BioMed Research International

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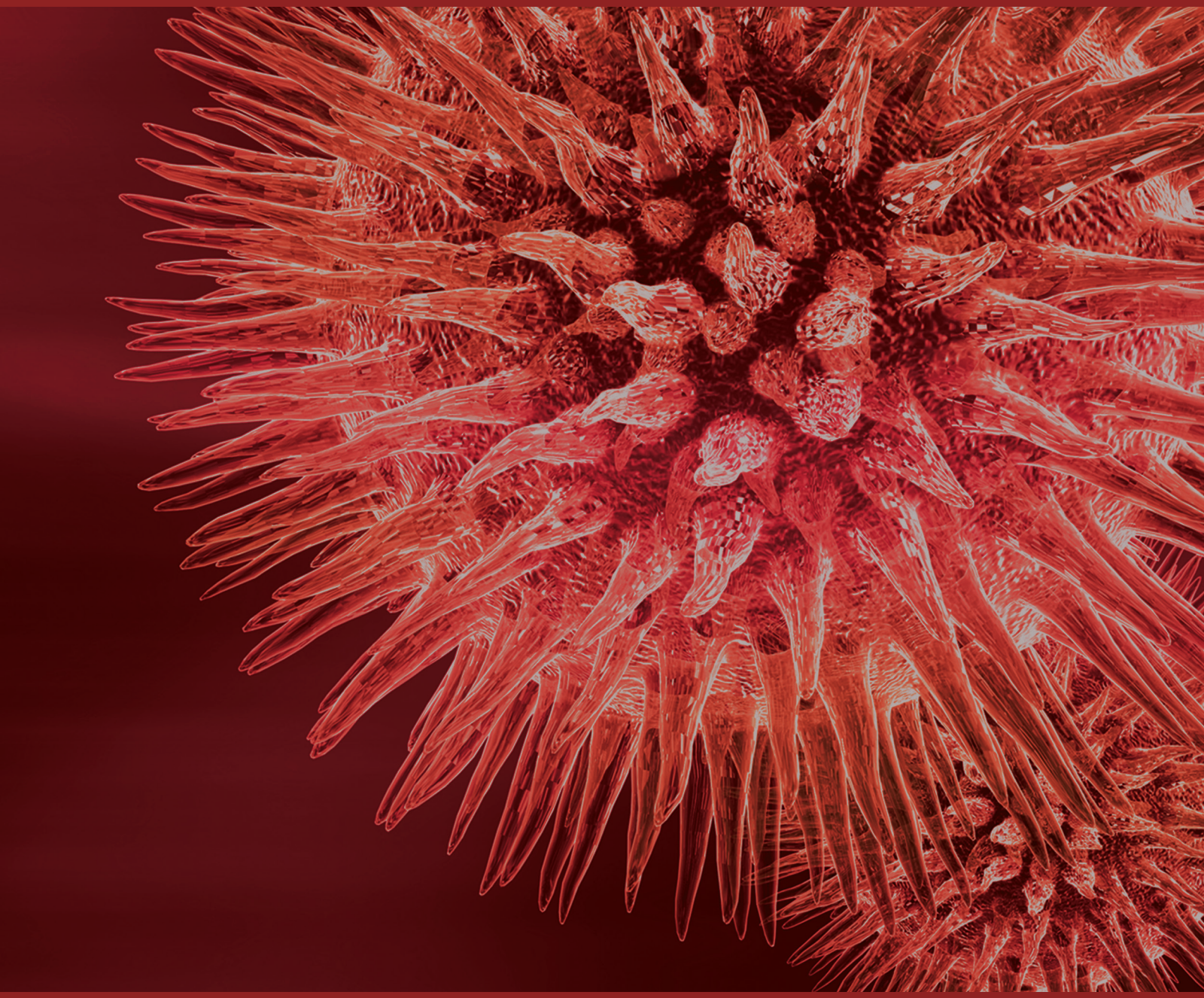
Guest Editors: Mario R. Romano, Xun Xu, and Kenneth K. W. Li



