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REVIEW ARTICLE

The concept of heavy tamponades—chances and limitations

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Abstract
Background Proliferative vitreoretinopathy in the inferior retina remains clinically challenging. Heavier than water intraocular tamponades have been developed to improve inferior tamponading properties. In addition to inferior PVR, there seem to be other applications such as persistent macular holes or PVR in trauma eyes.
Materials and methods Review of the literature on clinical application of heavy tamponades. The review also discusses the theoretical background of heavy tamponades and possible future developments.
Results The parameters of an optimal intraocular tamponade are defined, and the influences of the specific gravity, buoyancy, interfacial tension, and viscosity are discussed. Perfluorocarbon liquids and partially fluorinated alkanes were associated with tamponade emulsification, intraocular inflammation, and rise in intraocular pressure that was less prominent in admixtures of these substances with silicone oil (heavy silicone oils). Two recently developed heavy silicone oil tamponades, Oxane HD and Densiron 68, are well-tolerated and have entered clinical practice. The side effects are associated with the chemical properties of the tamponading agent, and seem comparable to the ones seen with conventional silicone oil.
Conclusion Heavy silicone oil tamponade improves inferior tamponade, and may be considered a new generation of intraocular tamponades.

Keywords Retina · Intraocular tamponade agents · PFCL

Introduction

Intraocular tamponade agents have been used by vitreoretinal surgeons for a long time. Traditional agents that are successfully used for most cases include gases such as sulphur hexafluoride (SF_6), perfluoropropane (C_3F_8), and silicone oil. All these substances float upwards in the vitreous cavity, as they are lighter than water due to their lower specific gravity. This results in a good tamponade of the upper retina, while the patient is in an upright position, but a less effective support of the lower retina. SF_6, as a short-acting gas with a tamponade duration of 2 weeks, therefore is appropriate for retinal holes in the upper periphery, and should not be used for holes below the meridian without thorough positioning. Thus, for retinal holes in the lower retina, heavier than water tamponade agents offer a more logical approach of sealing the hole and thus preventing the development of proliferative vitreoretinopathy (PVR). In the past, investigation in the use of fluorinated silicone oils as a heavy tamponade revealed high complication rates, with the development of intraocular inflammation and the development of PVR [10, 29].

Subsequently, a second group of heavier substances, the perfluorcarbon liquids (PFCL), have gained an important role as a tool for intraoperative manipulation of the retina. However, there are reports of retinal degeneration after longterm use that prevents their use as tamponade agents [4].

Semifluorinated alkanes are a group of substances with a specific gravity greater than water but less than PFCL which have a good retinal tolerability [54]. A pilot study

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into the use of one such substance, perfluorohexyloctane (F6H8), as a long-term tamponade in humans with complicated retinal detachments, demonstrated favourable re-attachment rates, but was associated with early and extensive emulsification, with dispersion of droplets into the anterior and posterior chamber [19]. Heavy silicone oils as admixtures of silicone oil with semifluorinated alkanes may combine a better tolerance with a satisfactory inferior tamponade. This review discusses the current options and future approaches, as well as limitations in the use of heavier than water tamponades.

Physical properties of tamponades and clinical consequences

Physical properties of an optimal tamponade

The effectiveness of an internal tamponade agent depends on its ability to displace aqueous from the retinal surface.

The following physical parameters influence this function:

– Specific gravity
– Buoyancy
– Interfacial tension
– Viscosity

1. Specific gravity

This governs whether a vitreous substitute will sink or float in aqueous, and will determine the shape of any intraocular bubble. If compared to water (specific gravity of 1.00), the specific gravity of aqueous and vitreous are a little higher than this (very close to Octane HD™). The gravity of silicone oil in comparison is a little lower (0.97). The specific gravity of F6H8 (1.35) or perfluorodecaline (1.93) is significantly higher than the gravity of water. The higher the specific gravity of the solution, the better the contact is with the retina.

There is an ongoing debate whether the specific gravity is responsible for retinal changes and retinal damage described after tamponade with perfluoro-octane, perfluorodecalin (PFD), and semifluorinated alkanes. Stolba et al. recently demonstrated that filling with either 0.8 ml or 0.2 ml perfluorophenanthrene led to retinal damage, depending on the amount of tamponade [40]. The different results in different areas of the retina were interpreted as being related to specific gravity. This contrasts with an in vivo study investigating retinal degeneration in long-term vitreous tamponade, perfluorohexyloctane (F6H8), perfluorodecalin (PFD), and a mixture of F6H8/PFD. In this study, histology of the retina showed that alterations in the cell counts within the inner and outer nuclear layer were not attributable to the gravity of the tamponading agent, concluding that gravity might not be causally linked to retinal damage [25]. Interestingly, Wong and co-workers strengthened this finding when they demonstrated in a model eye chamber that a complete filling with F6H8 increased the pressure on the retina by only 0.52 mmHg [49]. These increases in pressure are only a small part of the total intraocular pressure and its diurnal variation [7, 49].

