This eliminates the need for correcting the measured axial length with a correction factor for the silicone oil.<sup>204</sup> Combined cataract

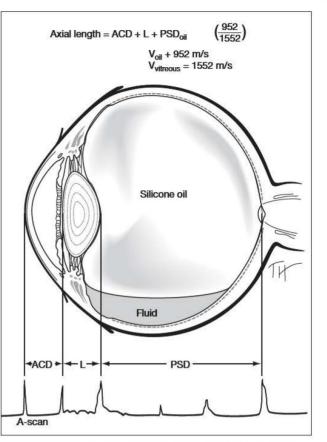


Fig. 130-12 Intraocular lens power calculations in the silicone oil-filled eye. In the phakic eye, A-scan ultrasonography is used to make separate measurements of the anterior-chamber depth (ACD), lens thickness (L) and the posterior-segment depth (PSD). The PSD must then be corrected for the different speed of sound in silicone oil ( $V_{cal}$ ). The correction factor is 986/1552 (986 m/s for oil versus 1552 m/s for physiologic saline).

extraction and oil removal may save patients an extra operation as well.  $^{\rm 205}$ 

#### Late visual loss

Whether or not the use of a silicone oil tamponade is associated with late visual loss has been controversial. While one early experimental study suggested this possibility,  $^{116,150,151}$  a number of other experimental studies appeared to refute this conclusion.  $^{13,42,43,54,58,71,74,97,99,102,118,147,152,154,161,186,193}$  In the Silicone Study, when the macula was attached at 36 months in eyes having undergone surgery for PVR, no subsequent loss of vision was likely to occur in either eyes randomized to silicone oil or in eyes randomized to  $C_3F_8$  gas with up to 6 years of follow-up.<sup>185</sup>

#### SILICONE OIL REMOVAL

#### Technique

Several techniques may be used for silicone oil removal.<sup>35,53,67,112,138,206</sup> Some surgeons prefer to allow the oil to egress through a small corneal incision in aphakic eyes. We

Novartis Exhibit 2317.0020 Regeneron v. Novartis, IPR2021-00816 generally utilize a two-port cannula system for the infusion of saline and the passive efflux or active aspiration of silicone oil (Fig. 130-13A). Once the main body of oil has been removed, residual oil droplets are passively effluxed through a 5/8-in. (1.5-cm), thin-walled 19-gauge cannula (Fig. 130-13B). One or two fluid-gas exchanges can also be employed at the end of the procedure to flush out remaining small globules of oil caught in the peripheral vitreous or under the base of the iris, but a recent study showed no benefit of this technique.<sup>207</sup> With any method, however, some tiny residual oil droplets usually remain. Patients with good vision may note some floaters due to these bubbles, although they usually resolve spontaneously. Of note, we rinse the conjunctiva with copious amounts of irrigating fluid after closing the sclerotomies but before closing the conjunctiva to minimize the risk of lipid granulomas from trapped residual subconjunctival silicone oil.208

Recently, combined phacoemulsification with aspiration of the silicone oil through a posterior capsulotomy using the irrigation–aspiration handpiece has been utilized by some when cataract surgery was combined with silicone oil removal.<sup>209,210</sup> When cataract removal with phacoemulsification is performed at the time of silicone oil removal, some authors advocate making a posterior capsulotomy through which the silicone oil may be removed using an anterior approach.<sup>209</sup>

#### Results

In the Silicone Study, silicone oil removal was allowed after a minimum of 8 weeks following surgery, and surgeons were

encouraged to remove the oil, if possible, at that time.<sup>211</sup> The ultimate decision of whether or not to remove the oil, however, was left to the study surgeon. The advisability of silicone oil removal remains controversial.<sup>212,213</sup> On the one hand, previous studies emphasized the complications of prolonged tamponade with silicone oil, and one study suggested that at least some complications were alleviated by relatively early removal of the oil (at 8 weeks).<sup>153,214-216</sup> On the other hand, the rate of recurrent retinal detachment following removal of silicone oil appeared substantial, so some surgeons preferred to allow it to remain if it was not causing any obvious problems.

The Silicone Study<sup>211</sup> contrasted the visual and anatomic outcomes in the cohort of eyes with silicone oil removal (oil-removed eyes) to the cohort of eyes with silicone oil retained (oil-retained eyes). Overall, 45% (99 of 222) of eyes underwent silicone oil removal. Compared with oil-retained eyes, the oil-removed eyes were more likely to have attached retinas (85% versus 40%, P < 0.0001), visual acuities of 5/200 or greater (63% versus 35%, P < 0.0001), and not be hypotonous (5% versus 22%, P < 0.001). Not unexpectedly, eyes with attached retinas at the time of oil removal had better vision at final follow-up compared to eyes with detached retinas at the time of oil removal (P < 0.0001).

Just comparing eyes in which silicone oil has been removed to eyes in which silicone oil is retained invites a bias of ascertainment because silicone oil-removed eyes were, in general, doing better than were the eyes in which silicone oil was retained. To correct for this bias, a matched-pair cohort analysis, matching eyes for length of exposure to silicone oil, visual acuity, retinal

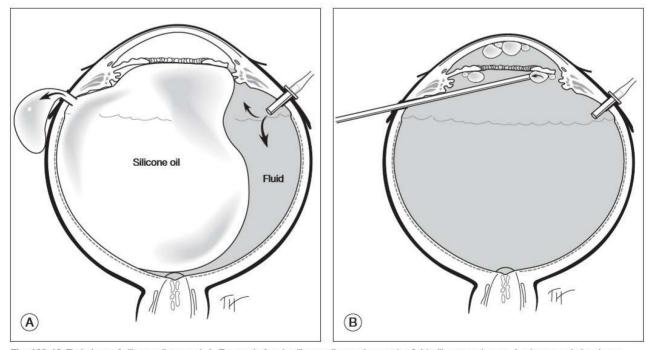


Fig. 130-13 Technique of silicone oil removal. A, Removal of main silicone oil mass by passive fluid-silicone exchange. A microcannula has been placed through the pars plana sclerotomy to facilitate efflux of silicone oil. B, Removal of residual silicone oil droplets using a thin-walled, 19-gauge needle or cannula.