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Contents

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Editorial

Vitreous Substitutes: From Tamponade Effect to Intraocular Inflammation

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Vitreous substitutes have been developed both as an intraoperative and as a postoperative tool for the surgical treatment of complicated vitreoretinal diseases. The tamponade effect of the vitreous substitutes depends on the arc of contact between the agent and the inner retinal surface, which mainly depends on 4 physical parameters, namely, specific gravity, buoyancy, interfacial tension, and viscosity. As reported by F. Barca et al., the choice of different intraocular tamponade agents depends on the location of retinal break(s), compliance of postoperative posture, type of vitreoretinal disease(s), and duration required for the tamponade. Due to the hydrophobic property of intraocular tamponade agent, a thin aqueous layer invariably exists between the tamponade agent and the retina. This thin aqueous layer is further exaggerated in highly myopic eyes with posterior staphyloma to become a pocket of fluid leading to a theoretical reduction of the tamponade effect. However, the debate remains open on whether it is still worthwhile to use silicone oil in these eyes as X. Valldeperas and J. Lorenzo-Carrero reported contradicting results. An increased improved anatomical success using silicone oil in highly myopic eyes in their study was probably due to the lower shear retinal stress of the compartmentalized fluid, scarcely influenced by ocular movements, allowing the macular hole to close and the retinal detachment to reattach.

Based on this hypothesis, K. Isakova et al. reported a theoretical model that predicted the stability conditions of the interface between the aqueous and a vitreous substitute. They showed that the presence of a thin layer of aqueous between the retina and intraocular tamponade is responsible for significant reduction in the retinal shear stress. Their model also explains the instability of the interface leading to the formation of intraocular emulsion that remains the main drawback of the use of intraocular tamponade agents. Although the tolerance for vitreous substitutes remains generally good, the recent introduction of new mixed compounds, such as heavy silicone oil (HSO), has been associated with relatively high complication rates. In particular, emulsification and severe inflammatory reactions can lead to poor functional prognosis. According to L. Ambrosone et al., the spontaneous formation of water-silicone oil is a rare event and the very low concentration of surface-active agents cannot account for the systematic production of emulsions. The authors suggested that gravitational instability, originated at the interface by tangential disturbances, plays a more significant role in the formation of emulsions.

Semifluorinated compounds and perfluorocarbon liquids (PFCLs), mainly used only as intraoperative tamponades, are more prone to induce inflammation and emulsification.

As reported by M. S. Figueroa and D. R. Casas, PFCLs have also been used as postoperative short-term tamponade agent with development of up to 30% inflammation and retinal infiltration due to foreign-body reaction, sustained by macrophages that phagocytosed the PFCL droplets. Q. Yu et al. suggested that the physical properties of these tamponade agents, mainly the low viscosity and surface tension, reduce their stability and the superficial forces and could lead to

significant clinical findings such as intraocular inflammation, raised intraocular pressure (IOP), and sticky oil formation.

From a retrospective study conducted on 100 eyes, H. Schwarzer et al. concluded that HSO does not induce alarming complications in the majority of cases. However, they suggested that long-term tamponade with HSO will require more frequent follow-up because of its high incidence of IOP elevations or intraocular inflammation. In fact D. Odrobina and I. Laudańska-Olszewska reported, at 3 months after the surgery, the topographic evidences of persistence of small hyperreflective round shaped SO droplets above the optic nerve and in the cystoid retinal spaces. Despite good anatomical success rate with HSO, J. Prazeres et al. reported a 52% rate of emulsification and 40% rate of keratic precipitates in their series with a 16% incident of IOP elevation. Interestingly F. Morescalchi et al. also reported more disturbing complications of HeavySil, a combination of high purity 75% silicone oil 5000 cSt and 25% perfluoroalkyloxyoctane, including early optic disc swelling, retinal edema, and intraretinal inflammation with diffuse narrowing of arteries and veins. The challenges of tamponade research remain the provision of a wider arc of tamponade and long-term intraocular permanence with inertness of the compound while at the same time providing uniform transport of nutrients to intraocular tissue. Despite years of effort, we still remain far from providing good solutions for these "solutions." S. Donati et al. reported that a promising alternative to the present compounds could be the smart hydrophilic polymers. They are capable of swelling by absorbing its own weight in water, with further possibilities of a thermosetting and with interactive properties with the environment (glucose, glutathione), pH, and light. These properties allow the molecules to be modulated inducing the gelification, better drug diffusion, and increased gel expansion. Perhaps the real solution for an ideal tamponade agent may involve a paradigm shift away from traditional agents.