2. Buoyancy

An intraocular bubble of tamponade agent is acted upon by two opposing forces: buoyancy (upward force) and the gravity on the bubble (downward force). Archimedes states that the buoyant force exerted on a submerged object is equal to the weight of the displaced fluid (aqueous). The net result is the force with which the bubble presses against the retina. For silicone oil the "pressing" force is relatively small, as the specific gravity is close to that of aqueous. Thus, a bubble of silicone oil is rounded when in contact with water [45]. This also applies to heavy silicone oil. The force is greatest with air or gas, as the specific gravity is very low at 0.001.

3. Interfacial tension

For any agent to be effective as a tamponade, it must be immiscible with water. For example, an aqueous viscoelastic solution (such as hyaluronic acid) cannot act as a tamponade, even though it does possess some necessary qualities such as high viscosity and cohesiveness. If an agent is immiscible with water, it will form an interface with it, and the term "interfacial tension" refers to the surface free energy between the agent and water. An agent with a high interfacial tension will have a greater tendency to stay as one large bubble, and will resist dispersion into small bubbles. Such an agent will not readily pass through small gaps (e.g. retinal holes) because to do so, it would need to deform its surface, and this too is resisted by a high surface energy. Gas or air has the highest interfacial tension against water at around 80 mN/m, whereas PFCL and silicone oil are lower around 40–45 mN/m and 35 mN/m respectively.

4. Viscosity

The tendency of a substance to emulsify and disperse into droplets over time is also dependent on its viscosity. The less viscous a substance, the lower the energy that is required to disperse a large bubble of the substance into small droplets. For example, F6H8 has a low viscosity of 2.5 mPas, close to that of water (1 mPas), in contrast to the high viscosity of silicone oil (5,000 mPas). Once dispersed, the small droplets will tend to re-coalesce back as a large bubble. However, once coated by surfactants the small droplets remain dispersed and can pass through retinal breaks or (e.g.) through the zonules into the anterior segment. Furthermore, there is evidence to suggest that this dispersion causes inflammation and activation of neutrophils [21].

Clinical problems associated with inferior retinal holes

The basic role of any tamponade agent is to make contact with the retina and prevent passage of aqueous through the break. Another important role is to displace water from the vicinity of the break, as aqueous contains a pro-inflammatory milieu that is responsible for the development of PVR. It is thought unlikely that direct pressure against the retina plays any great part in break closure [49, 52]. It is logical to assume that a floating tamponade would be most effective for pathology of the upper fundus, and a sinking tamponade most effective for that of the inferior fundus.

Recently, the management of inferior breaks with pars plana vitrectomy, air tamponade and without postoperative posturing has been advocated, and received with enthusiasm [28]. The technique puts emphasis on the suggestion that adhesion and sealing with photocoagulation may be instant. It asserts that tamponade is not necessary. However, even if the tamponade is not directly displacing aqueous away from the retinal break, it may act to reduce fluid currents. The tamponade prevents sufficient intraocular fluid currents from gaining access to the subretinal space through open breaks in vitrectomised eyes. Whilst this strategy may work for rhegmatogenous retinal detachment without any static traction, it would be inappropriate to use this technique in the presence of PVR.

The gravitational limitations of current lighter than water agents means that they make poor contact with the inferior retina, particularly in an under-filled eye. In fact, some would argue that a sustained total fill can never really be achieved, and when silicone oil is used there is a tendency for aqueous fluid to accumulate beneath the bubble. This makes a floating tamponade less useful for the closure of inferior retinal breaks, and especially given the limitations of postoperative posturing. The inferior retina is exposed to growth factors that have been measured under silicone oil [1]. The inferior retina is therefore the prime site for harbouring tractional breaks as a result of PVR, and the most common site for re-detachment following internal tamponade with silicone oil. A heavier than water agent should be a more effective tamponade in the management of inferior retinal breaks by displacing aqueous upwards and away from the inferior retinal breaks, conferring a big advantage in the management of PVR.