Novartis Exhibit 2317.0021 Regeneron v. Novartis, IPR2021-00816

2231

attachment, and length of follow-up was performed. In this analysis, there was an increased risk of recurrent retinal detachment in oil-removed eyes compared with oil-retained eyes (odds ratio+2.1, P +0.9). Overall, however, visual acuity improved in 29% of oil-removed eyes in contrast with 2% of oil-retained eyes (P < 0.0001). Although statistically nonsignificant, there was also a trend towards less keratopathy and hypotony in oil-removed eyes.

# Recommendations

As a general principle, silicone oil should be removed once the objectives of the tamponade have been achieved and the retinal status is stable in order to minimize the long-term complications associated with its use.<sup>154,195,217-219</sup> In most cases, we generally remove the silicone oil between 6 weeks and 6 months if the retina remains attached and the intraocular pressure is normal. If partial recurrent retinal detachment is present, we will generally reoperate to repair the detachment and leave the oil in place until the retina is entirely attached. If the anatomic or visual prognosis is very poor, especially with a healthy fellow eye and a history of multiple reoperations, the patient and surgeon may not choose to reoperate and may leave the oil in place. Even if the retina is attached, we will avoid silicone oil removal if the eye is chronically hypotonous, as we have seen rapid progression to phthisis when oil is removed in this situation. In cases associated with trauma, we may leave the oil longer due to the apparently prolonged time course of reproliferation in this subset of patients.154

# SUMMARY AND CONCLUSIONS

Silicone oil remains a very valuable, if imperfect, material for use as an extended intraocular tamponade. The management of the highly complex retinal problems necessitating the use of silicone oil is difficult, associated with serious complications, and frequently requires multiple reoperations. When the physician and patient make a decision to use silicone oil, each should be prepared for a long and potentially complicated course, with the ultimate goals of complete retinal reattachment, maximum restoration of visual function, and eventual removal of the oil kept clearly in mind.

Much has been said and written about the relative merits of an extended intraocular tamponade with a long-acting gas compared to silicone oil. Although each modality has its relative advantages and disadvantages, a randomized, prospective clinical trial has found that silicone oil and  $C_3F_8$  gas were equally efficacious in the treatment of rhegmatogenous retinal detachment complicated by severe PVR.<sup>79</sup> Careful evaluation of the individual patient and of the specific ocular problem will help the surgeon to choose the best tamponade for any particular situation.<sup>220</sup> Ultimately, we believe that surgical technique and assiduous attention to the relief of retinal traction are far more important determinants of the likelihood of the success of vitreoretinal surgery in the management of complicated retinal detachment than is the decision as to whether to use silicone oil or a longacting gas.

# REFERENCES

- Stone W Jr. Alloplasty in surgery of the eye. N Engl J Med 1958; 258:486–490.
   Armaly MF. Ocular tolerance to silicones: I. Replacement of acueous and
- vitreous by silicone fluids. Arch Ophthalmol 1962; 68:390–395. 3. Cibis PA. Vitreous transfer and silicone injections. Trans Am Acad Ophthalmol
- Otolaryngol 1964; 68:983–997. 4. Cibis PA. Recent methods in the surgical treatment of retinal detachment:
- intravitreal procedures. Trans Ophthalmol Soc UK 1965; 85:11–127. 5. Cibis PA. Vitreoretinal pathology and surgery in retinal detachment. St. Louis:
- CV Mosby; 1965. CV Mosby; 1965. 6 Cibis PA Becker B Okun E et al. The use of liquid silicone in retinal
- Cibis PA, Becker B, Okun E et al. The use of liquid silicone in retinal detachment surgery. Arch Ophthalmol 1962; 68:590–599.
- Machemer R, Buttner H, Norton EWD. Vitrectomy: a pars plana approach. Trans Am Acad Ophthalmol Otolaryngol 1971; 75:813–820.
   Machemer R, Lagua H. Pigment epithelium proliferation in retinal detach-
- Machemer R, Laqua H. Pigment epithelium proliferation in retinal detachment (massive periretinal proliferation). Am J Ophthalmol 1975; 80:1–23.
   Cockerham WD. Schepens CL, Freeman HM. Silicone injection in retinal detachment. Arch Ophthalmol 1970; 83:704–712.
- Dufour R. Experience with intraocular silicone injection: new and controversial aspects of retinal detachment surgery. New York: Harper & Row; 1968:377.
- Kanski JJ, Daniel R. Intravitreal silicone injection in retinal detachment. Br J Ophthalmol 1973; 57:542–545.
- Liesenhoff HH, Schmitt J. Komplikationen durch Flussiges Silikon in der Vorderkammer. Berl Dtsch Ophthalmol Ges 1969; 69:643–644.
- Okun E. Intravitreal surgery utilizing liquid silicone: a long-term follow-up. Trans Pac Coast Oto-Ophthalmol Soc 1968; 49:141–159.
- Okun E, Arribas NP. Therapy of retinal detachment complicated by massive preretinal fibroplasias (long-term follow-up of patients treated with intravitreal liquid silicone). In: Symposium on retina and retinal surgery; Transactions of the New Orleans Academy of Ophthalmology. St. Louis: CV Mosby; 1969:278–293.
- Sugar HS, Okamura ID. Ocular findings six years after intravitreal silicone injection. Arch Ophthalmol 1976; 94:612–615.
- Watzke RC. Silicone retinopiesis for retinal detachment: a long-term clinical evaluation. Arch Ophthalmol 1967; 77:185–196.
- Watzke RC. Use of silicone oil (letter). Arch Ophthalmol 1982; 100:1354–1355.
- Scott JD. Treatment of the detached immobile retina. Trans Ophthalmol Soc UK 1972; 92:351–357.
- Scott JD. The treatment of massive vitreous retraction. Trans Ophthalmol Soc UK 1973; 93:417–423.
- Scott JD. A rationale for the use of liquid silicone in retinal detachment surgery. Acta XXIII concilium ophthalmologica, part I. Kyoto, 1978, Excerpta Medica, 1979, Amsterdam
- 21. Scott JD. Silicone oil as an instrument. In: Ryan S, ed. Retina, vol. 2. B. Glaser: 1994: Ch. 135.
- Haut J, Larricart JP, Van Effenterre G et al. Some of the most important properties of silicone oil to explain its action. Ophthalmologica 1985; 191:150–153.
- Haut J, Leon M-C, Van Effenterre G et al. Traitement en premiere intention de certains décollements de rétine souple (trou maculaire, dechirure géante) par la technique de vitrectomie-silicone. Bull Soc Ophthalmol Fr 1982; 82:305–309.
- Haut J, Ullern M, Boulard ML et al. Utilisation du silicone intra-oculaire après vitrectomie comme traitement des retractions massive du vitre (note preliminaire). Bull Soc Ophthalmol Fr 1978; 78:361–365.
- Haut J, Ullern M, Chermet M et al. Complications of intraocular injections of silicone combined with vitrectomy. Ophthalmologica 1980; 180:29–35.
- Haut J, Ullern M, Chatellier PH et al. Resultats de 200 cas d'injection intraoculaire de silicone associée à la vitrectomie. Bull Mem Sco Fr Ophthalmol 1979; 91:180–184.
- Zivojnovic R. Silicone oil in vitreoretinal surgery. Dordrecht, The Netherlands: Martinus Nijjof/Dr W Junk; 1987.
- Zivojnovic R, Mertens DAE, Baarsma GS. Das Flussige Silikon in der Amotiochirurgie: Bericht uber 90 Falle. Klin Monatsbl Augenheilkd 1981; 179:17–22.
- Zivpjnovic R, Mertens DAE, Peperkamp E. Das Flussige Silikon in der Amotiochirurgie: II. Bericht uber 280 Falleweitere Entwicklung der Technik. Klin Monatsbl Augenheilkd 1982; 181:444–452.
- Gray RH, Leaver PK. Results of silicone oil injection in massive preretinal retraction. Trans Ophthalmol Soc UK 1977; 97:238–241.
- Grey RHB, Leaver PK. Silicone oil in the treatment of massive preretinal retraction: I Results in 105 eyes. Br J Ophthalmol 1979; 63:355–350.
- Leaver PK. Silicone oil injection in the treatment of massive preretina retraction. In: McPherson A, ed. New and controversial aspects of vitreoretinal surgery. St. Louis, MO: CV Mosby; 1977:397–401.