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Research Article

Mechanical Models of the Dynamics of Vitreous Substitutes

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We discuss some aspects of the fluid dynamics of vitreous substitutes in the vitreous chamber, focussing on the flow induced by rotations of the eye bulb. We use simple, yet not trivial, theoretical models to highlight mechanical concepts that are relevant to understand the dynamics of vitreous substitutes and also to identify ideal properties for vitreous replacement fluids. We first recall results by previous authors, showing that the maximum shear stress on the retina grows with increasing viscosity of the fluid up to a saturation value. We then investigate how the wall shear stress changes if a thin layer of aqueous humour is present in the vitreous chamber, separating the retina from the vitreous replacement fluid. The theoretical predictions show that the existence of a thin layer of aqueous is sufficient to substantially decrease the shear stress on the retina. We finally discuss a theoretical model that predicts the stability conditions of the interface between the aqueous and a vitreous substitute. We discuss the implications of this model to understand the mechanisms leading to the formation of emulsion in the vitreous chamber, showing that instability of the interface is possible in a range of parameters relevant for the human eye.

1. Introduction

Retinal detachment is a serious, sight threatening condition that occurs when fluid enters the potential space between the neurosensory retina and the retinal pigment epithelium. Posterior vitreous detachment is primarily responsible for the generation of tractions on the retina that might produce retinal tears. These can possibly evolve into retinal detachment, since the detached vitreous often displays tight attachment points with the retina, where concentrated mechanical stimuli occur [1]. In the general population, nontraumatic phakic rhegmatogenous retinal detachment occurs in about 5.4 out of 100,000 persons and is among the most frequent causes of blindness in Western countries [2].

Surgery is the only viable way to treat retinal detachment [3]. One of the most common surgical treatments consists in removing the vitreous gel from the eye, peeling epiretinal traction, flattening the retinal detachment and closing retinal tears, and inducing chorioretinal adhesion. Materials that form an interface with the aqueous environment of the eye can be effective in closing retinal breaks and holding the retina in place against the retinal pigment epithelium. They are called vitreous substitutes or tamponade fluids.

Various vitreous substitutes are employed in the surgical practice, with largely different mechanical properties [4, 5]. In particular, artificial vitreous substitutes can be classified into three categories: gases, liquids, and gels. Polymetric hydrogels are only used as a support for sustained drug delivery in the vitreous. Currently, the most commonly used fluids employed as vitreous substitutes are gases, silicone oils, perfluorocarbon liquids, and semifluorinated liquids. Gases and perfluorocarbon liquids are used as short-term substitutes, especially during intraoperative procedures. Semifluorinated liquids, owing to their toxicity, are also only used as short-term vitreous substitutes.

At present, the only long-term vitreous substitutes widely employed in the clinical practice are silicone oils. They have suitable properties of chemical stability and transparency and have a high surface tension with the aqueous humour, which is a desirable property. The rational of using silicone

oil as intraocular tamponade is to interrupt the open communication between the subretinal space/retinal pigment epithelial cells and the preretinal space with the aim of securing, in the first few days after surgery, chorioretinal adhesion induced by cryo- or laser treatment. Depending on the location of the retinal break oils with different densities (either higher or lower than the aqueous) can be adopted [6, 7]. Proper patient posture is required after the injection, in order to maintain the contact of the tamponade with the retinal break. Direct contact between the tamponade fluid and retina is indeed difficult to determine. Due to the oil hydrophobicity a thin layer of aqueous is likely to form between the retina and vitreous substitute. This is irrelevant where the retina is attached to the pigment epithelium but is crucial in correspondence with the break. It has been shown theoretically and experimentally that, the supported area of the retina is strongly affected by the contact angle between the oil and the retina [8].

The mechanical properties of tamponade fluids (density, viscosity, and surface tension with the aqueous) influence the efficiency of the treatment and, therefore, a full understanding of the mechanical implications associated with the surgery is desirable. With the present work we aim at clarifying, from a purely mechanical point of view, the implications of adopting tamponade fluids with different mechanical properties. The problem is extremely complex even if only mechanics is accounted for, and, therefore, we proceed in this paper by introducing simple theoretical models that shed some light on specific, yet crucial, aspects of the problem.