Development of a “heavier than water tamponade” with good retinal tolerabiliy

Model eye chamber studies have given insight into the relationship between interfacial tension, specific gravity and the effectiveness of tamponade agents. Previous attempts to find a heavy endotamponade have failed either because of intrinsic toxicity of the agents or inflammation that might be predisposed by dispersion: perfluorodecalin has been proposed as an efficient intermediate tamponade (Charles S, personal communication); however, due to its long-term toxicity [4], a less retinotoxic heavy tamponade agent might be advantageous in this setting. Semifluorinated alkanes are less retinotoxic, but clinically associated with early and extensive emulsification [19]. Experimental studies have demonstrated that partially fluorinated alkanes, due to their capacity to dissolve in silicone oil, result in admixtures with diverse properties regarding emulsification, tissue penetration and mobilization of oligosiloxanes and long-term stability [15]. However, these admixtures could combine advantages of a heavy tamponade and the tolerability of silicone oil.

Fluorosilicone oil was one of the first agents proposed for temporary tamponade, but did not reach a widespread clinical use [24]. Heavy silicone oil (HSO) is a transparent homogenous solution of two substances used as a single tamponade agent with improved properties. The combination of different substances, each with unique physical properties, allows the desirable properties of the individual components to be used to a maximum advantage, and their limitations to be overcome to a greater or lesser extent.

There are currently three products licensed. Densiron 68, Densiron 68 (LV) and Oxane HD. Oxane HD® is a mixture of ultra-purified silicone oil (Oxane 5700) and RMN3, a partially fluorinated and hydrocarbonated olefin with a density of 1.02 and a viscosity of 3,300 mPas. Densiron® 68 has been designed to take advantage of the high specific gravity of F6H8 and the high viscosity of silicone oil. The resulting solution has a density of 1.06 (higher than water) and a viscosity of 1,400 mPas (substantially higher than F6H8) (Fig. 1). Densiron 68 LV is a mixture of silicone oil (Siluron 1000) and F6H8 with a density of 1.05 g/cm^3 and a viscosity of 300 mPas at 25°C. Densiron 68 allows a visible interface against perfluorodecalin and perfluoro-octane, permitting a direct exchange without turbidity at the interface [18]. Experiments using model eye chambers designed to replicate the vitreous cavity have shown that Densiron behaves rather like an inverted silicone oil bubble, in that it sinks inferiorly and exerts pressure on the inferior retina [44].

Heavy silicone oil in complicated inferior retinal detachment

The prime indication for the use of HSO is in the treatment of inferior rhegmatogenous retinal detachments complicated by PVR [2] (Fig. 2). Similarly, in cases where postoperative posturing is deemed necessary and the patient is unable to adopt a face-down position, then HSO may have a role to

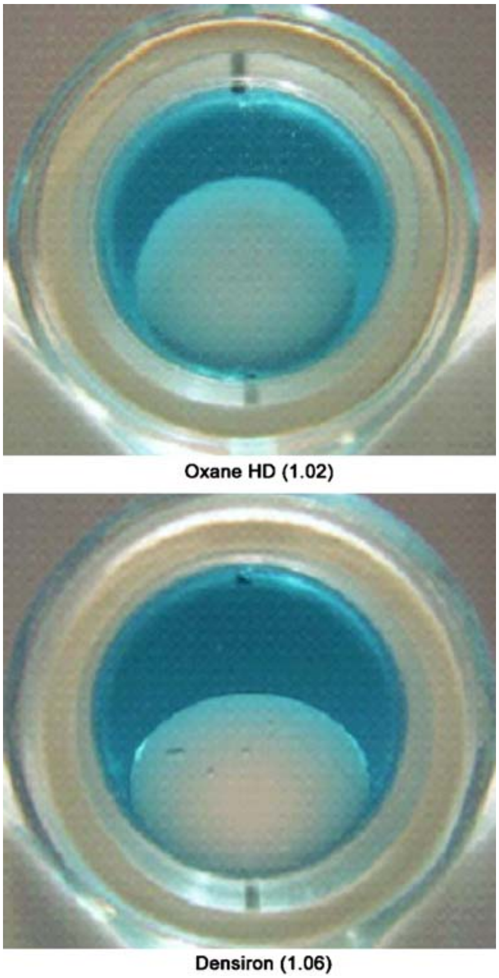

Fig. 1 Oxane HD® has a density of 1.02 and a viscosity of 3300 mPas, in contrast to Densiron® 68 with a density of 1.06 and a viscosity of 1400 mPas. This results in a more round bubble of Oxane HD in water compared to a more flat bubble of Densiron 68