Novartis Exhibit 2317.0022 Regeneron v. Novartis, IPR2021-00816

#### Section 3 Special Adjuncts to Treatment

- Leaver PK, Garner A, Grey RHB et al. Effects of intraocular silicone oil. Trans Ophthalmol Soc UK 1977; 97:633.
- Leaver PK, Billington BM. Vitrectomy and fluid/silicone oil exchange for giant retinal tears: 5 years follow-up. Graefes Arch Clin Exp Ophthalmol 1989; 227:323–327.
- Leaver PK, Cooling RJ, Feretis EB et al. Vitrectomy and fluid/silicone exchange for giant retinal tears: results at six months. Br J Ophthalmol 1984; 68:432–438.
- Leaver PK, Grey RHB, Garner A. Complications following silicone-oil injection. Mod Probl Ophthalmol 1979; 20:290–294.
- Leaver PK, Grey RHB, Garner A. Silicone oil injection in the treatment of massive preretinal retraction: II. Late complications in 93 eyes. Br J Ophthalmol 1979; 63:361–367.
- Leaver PK, Lean JS. Management of giant retinal tears using vitrectomy and silicone oil/fluid exchange: a preliminary report. Trans Ophthalmol Soc UK 1981; 101:189–195.
- Ando F. Intraocular hypertension resulting from pupillary block by silicone oil. Am J Ophthalmol 1985; 99:87–88.
- Beekhuis WH, Ando F, Zivojnovic ER et al. Basal iridectomy at 6 o'clock in the aphakic eye treated with silicone oil: prevention of keratopathy and secondary glaucoma. Br J Ophthalmol 1987; 71:197–200.
- Machemer R. Retinotomy. Am J Ophthalmol 1981; 90:768–774.
   Machemer R, McCuen BW II, de Juan E Jr. Relaxing retinotomies and
- Machemer R, McCuen BW II, de Juan E Jr. Relaxing retinotomies and retinectomies. Am J Ophthalmol 1986; 102:7–12.
- Moorse LS, McCuen BW II, Machemer R. Relaxing retinotomies. Analysis of anatomical and visual results. Ophthalmology 1990; 97:642–648.
- Alexandridis E, Daniel H. Results of silicone oil injection into the vitreous. Dev Ophthalmol 1981; 2:24–27.
- Bacin F, Gilbert C. Resultats du traitement des décollements de rétine avec retraction du vitre par injections de silicone liquide intra-oculaire. Bull Soc Ophthalmol Fr 1982; 82:367–372.
- Beekhuis WH, van Rij G, Zivojnovic R. Silicone oil keratopathy: indications for keratoplasty. Br J Ophthalmol 1985; 69:247–253.
- Cairns JD, Anand N. Combined vitrectomy, intraocular microsurgery and liquid silicone in the treatment of proliferative vitreoretinopathy. Aust J Ophthalmol 1984; 12:133–138.
- Constable I, Mohamed S, Tan PL. Superviscous silicone liquid in retinal surgery. Aust J Ophthalmol 1982; 10:5–11.
- Cox MS, Trese MT, Murphy PL. Silicone oil for advanced proliferative vitreoretinopathy. Ophthalmology 1986; 93:646–650.
- Federman JL, Schubert HD. Complications associated with the use of silicone oil in 150 eyes after retina-vitreous surgery. Ophthalmology 1988; 95:870–876.
- Heimann K, Dimopoulos S, Paulmann H. Silikonolinjektion in der Behandlung komplizierter netzhautablosungen. Kin Monatsbl Augenheilkd 1984; 185:505–208.
- Kampik A, Gabel V-P, Spiegel D. Intraokulare Tamponade mit Hochviskosem Silikonol bei Massiver Proliferativer Vitreoretinopathy. Klin Monatsbl Augenheilkd 1984; 185:368–370.
- Kroll P, Gerding H, Busse H. Zum Zeitpunkt retinaler Komplikationen durch Reproliferationen nach Vitreoretinaler Silikonchirurgie. Klin Monatsbl Augenheilkd 1989; 195:145–149.
- Laqua H, Lucke K, Foerster MH. Development and present status of silicone oil surgery. Klin Monatsbl Augenheilkd 1988; 192:277–283.
- 55. Lean JS. Use of silicone oil as an additional technique in vitreoretinal surgery.
- In: Glasser B, Ryan S, eds. Retina 2e. St Louis, USA: Mosby; 1994: 2151–2164. 56. Lean JS. Origin of simple glial epiretinal membranes in an animal model.
- Grafes Arch Clin Exp Ophthalmol 1987; 225:421–425. 57. Lean JS, Leaver PK, Cooling RJ et al. Management of complex retinal
- Lean JS, Leaver PK, Cooling RJ et al. Management of complex retinal detachments by vitrectomy and fluid/silicone exchange. Trans Ophthalmol Soc UK 1982; 102:203–205.
- Lean JS, Van der Zee, W AM et al. Experimental model of proliferative vitreoretinopathy (PVR) in the vitrectomised eye: effect of silicone oil. Br J Ophthalmol 1984; 68:332–335.
- Lucke KH, Foerster MH, Laqua H. Long-term results of vitrectomy and silicone oil in 500 cases of complicated retinal detachments. Am J Ophthalmol 1987; 104:624–633.
- Lucke K, Laqua H, Foerster MH. Results of silicone oil surgery for proliferative vitreoretinopathy. In: Wiedermann K, Heimann P, eds. Proliferative vitreoretinopathy. Heidelberg, Germany: Kaden Verlag; 1988:212–216.
   McCuen BW II, de Juan E Jr, Machemer R. Silicone oil in vitreoretinal
- McCuen BW II, de Juan E Jr, Machemer R. Silicone oil in vitreoretinal surgery, part 1. Surgical techniques. Retina 1985; 5:189–197.
- McCuen BW II, de Juan E Jr, Landers MB III et al. Silicone oil in vitreoretinal surgery: 2. Results and complications. Retina 1985; 5:198–205.
- McCuen BW II, Klombers L. The choice of posterior chamber intraocular lens style in patients with diabetic retinopathy. Arch Ophthalmol 108:1376–1377.
- McCuen BW II, Landers MB III, Machemer R. The use of silicone oil following failed vitrectomy for retinal detachment with advanced proliferative vitreoretinopathy. Ophthalmology 1985; 92:1029–1033.