We start by considering the effect of viscosity of the tamponade fluid on the mechanical actions exerted on the retina during eye rotations.

Due to the limited tamponade effect of silicone oils we then investigate further factors leading to the successful surgery. In particular, we investigate the changes of the maximum wall shear stress when silicone oils are used, accounting for the possible presence of a thin layer of aqueous separating the retina from the tamponade fluid.

The success rate of surgery when silicone oils are used is about 70%. One of the common problems after vitrectomy, especially in the long run, is the formation of an oil emulsion. The reasons why this happens when silicone oils are used as tamponades are still unclear. A further aim of this paper is to present a simple theoretical model that predicts the role of oil properties (particularly, viscosity and surface tension) in the process of emulsion formation. To this end we study the stability of the interface between two superposed immiscible fluids set in motion by movements of the eye.

2. Materials and Methods

The results presented in this paper are based on solutions of the mathematical equations that govern the motion of fluids. Fluid dynamics is a very well developed branch of physics, the modern foundations of which date back to the 19th century. The so-called Navier-Stokes equations, named after Claude-Louis Navier and George Gabriel Stokes, are known to accurately model the motion of a viscous fluid described as a continuum body. These equations are mathematically very complex and admit closed-form solutions, that is, solutions that can be expressed analytically in terms of known functions, only in very special cases. If an analytical solution of a problem can be found, its dependency on the controlling parameters (e.g., in the present case the size of the vitreous chamber, the viscosity of the fluid, and so forth) can be easily determined, without the need of computational simulations, and physical insight on the problem is therefore effectively obtained. In this paper we discuss some analytical solutions of the Navier-Stokes equations, which are relevant to understanding the dynamics of vitreous substitutes.

We consider purely viscous fluids, that is, fluids whose mechanical properties are completely characterized by the density ρ (mass per unit volume) and the (dynamic) viscosity μ (which is a measure of resistance to flow) and in which the stress is linearly proportional to the rate of deformation. Water, aqueous humour, and oils fall into this category.

Fluid motion in the vitreous chamber can be driven by different mechanisms, in particular, rotations of the eyeball or thermal differences between the anterior and posterior segments of the eye. However, it can be shown by simple order-of-magnitude arguments that the motion induced by eye rotations is much stronger than the thermally driven flow [9] and, therefore, we restrict our attention to the former. Eye rotations induce motion in the fluid contained in the eye owing to the so-called no-slip boundary condition, according to which fluid particles in contact with a rigid wall (e.g., the vitreous chamber wall) move at the same velocity as the wall itself. In other words, fluid particles do not flow across the wall and they do not slip over it.

We consider three different, relatively simple, models that shed light on important aspects of the dynamics of vitreous substitutes in the vitreous chamber. Proper interpretation of results from experimental or more complex theoretical models requires a full understanding of the results presented here. The details of the mathematical models are briefly reported in the appendices.

Model 1. We first review results obtained by previous authors concerning the case of a rigid hollow sphere of radius R, modelling the vitreous chamber, filled with a fluid and study fluid motion generated by small-amplitude, periodic, torsional oscillations of the sphere (see Figure 1(a)). This problem has been studied in [10, 11] for the case of viscoelastic fluids. In reality, the vitreous chamber is not perfectly spherical, particularly owing to the indentation produced in its anterior part by the lens. The effect of departure from the spherical shape on fluid motion has been studied theoretically and experimentally by several authors [12–16]; however, for the present purposes and for the sake of the simplicity, it is sufficient here to consider a spherical shape. Fluid motion generates stresses on the wall, which we determine analytically. We discuss the qualitative characteristics of the flow and show the dependency of the stress at the wall on fluid viscosity.