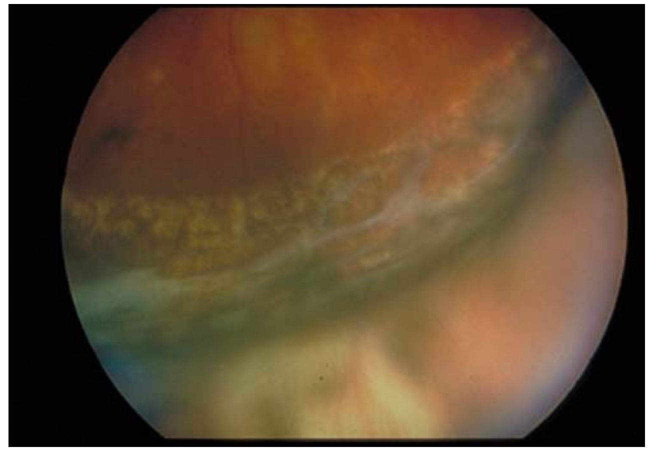

Fig. 2 Clinical appearance of an inferior retinotomy central to the encircling band after tamponade with heavy silicone oil. There are no active epiretinal membranes

play. The forte of HSO may well lie in the sequential use of a light and then heavy tamponade agent in succession for eyes with retinal detachment and PVR, where conventional agents such as silicone oil of gas have failed and resulted in inferior re-detachment [51, 52]. In this situation, the superior retina and macula region are often well-attached, and replacement of the conventional agent with HSO would displace the aqueous superiorly to where the retina is most secure, and provide tamponade to the detached retina and, critically, the macula.

In the first report on the use of Oxane HD, Wolf et al. demonstrated that, in 33 eyes with PVR detachment, macular attachment was achieved in all eyes [48]. A similar report on 28 patients demonstrated a primary re-attachment in 15 patients when Oxane HD was removed after an average of 88 days [33]. There are similar results of pilot studies into the use of Densiron [37, 52]. The non-controlled study by Wong and co-workers describes the use of Densiron in 42 consecutive patients with retinal detachment resulting from inferior breaks and PVR. The mean duration of tamponade was 72 days. Anatomical success was achieved in 81% (43 patients) after one operation, and 93% (39 patients) with further surgery [52]. A slightly less favourable success rate was reported by Sanders et al. In their series, they had an anatomical success rate of 45.8% without further intervention after primary surgery using Densiron tamponade, and 22.9% recurrent re-detachment with Densiron tamponade in situ [37]. Overall, the results concur with other, smaller pilot studies utilizing slightly different compounds [16, 36, 42, 48].

Up to now, the largest groups contain over a hundred clinical cases and long-term observations for 12 months [13, 37, 50] demonstrating a high anatomical success of up to 87.6%. Compared to conventional silicone oil, the use of heavy silicone oil is associated with a higher anatomical success but a similar number of adverse effects. Whether early optimism regarding HSO is realized depends on whether its safety and efficacy are sustained across larger numbers and longer follow-up. A multicentered randomized control study, the Heavy Silicone Oil Study is currently under way [17].

Heavy silicone oil for various clinical applications

There are several non-comparative interventional studies demonstrating a role for HSO in various retinal diseases other than PVR. Preliminary observations on the use of HSO in trauma eyes demonstrated promising results (Heimann et al., personal communication). However, first observations using heavy silicone oil in an iatrogenic trauma model (choroidal patch translocation) (Joussen et al., in press Br J Ophthalmol) has demonstrated that the use of heavier than water tamponade agents in patients with a high risk of PVR results in a shift of the PVR milieu from the lower part of the retina to the upper part.

Giant retinal tears managed with traditional floating tamponade agents are associated with high re-detachment rates as a consequence of their predilection for PVR development. PFCL is well established as an intraoperative tool in the management of giant retinal tears.

Despite the aforementioned concerns about retinal toxicity, this role has been successfully extended to short-term postoperative tamponade, with reduced re-detachment rates [35, 39]. Here HSO could eventually reduce PVR rates compared to standard silicone oils; however, randomized controlled trials are required to finally solve this question.

Another potential role for HSO might be for macular hole surgery, in cases where traditional vitrectomy and gas tamponade have failed [32]. Still, the advantages over surgery with platelets for example have to be investigated. Treatment of retinal detachment arising from macular holes in high myopia has been described [5, 47]. All of the above indications will need randomized trials to demonstrate whether there HSO is superior to conventional tamponades.