- Riedel KG, Gabel V-P, Neubauer L et al. Intravitreal silicone oil injection: complications and treatment of 415 consecutive patients. Graefes Arch Clin Exp Ophtalmol 1990; 228:19–23.
- Roussat B, Ruellan Y-M. Traitement du décollement de rétine par vitrectomie et injection d'huile de silicone: resultats à long terme et complications dans 106 cas. J Fr Ophthalmol 1984; 7:11–18.
- Sell CH, McCuen BW II, Landers MB et al. Long-term results of successful vitrectomy with silicone oil for advanced proliferative vitreoretinopathy. Am J Ophthalmol 1987; 103:24–28. 1987
- Unosson K, Stenkula S, Tornqvist P et al. Liquid silicone in the treatment of retinal detachment. Acta Ophthalmol 1985; 63:656–660.
- Wilson-Holt N, Leaver PK. Extended criteria for vitrectomy and fluid/silicone oil exchange. Eye 1990; 4:850–854.
- Charles S, Mccarthy C, Eichenbaym D. Mechanical syringe drive for vitreous surgery. Am J Ophthalmol 1975; 79:879.
- Charles S, Wang C. A motorized gas injector for vitreous surgery. Arch Ophthalmol 1981; 99:1398.
- 72. Grizzard WS, Slagel C, Gordon S. Infusion of intraocular gas with a pressure-controlled system. Am J Ophthalmol 1979; 88:1096.
- McCuen BW II, Bessler M, Hickingbotham D et al. Automated fluid–gas exchange. Am J Ophthalmol 1983; 95:717.
- Chang S, Lincoff H, Coleman DJ et al. Perfluorocarbon gases in vitreous surgery. Ophthalmology 1985; 92:651–656.
- Lincoff H, Coleman DJ, Kreissig I et al. The perfluorocarbon gases in the treatment of retinal detachment. Ophthalmology 1983; 90:546–551.
- Azen SP, Boone DC, Barlos W et al. Methods, statistical features and baseline results of a standardized, multicenter ophthalmologic surgical trial: the Silicone Study. Controlled Clin Trials 1991; 12:438–455.
- Silicone Study Group. Proliferative vitreoretinopathy. Am K Ophthalmol 1984; 99:593–595.
- Silicone Study Group. Silicone Study report 1. Vitrectomy with silicone oil or sulphur hexafluoride gas in eyes with severe proliferative vitreoretinopathy: results of a randomized clinical trial. Arch Ophthalmol 1992; 110:779–791.
- Silicone Study Group. Silicone Study report 2. Vitrectomy with silicone oil or sulphur hexafluoride gas in eyes with severe proliferative vitreoretinopathy: results of a randomized clinical trial. Arch Ophthalmol 1992; 110:792–805.
- Silicone Study Group. Silicone Study report 3. Vitrectomy with silicone oil or perfluoropropane gas in eyes with severe proliferative vitreoretinopathy: results of a randomized clinical trial. Retina 1993; 13:278–284.
- Haller JA, Campochiaro PS. Oil and gas on troubled waters: the proliferative vitreoretinopathy studies. Arch Ophthalmol 110:768–769
- Silicone Study Group. Silicone Study report 11. Vitrectomy with silicone oil or long-acting gas in eyes with severe proliferative vitreoretinopathy: results of additional and long-term follow-up. Arch Ophthalmol 1997; 115:335–344.
- Silicone Study Group. Silicone Study report 10. Anterior proliferative vitreoretinopathy in the silicone study. Ophthalmology 1996; 107:1092–1099.
- Silicone Study Group. Silicone Study report 5. Relaxing retinotomy with silicone oil or long-acting gas in eyes with severe proliferative vitreoretinopathy: results of a randomized clinical trial. Am J Ophthalmol 1993; 116:557–564.
- Brown GC, Brown MM, Sharma S et al. A cost–utility analysis of interventions for severe proliferative vitreoretinopathy. Am J Ophthalmol 2002; 133:365–372.
- Bodanowitz S, Kir N, Hesse L. Silicone oil for recurrent vitreous hemorrhage in previously vitrectomized diabetic eyes. Ophthalmologica 1997; 211:219–222.
- Gabel V-P, Beck P. Does silicone oil improve the prognosis in advanced proliferative diabetic retinopathy? Klin Monstsbl Augenheilkd 1990; 197:112–117.
- Gonvers M. Temporary silicone oil tamponade in the treatment of complicated diabetic retinal detachments. Graefes Arch Clin Exp Ophthalmol 1990; 228:415–422.
- Heimann K, Dahl B, Dimopoulos S et al. Pars plana vitrectomy and silicone oil injection in proliferative diabetic retinopathy. Graefes Arch Clin Exp Ophthalmol 1989; 227:152–156.
- Brourman ND, Blumenkranz MS, Cox MS et al. Silicone oil for the treatment of severe proliferative diabetic retinopathy. Ophthalmology 96:769–764
   McLeod D, Silicone oil injection during closed microsurgery for diabetic
- McLeod D. Silicone oil injection during closed microsurgery for diabetic retinal detachment. Graefes Arch Clin Exp Ophthalmol 1986; 224:55–59.
   McLeod D. Microsurgical management of neovascularization secondary to
- McLeou D. McLeou Sugger management of metovascularization secondary to posterior segment ischaemia. Eye 1991; 5:252–259.
   Oldendoerp J, Spitznas M. Factors influencing the results of vitreous surgery
- Oldendoerp J, Spitznas M. Factors influencing the results of vitreous surgery in diabetic retinopathy: I. Iris rubeosis and/or active neovascularization at the fundus. Graefes Arch Clin Exp Ophthalmol 1989; 227:1–8.
- Castellarin A, Grogorian R, Bhagat N et al. Vitrecctomy with silicone oil infusion in severe diabetic retinopathy. Br J Ophthalmol 2003; 87:318–321.
- McCuen BW II, Rinkoff JS. Silicone oil for progressive anterior ocular neovascularization after failed diabetic vitrectomy. Arch Ophthalmol 107:677–682