Limitations of heavy silicone oil

Heavy silicone oil shares some limitations with silicone oil, such as the inability to fit into small recesses and make uninterrupted contact with the retina [9, 44]. However, this relatively poor contact with the retina is not wholly disadvantageous, as it allows a thin film of aqueous to remain in contact with the retinal surface, thought to be important for retinal cell equilibrium that is considered to be dependent on the potassium siphoning of retinal Müller cells [46].

Sticky silicone oil, leaving remnants of silicone oil on the retinal surface and in the worst case on the macula, has been reported by various surgeons for conventional silicone oil as well as for heavy silicone oil. In the experience of the authors, sticky silicone oil is mostly seen in patients with posterior vitreous remnants that allow for adhesion with the retinal surface. Another reasoning for “sticky silicone oil” is given by an in vitro study using gas chromatography-coupled mass spectroscopy of the headspace (GC/MS/HS) and gel permeation chromatography (GPC) to detect volatile compounds in silicone oil samples explanted from patients, which demonstrated higher concentrations of perfluorodecalin in seven “sticky” samples than in 14 non-sticky samples [8]. The observed stickiness of silicone oil seems to be a matter of reduced surface tension of the surrounding aqueous material and/or contamination of silicone oil with perfluorocarbon liquid, which creates interruption of the material flow, giving the impression of adherence of the silicone oil to the retina. Clinically, both sticky conventional silicone oil as well as sticky heavy silicone oil can be easily removed from the retina after displacement with semifluorinated alkanes or perfluorocarbons.

The removal of heavy silicone oil requires special attention and the use of elevated vacuum relatively close to the retina. To avoid complications like inadvertent touching of the retina or sudden pressure loss, “tubeless siphoning” allows the use of small-gauge short needles at greater distance from the retina (Wong et al., in press Br J Ophthalmol).

There are several well-recognized complications associated with the use of conventional silicone oils, including cataract, glaucoma, uveitis and emulsification into droplets that can be similarly found to various extents after heavy silicone oils.

After tamponade with Oxane HD keratic precipitates (KP), pigmented clumps in the inferior part of the anterior chamber and increased anterior chamber cellular reaction that did not react to topical steroids were observed. These inflammatory precipitates resolved completely after removal of the tamponade [41].

The influence of human serum albumin and hydrofluorocarbons on monocyte activation has been discussed [20]. In vitro experiments, however, did not support the hypothesis that emulsification of the tamponades silicone oil or F6H8 in the microenvironment of the eye might easily activate neutrophils or stimulate phagocytosis by monocytes. A prerequisite for activation of inflammatory cells is the combination of a vesicle shape of the tamponades with specific stabilizing or modifying surfactants. Emulsified tamponades stabilised by artificial surfactants, but not by human serum albumin, favor cell activation by cell membrane attachment [21].

Retrolental and epiretinal membranes were a prominent feature of F6H8 use [14, 21]; this was not observed with Densiron. The relatively high viscosity and stability of the solution formed by mixing F6H8 with silicone oil make it much less prone to dispersion. This could be the main reason for the lesser degree of inflammation seen after the use of Densiron. Majid et al. reported on an emulsification rate of only 20% after 12 weeks tamponade with Densiron [27]. Data concerning the stability and homogeneity of Oxane HD is currently ongoing [43], as well as a randomized control trial (RCT) comparing the complication rates of Densiron and Oxane HD (Tilanus et al., personal communication).

In their pilot study into the use of Densiron, Wong et al. found that all phakic patients developed slight nuclear sclerotic cataract, with posterior subcapsular changes in the early postoperative period similar to that seen with conventional silicone oil [52]. Similar observations of early cataract and adhesion of HSO to the posterior capsule or intraocular lenses have been reported by others in clinical and experimental observations [22, 38, 53].

An intraocular pressure >30 mmHg was noted in 14% (six patients) in the early postoperative period, and persisted at 3 months post Densiron removal in 5% (two patients). In every case, raised IOP was successfully managed with medical therapy [50].

Newer products that can have theoretical advancement over the currently available HSO are already being studied with respect to their side effects.

Future developments in the use of heavy tamponades

Double filling with perfluorodecalin and silicone oil has been suggested as a method of achieving superior and inferior retinal tamponade in phakic eyes [11, 30]; however, this was not recommended for long-term use due to the retinal toxicity of perfluorodecalin. As expected, combined tamponade with silicone and fluorosilicone oil has demonstrated that this double filling creates a new residual fluid space, lying horizontally between the bubbles and expanding in a triangular shape nasally to the optic disc and temporally to the macula [3, 6]. Double filling with F6H8 and silicone oil demonstrated comparable results [12, 33, 34]. Interestingly, the combined use of F6H8 and silicone oil demonstrated a reduced emulsification rate in vitro [23]. This supports again the concept that compartmentalisation is of major importance in determining postoperative cell proliferation.

In order to generate new silicone oils with less side effects and better tolerability, several admixtures on the basis of the perfluoalkanes F4H5, F4H6 and F4H8 have been generated and investigated in vivo [26]. The F4Hn species have a better solubility in silicone oil compared to F6H8, and are thus prone to create high-density silicone oils. Interestingly, all silicone oils based on F4H5 (HSO45 with 1,000, 3,000 and 5,000 mPas) were well-tolerated, whereas all oils based on F4H6 and F4H8 showed greater inflammatory reactions and retinal complications. Obviously, biocompatibility is dependent on the lipophilic behaviour (RF/RH ratio) and furthermore on the molecular dimension of the semifluorinated alkanes (SFAs) which are used. Nevertheless, in a pilot study with 32 patients with inferior PVR detachment, even HSO 46 (Heavy silicone oil on the base of F4H6) with 3,000 mPas was well tolerated, and resulted in a primary attachment rate of 84.6% without emulsification and intraocular inflammation [31].

There is a complex correlation between viscosity and density for perfluorobutylalkanes/silicone oil mixtures (Fig. 3). For stable heavier than water silicone oils with a high density and an adequate viscosity (about 1,000 mPas) at the same time, silicone oils with a high viscosity and semifluorinated alkanes with extremely good solubility are required.

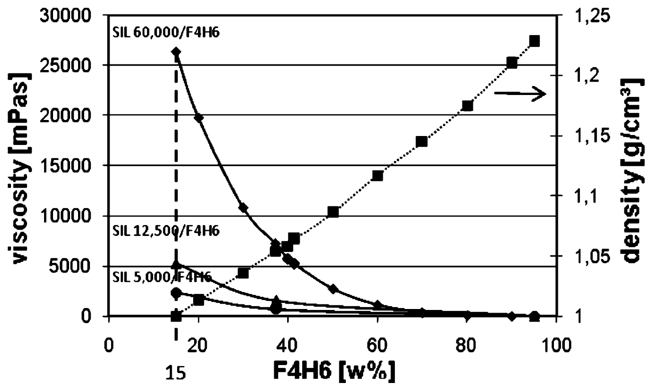

Fig. 3 Correlation between viscosity and density for perfluorobutylalkanes/silicone oil mixtures. The viscosity and density of several F4H6 mixtures with silicone oil 5,000, 12,500 and 60,000 mPas are plotted. The *squares* present the density of all three F4H6/silicone oil mixtures. That is possible because all used silicone oils (5,000, 12,500 and 60,000 mPas) have the same density of 0.97. For example, a silicone oil 60,000/F4H6 mixture with the concentration of 30 weight % F4H6 has a viscosity of 12,500 mPas and a density of 1.04 (Figure provided by B. Theisinger, Fluron GmbH)

If comparing conventional silicone oil, most surgeons switched from the use of 1,000 mPas to 5,000 mPas, as the higher viscosity results in a reduced emulsification tendency.

It would be desirable to have silicone oil that is more liquid, but still does not emulsify. The fluorosilicone oil proposed by Peyman and coworkers did not enter larger clinical trials due to retinal toxicity [24].

New silicone oils based on high molecular weight silicone chains resulting in an overall viscosity of 2,000 Pst could eventually combine the advantage of a silicone oil less prone to emulsification and a low viscous oil that allows use with (e.g.) 23-gauge instruments. These high-molecular weight silicone admixtures have a densitiy of 0.97 and are lighter than water, but have a higher resistance against emulsification. One could similarly think of heavy oils generated in a similar way that might then combine a reduced emulsification with a better inferior tamponade.

Conclusion

In conclusion, heavy silicone oils allow for better tamponade of the inferior retina. Still, side effects such as cataract formation, emulsification, and secondary glaucoma, previously seen with conventional silicone oils and semifluorinated alkanes, are seen with heavy silicone oil as well. Whether heavy silicone oils prevent PVR or rather cause a shift of the PVR to the upper retina will be shown in randomized clinical trials. Improvements can be expected from new silicone oils with altered physical properties.

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