Novartis Exhibit 2317.0023 Regeneron v. Novartis, IPR2021-00816

Chapter 130

Silicone Oil in Vitreoretinal Surgery

- de Juan E, Hardy M, Hatchell DL et al. The effect of intraocular silicone oil on anterior chamber oxygen pressure in cats. Arch Ophthalmol 1986; 104:1063–1064.
- Wilson CA, Berkowitz BA, McCuen BW II et al. Measurement of preretinal oxygen tension in the vitrectomized human eye using fluirine-19 magnetic resonance spectroscopy. Arch Ophthalmol 1992; 110:1098–1100.
- 98. Douglas MJ, Scott IU, Flynn HW Jr. Pars plana lensectomy, pars plana vitrectomy, and silicone oil tamponade as initial management of cataract and combined traction/rhegmatogenous retinal detachment involving the macula associated with severe proliferative diabetic retinopathy. Ophthalm Surg Lasers Imaging 2003; 34:270–278.
- Rinkoff JS, de Juan E Jr, McCuen BW II. Silicone oil for retinal detachment with advanced proliferative vitreoretinopathy following failed vitrectomy for proliferative diabetic retinopathy. Am J Ophthalmol 1986; 101:181–186.
- Gonvers M. Macular hole and retinal detachment. In: Blankenship GW, Binder S, Gonvers M et al., eds. Basic and advanced vitreous surgery, vol. 2. New York: Springer-Verlag, 1986.
- Gonvers M, Machemer R. A new approach to treating retinal detachment and macular hole. Am J Ophthalmol 1982; 94:468–472.
- 102. Rashed O, Sheta S. Evaluation of the functional results after different techniques for treatment of retinal detachment due to macular holes. Graefes Arch Clin Exp Ophthalmol 1989; 227:508–512.
- Kalvadova B, Karel I, Bohacova E et al. Pars plana vitrectomy in retinal detachment with a macular hole [Czech]. Ceska A Slov Oftalmol 1996; 52 (suppl.):34–41.
- Goldbaum MH, McCuen BW et al. Silicone oil tamponade for idiopathic macular hole surgery. Ophthalmology 1998; 105:2140–2147.
   Lai JC, Stinnett SS, McCuen BW II. Comparison of silicone oil vs. gas
- 105. Lai JC, Stinnett SS, McCuen BW II. Comparison of silicone oil vs. gas tamponade in the treatment of idiopathic full-thickness macular hole. Ophthalmology 2003; 110:1170–1177.
- Jumper JM, Gallemore RP, McCuen BW II et al. Features of macular hole closure in the early postoperative period using optic coherence tomography. Retina 2002; 20:232–237.
- Blumenkranz MS. The use of silicone oil for HIV-related retinal detachment. Arch Ophthalmol 1995; 113:1366.
- 108. Machemer R, Allen AW. Retinal tears 180° and greater: management with vitrectomy and intravitreal gas. Arch Ophthalmol 1976; 94:1340–1346.
- Unlu N, Kocaoglan H, Acar MA et al. The management of giant retinal tears with silicone oil. Eur J Ophthalmol 2003; 13:192–195.
- 110. Jesberg DO, Schepens CL. Retinal detachment associated with coloboma of the choroids. Arch Ophthalmol 1961; 65:163.
- Patnaik B, Kalsi R. Retinal detachment with coloboma of the choroids. Ind J Ophthalmol 1981; 29:345.
- Unlu N, Kocaoglan H, Acar MA et al. Surgical management of retinal detachment with choroidal coloboma. Eur J Ophthalmol 2003; 12:299–303.
- 113. Gonvers M. Temporary use of intraocular silicone oil in the treatment of special cases of return detachment. Ophthalmologica 1983; 187:202.
- 114. Hanneken A, de Juan E, McCuen BW II. The management of retinal detachments associated with choroidal colobomas by vitreous surgery. Am J Ophthalmol 1991; 111:271–275.
- Jalali S, Das T. Selection of surgical techniques for retinal detachment with coloboma of the choroids. Ind J Ophthalmol 1994; 42:27–30.
- Algrere P, Alanko H, Dickhoff K et al. Pars plana vitrectomy in the management of intraocular inflammation. Acta Ophthalmol (Copenh) 1981; 59:727–736.
- Belmont JB, Michelson JB. Vitrectomy in uveitis associated with ankylosis spondylitis. Am J Ophthalmol 1982; 94:300–304.
- 118. Diamind JG, Kaplan HJ. Lensectomy and vitrectomy for complicated cataract secondary to uveitis. Arch Ophthalmol 1978; 96:1798-1804.
- Diamond JG, Kaplan HJ. Uveitis: effect of vitrectomy conbined with lensectomy. Ophthalmology 1979; 86:1320–1327.
   Fitzgerald CR. Pars plana vitrectomy for vitreous opacity secondary to
- presumed toxoplasmosis. Arch Ophthalmol 1980; 98:321–323.
- 121. Hooper P, Kaplan HJ. Surgical management of non-infectious endophthalmitis. In: Glaser BM, Michels RG, eds. Retina, vol. 3. St. Louis: 1994, p. 2539
- Moorse LS, McCuen BW II. The use of silicone oil in uveitis and hypotony. Retina 1991; 11:399–404.
- Davis JL, Serfass MS, Lai MY et al. Silicone oil in repair of retinal detachments caused by necrotizing retinitis in HIV infections. Arch Ophthalmol 1995; 113:1401–1409.
- Dugel PU, Liggett PE, Lee MB et al. Repair of retinal detachment caused by cytomegalovirus retinitis in patients with the acquired immune deficiency syndrome. Am J Ophthalmol 1991; 112:235–242.
- Freeman WR, Henderly DE, Wan WI et al. Prevalence, pathophysiology, and treatment of rhegmatogenous retinal detachment in treated cytomegalovirus retinitis. Am J Ophthalmol 1987; 103:527–536.
- 126. Freeman WR, Quinceno JI, Crapotta JA et al. Surgical repair of rhegmatogenous retinal detachment in immunosuppressed patients with cytomegalovirus retinitis. Ophthalmology 1992; 99:466.

- Garcia RF, Flores-Aguilar M, Quinceno JI et al. Results of rhegmatogenous retinal detachment repair in cytomegalovirus retinitis with and without scleral buckling. Ophthalmology 1995; 102:236.
- Lucke K, Reinking U, El-Hifnawi E. Acute retinal necrosis. Klin Monatsbl Augenheilkd 1988; 193:602–607.
- Sidikara Y, Silver L, Holland GN et al. Rhegmatogenous retinal detachments in patients with AIDS and necrotizing retinal infections. Ophthalmology 1991; 98:129–135.
- Girard P, Mimoun G, Karpuizas I et al. Clinical risk factors for vitreoretinopathy after retinal detachment surgery. Retina 1994; 14:417–424.
   Spiegel D, Nasermann J, Nawrocki J et al. Severe ocular trauma managed with
- primary pars plana vitrectomy and silicone oil. Retina 1997; 17:275–285.
- Antoszyk AN, McCuen BW, de Juan E et al. Silicone oil injection after failed primary vitreous surgery in severe ocular trauma. Am J Ophthalmol 1989; 107:537–543.
- Miyake Y, Ando F. Surigcal results of vitrectomy in ocular trauma. Retina 1983; 3:265–268.
- 134. Skorpik C, Menapace R, Gnad HD et al. Silicone oil implantation in penetrating injuries complicated by PVR. Retina 1989; 9:8–14.
- Ferrone PJ, McBuen BW II, de Juan E et al. The efficacy of silicone oil for complicated retinal detachments in the pediatric population. Arch Ophthalmol 1994; 112:773–777.
- Weinberg DV, Lyon AT, Greenwald MJ et al. Rhegmatogenous retinal detachments in children: risk factors and surgical outcomes. Ophthalmology 2003; 110:1708–1713.
- 137. Aras C, Ozdamar A, Karacorlu M et al. Silicone oil in the surgical treatment of endophthalmitis associated with retinal detachment. Int Ophthalmol 2001; 24:147–150.
- Azad R, Ravi K, Talwar D et al. Pars plana vitrectomy with or without silicone oil endotamponade in posttraumatic endophthalmitis. Graefes Arch Clin Exp Ophthalmol 2003; 241:478–483.
- Bali E, Huyghe P, Caspers L et al. Vitrectomy and silicone oil in the treatment of acute endophthalmitis. Preliminary results. Bull Soc Belge Ophtalmol 2003; 288:9–14.
- Crisp A, de Juan E, Tiedeman J. Effect of silicone oil viscosity on emulsification. Arch Ophthalmol 1987; 105:546–550.
- 141. Failer J, Faulborn J, Erb P. Die Phagozytose von Silikon-Olen unterschiedlicher Viskositat durch Peritoneal-Makrophagen der Maus. Klin Monatsbl Augenheilkd 1984; 184:450–452.
- Gabel V-P, Kampik A, Burkhardt J. Analysis of intraocularly applied silicone oil of various origins. Graefes Arch Clin Exp Ophthalmol 1987; 225:160–162.
- Gabel V-P, Kampik A, Gabel CH et al. Silicone oil with high specific gravity for intraocular use. Br J Ophthalmol 1987; 71:262–267.
   Wolf S, Schon V, Meier P et al. Silicone oil-RMN3 mixture ("heavy silicone")
- Wolf S, Schon V, Meier P et al. Silicone oil-RMN3 mixture ("heavy silicone oil") as internal tamponade for complicated retinal detachment. Retina 2003; 23:335–342.
- de Juan E, McCuen BW II, Tiedeman J. Intraocular tamponade and surface tension. Surv Ophthalmol 1985; 30:47–51.
- Zauberman H, de Guillebon H, Holly FJ. Retinal traction in vitro: biophysical aspects. Invest Ophthalmol 1972; 11:46–55.
   Labelle P, Okun E, Ocular tolerance to liquid silicone: an experimental study.
- Labelle P, Okun E. Ocular tolerance to liquid silicone: an experimental study, Can J Ophthalmol. 1972; 7:199–204.
   Machemer R. Hickingdothan D. The three-port microcannular system for
- Machemer R, Hickingbothan D. The three-port microcannular system for closed vitrecctomy. Am J Ophthalmol 1985; 100:590–592.
   Bonnet M, Sanamaria E, Mouche J, Intraoperative use of pure profluoro-
- 149. Bonnet M, Sanamaria E, Mouche J. Intraoperative use of pure profluoropropane gas in the management of proliferative vitreoretinopathy. Graefes Arch Clin Exp Ophthalmol 1987; 225:299–302.
- Chang S. Low viscosity liquid fluorechemicals in vitreous surgery. Am J Ophthalmol 1987; 103:38–43.
- Chang S, Ozmert E, Zimmerman NJ. Intraoperative perfluorocarbon liquids in the management of proliferative vitreoretinopathy. Am J Ophthalmol 1988; 106:688–674.
- Thompson JT. Use of perfluorocarbon liquids in vitreoretinal surgery. In: Glaser BM, Michels RG, eds. Retina, vol. 3. St. Louis: 1994:2191–2201.
- Gonvers M. Temporary silicone oil tamponade in the management of retinal detachment with proliferative vitreoretinopathy. Am J Ophthalmol 1985; 100:239–245.
- Zilis JD, McCuen BW II, de Juan E Jr et al. Results of silicone oil removal in advanced proliferative vitreoretinopathy. Am J Ophthalmol 1989; 108:15–21.
- 155. MacCumber MW, Packo KH, Civantos JM et al. Preservation of anterior capsule during vitrectomy and lensectomy for retinal detachment with proliferative vitreoretinopathy. Ophthalmology 2002; 109:329–333.
- 156. Kroll P, Hesse L, Bodanowitz, et al. Cataract surgery in proliferative vitreoretinopathy grade C. In: Stirpe M, ed. Anterior and posterior segment surgery: mutual problems and common interests. Acta of the Fifth International Congress on Vitreoretinal Surgery. New York, NY: Ophthalmic Communications Society; 1998.

Novartis Exhibit 2317.0024 Regeneron v. Novartis, IPR2021-00816

#### Section 3 Special Adjuncts to Treatment

- 157. Laganowski HC, Leaver PK. Silicone oil in the aphakic eye: the influence of a six o'clock peripheral iridectomy. Eye 1989; 3:338–348.
- Thumann G, Kirchhof B, Bartz-Schmidt KU et al. The artificial iris diaphragm for vitreoretinal silicone oil surgery. Retina 1997; 17:330–337.
   Navas F, Boyer DS, Thomas EL et al. Management of pupillary block glaucoma
- in phakic patients after vitrectomy with silicone oil injection. Am J Ophthalmol 2002; 134:634–635.
- Gedde SJ. Management of glaucoma after retinal detachment surgery. Curr Opin Ophthalmol 2002; 13:103–109.
- Khawly J, Lambert RJ, Jaffe GJ. Intraocular lens changes after short- and long-term exposure to intraocular silicone oil. An in vivo study. Ophthalmology 1998; 105:1227–1233.
- 162. Gallemore RP, Jumper JM. The ins and outs of silicone oil, retinal insider 163. Hoeruf H, Faude F, Menz DH et al. Determination of the solubility of perfluorocarbon liquids in silicone oil in vitreo and in vivo. Retina 2002; 22:163–168.
- Jaffe GJ, Lewis H, Han DP et al. Treatment of postvitrectomy fibrin pupillary block with tissue plasminogen activator. Am J Ophthalmol 1989; 108:170–175.
- Jaffe GJ, Abrams GW, Williams GA et al. Tissue plasminogen activator for postvitrectomy fibrin formation. Ophthalmology 1990; 97:184–189.
- MacCumber MW, McCuen BW II, Toth CA et al. Tissue plasminogen activator for preserving inferior peripheral iridectomy patency in eyes with silicone oil. Ophthalmology 1996; 103:269–273.
- 167. Madreperla SA, McCuen BW II. Inferior peripheral iridectomy in patients receiving silicone oil. Retina 1995; 15:87–90.
- Jaffe GJ, Schwartz D, Han DP et al. Risk factors for postvitrectomy fibrin formation. Am J Ophthalmol 1990; 109:661–667.
- Zarbin MA, Micels RG, Green WR. Dissection of epiciliary tissue to treat chronic hypotony after surgery for retinal detachment with proliferative vitreoretinopathy. Retina 1991; 1:208–213.
- 170. Betis F, Leguay JM, Gastaud P et al. Multinucleated giant cells in periretinal silicone granulomas are associated with progressive proliferative vitreoretinopathy. Eur J Ophthalmol 2003; 13:634–641.
- 171. Sharma T, Gopal L, Shanmugan MP et al. Management of recurrent retinal detachment in silicone oil-filled eyes. Retina 2002; 22:153–157.
- 172. Malchiodi-Albedi F, Morgillo A, Formisano G et al. Biocompatibility assessment of silicone oil and perfluorocarbon liquids used in retinal reattachment surgery in rat retinal cultures. J Biomed Mater Res 2002; 60:548–555.
- 173. Silicone Study Group. Silicone Study report 7. The incidence of corneal abnormalities in the silicone study: results of a randomized clinical trial. Arch Ophthalmol 1995; 113:764–769.
- 174. Gao R, Neubauer L, Tang S et al. Silicone oil in the anterior chamber. Graefes Arch Clin Exp Ophthalmol 1989; 227:106–119.
- Levenson DS, Stocker FW, Georgiade NG. Intracorneal silicone fluid. Arch Ophthalmol 1965; 73:90–93.
- Sternberg P Jr, Hatchell DL, Foulks GN et al. The effect of silicone oil on the cornea. Arch Ophthalmol 1985; 103:90–94.
- 177. Martola E-L, Dohlman CH. Silicone oil in the anterior chamber of the eye: effect on corneal hydration. Acta Ophthalmol 1963; 41:75–79.
- Noorily SW, Foulks GN, McCuen BW II. Results of penetrating keratoplasty associated with silicone oil retinal tamponade. Ophthalmology 1991; 98:1186–1189.
- 179. Roters S, Hamzei P, Szurman P et al. Combined penetrating keratoplasty and vitreoretinal surgery with silicone oil: a 1-year follow-up. Graefes Arch Clin Exp Ophthalmol 2003; 241:24–3.
- Burk LL, Shields MB, Proia AD et al. Intraocular pressure following intravitreal silicone oil injection. Ophthalm Surg 1988; 19:565–569.
   Lucke K, Strobel B, Foerster M et al. Secondary glaucoma after silicone oil
- Bucke K, Strober B, Poerster M et al. Secondary grational arter sincone on surgery. Klin Monatsbl Augenheilkd 1990; 196:205–209.
   Zborowski-Gutman L, Treister G, Naveh N et al. Acute glaucoma following
- vitrectomy and silicone oil injection. Br J Ophthalmol 1987; 71:903–906.
- Bartov E, Huna R, Ashkenazi I et al. Identification, prevention and treatment of silicone oil pupillary block after an inferior iridectomy. Am J Ophthalmol 1991; 111:501–504.
- Silicone Study Group. Silicone Study report 4. Postoperative intraocular pressure abnormalities in the Silicone Study: results of a randomized clinical trial. Ophthalmology 1993; 100:1629–1635.
- Champion R, Faulborn J, Bowald S et al. Peritoneal reaction to liquid silicone: an experimental study. Graefes Arch Clin Exp Ophthalmol 1987; 225:141–145.
- Parwar BL, Coleman AL, Small KW. Silicone oil migration through an Ahmed valve. Retina 2002; 22:657–658.
- 187. Manschot WA. Intravitreal silicone injection. Adv Ophthalmol 1978; 36:197-207.
- Silicone Study Group. Silicone Study report 8. Macular pucker after successful surgery for proliferative vitreoretinopathy: results of a randomized clinical trial. Ophthalmology 1995; 102:1884–1891.
- Stefansson E, Anderson MM, Lander MB III et al. Refractive changes from the use of silicone oil in vitreous surgery. Retina 1988; 8:20–23.
- Stefansson E, Tiedeman JS. Optics of the eye with air or silicone oil. Retina 1988; 8:10–19.

- 191. Karel I, Dotrelova D, Kalvodova B et al. Complicated cataract following intravitreal silicone oil injection and its surgery. In: Wiederman P, Heimann K, eds. Proliferative vitreoretinopathy. Heidelberg, Germany: Kaden Verlag; 1988:242–246.
- Scott JD. Lens changes in retinal detachment. Trans Ophthalmol Soc UK 1979; 99:241–242.
- Scott JD. Lens epithelial proliferation in retinal detachment. Trans Ophthalmol Soc UK 1982; 102:385–389.
- Billington BM, Leaver PK. Vitrectomy and fluid/silicone–oil exchange for giant retinal tears: results at 18 months. Graefes Arch Clin Exp Ophthalmol 1986; 224:7–10.
- Chan C, Okun E. The question of ocular tolerance to intravitreal liquid silicone: a long-term analysis. Ophthalmology 1986; 93:651–660.
- Gonvers M. Temporary use of intraocular silicone oil in the treatment of detachment with massive periretinal proliferation. Ophthalmologica 1982; 184:210–218.
- Spraul CW, Jakobczyk-Zmija MJ, Aigner T et al. Posterior fibrous pseudometaplasia of lens epithelial cells in placic eyes filled with silicone oil. Graefes Arch Clin Exp Ophthalmol 2002; 240:829–834.
- 198. Engstrom RE Jr, Goldenberg DT, Parnell JR et al. Clear lens extraction with intraocular lens implantation during retinal detachment repair in patients with acquired immune deficiency syndrome (AIDS) [correction of autoimmune deficiency syndrome] and cytomegalovirus retinitis. Ophthalmology 2002; 109:666–673.
- Eaton AM, Jaffe GJ, McCuen BW II et al. Condensation on the posterior surface of silicone intraocular lenses during fluid–air exchange. Ophthalmology 1995; 102:733–736.
- McCartney DL, Miller KM, Stark WJ et al. Intraocular lens style and refraction in eyes treated with silicone oil. Arch Ophthalmol 1987; 105:1385–1387.
- 201. Byrne SF, Green RL. Ultrasound of the eye and orbit. St. Louis: Mosby; 1992:215-242.
- Shugar JK, de Juan E Jr, McCuen BW II et al. Ultrasonic examination of the silicone-filled eye: theoretical and practical considerations. Graefes Arch Clin Exp Ophthalmol 1986; 224:361–367.
- Murray DC, Durrani OM, Good P et al. Biometry of the silicone oil-filled eye: II. Eye 2002; 16:727–730.
- el-Baha SM, el-Samadoni A, Idris HF et al. Intraoperative biometry for intraocular lens (IOL) power calculation at silicone oil removal. Eur J Ophthalmol 2003; 13:622–626.
- Kloti R. Vitrektomie II. Chirurgische Technik mit dem Vitreus Stripper. Graefes Arch Klin Exp Med 1974; 189:125.
- Krepler K, Mozaffarieh M, Biowski R et al. Cataract surgery and silicone oil removal: visual outcome and complications in a combined vs. two-step surgical approach. Retina 2003; 23:647–653.
- Dabil H, Akduman L, Olk RJ et al. Comparison of silicone oil removal with passive drainage alone versus passive drainage combined with air-fluid exchange. Retina 2002; 22:597–601.
- Srinivasan S, Singh AK, Desai SP et al. Foreign body episcleral granulomas complicating intravitreal silicone oil tamponade: a clinicopathological study. Ophthalmology 2003; 110:1837–1840.
- 209. Frau E, Lautier-Frau M, Labetoulle M et al. Phacoemulsi- fication combined with silicone oil removal through the posterior capsulorhexis tear. Retina 2002; 22:158–162.
- Dada VK, Talwar D, Sharma N et al. Phacoemulsification combined with silisone oil removal through a posterior capsulorhexis. J Cataract Rrefract Surg 2001; 27:1243–1247.
- 211. Silicone Study Group. Silicone Study report 6. The effects of silicone oil removal: results of a randomized clinical trial. Arch Ophthalmol 1994; 112:778–785.
- 212. Franks WA, Leaver PK. Removal of silicone oil: rewards and penalties. Eye 1991; 5:333–337.
- Gnad H, Skorpik C, Paroussis P et al. Funktionelle und anatomische Resultate nach temporarer Silikonolimplantation. Klin Monatsbl Augenheild 1984; 185:364–367.
- 214. Gonvers M, Thresher R. Temporary use of silicone oil in the treatment of proliferative vitreoretinopathy: an experimental study with a new animal model. Graefes Arch Clin Exp Ophthalmol 1983; 221:46–53.
- 215. Watzke RC. Silicone retinopoiesis for retinal detachment: a pathologic report. Surv Ophthalmol 1967; 12:333–337.
- Yeo JH, Glaser BM, Micels RG. Silicone oil in treatment of complicated retinal detachment with proliferative vitreoretinopathy. Ophthalmology 1987; 94:1109–1113.
- Casswell AG, Gregor ZJ. Silicone oil removal: 1. The effect on the complications of silicone oil. Br J Ophthalmol 1987; 71:893–897.
   Casswell AG, Gregor ZJ. Silicone oil removal: 2. Operative and postoperative
- Casswell AG, Gregor ZJ. Silicone oil removal: 2. Operative and postoperative complications. Br J Ophthalmol 1987; 71:898–902.
- 219. Fan RFT, Chung H, Tolentino FI et al. Effectiveness of silicone oil removal from rabbit eyes. Graefes Arch Clin Exp Ophthalmol 1987; 225:338–340.
- 220. Silicone Study Group. Silicone Study report 9. The prognostic utility of the Silicone Study classification system: results of a randomized clinical trial. Arch Ophthalmol 1996; 114:286–292.

Novartis Exhibit 2317.0025 Regeneron v. Novartis, IPR2021-00816