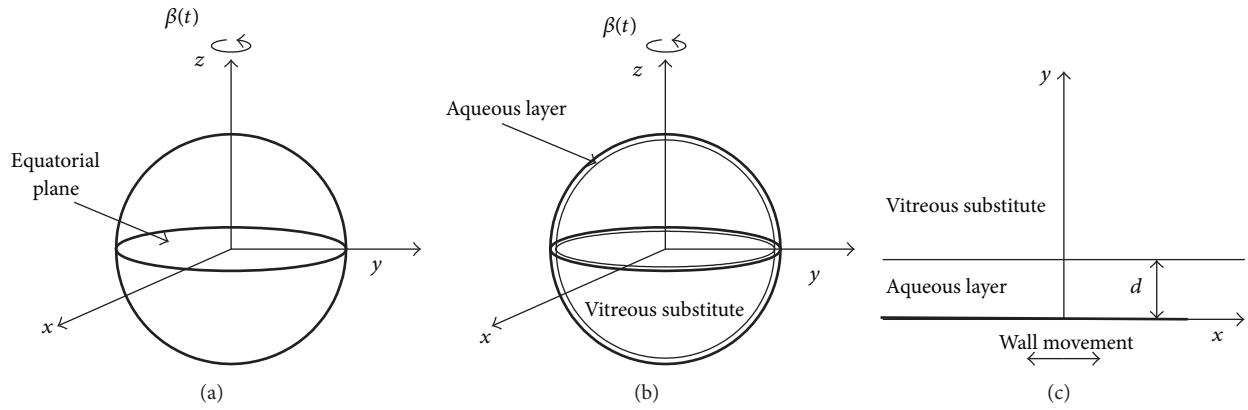

Figure 1: Sketch of the three models adopted in the paper.

Model 2. We then investigate how the stress on the wall is modified when a second fluid is present within the domain (see Figure 1(b)). This typically happens when a hydrophobic vitreous substitute, such as silicon oil, is injected into the vitreous chamber: a thin layer of aqueous close to the wall separates the vitreous substitute from the retina. In order to model this condition we adopt an idealized geometry consisting of a rigid sphere filled with two immiscible fluids (aqueous and vitreous substitute) arranged concentrically, with the aqueous in the external layer. In other words we assume that the thickness d of the aqueous is uniform. This allows us to solve the problem for the motion of the two fluids analytically. We then compute the wall shear stress on the equatorial plane.

Model 3. Finally, we study the stability of the interface between the aqueous layer and the vitreous substitute, when the two fluids are set in motion by eye rotations. For the sake of simplicity we assume that the thickness of the aqueous layer is much smaller than the eye radius, which is often a realistic assumption, and, as a first approach to the problem, we neglect the curvature of the retinal surface and consider a flat wall (see Figure 1(c)). The configuration of the interface between the two fluids is assumed to be perturbed by small (formally infinitesimal) sinusoidal waves (normal mode analysis) and we study whether the amplitude of these disturbances grows or decays in time. In the former case we infer instability of the system, and in the latter we infer stability. Some details of the mathematical analysis, which is quite technical, are given in the appendices. Instability of the interface may be considered as a possible incipient condition leading to the breakdown of the interface and can, therefore, represent a route towards emulsification. We note that the model is based on a so-called linear stability analysis: this allows us to establish whether perturbations will grow or decay in time (the model actually predicts exponential growth or decay), providing a threshold value for the onset of instability. The model allows us to establish how the interface stability conditions depend on the properties of the vitreous substitute, particularly, its surface tension with the aqueous and its viscosity.

3. Results and Discussion

3.1. Wall Shear Stress in a Periodically Rotating Sphere. We first consider the motion of a fluid contained in a sphere of radius R, performing periodic rotations of amplitude A and frequency ω. If the rotation amplitude A is small, it can be shown that, at leading order, the fluid velocity vectors are everywhere orthogonal to the axis of rotation [10, 11]. In other words, the velocity has only the azimuthal component. Moreover, the velocity oscillates with the same frequency as the sphere rotations. In Figures 2(a) and 2(b) we plot velocity profiles attained in a viscous fluid on the equatorial plane orthogonal to the axis of rotation. We note that this is the plane where the stress on the wall attains its maximum value. In the figure we show the variation of the azimuthal velocity in the radial direction and each curve corresponds to a different time within the period. The velocity is zero at the centre of the domain ($r = 0$) and has the same velocity of the wall at $r = R$. In the two cases the frequency is kept constant and is equal to 20 rad/s, which is a realistic value for real eye rotations. In Figure 2(a) we use a viscosity typical of a silicon oil ($\mu = 0.96$ Pa·s [17]), whereas Figure 2(b) is obtained assuming the viscosity of water ($\mu = 0.001$ Pa·s). In the two cases the velocity profiles are significantly different. In the high viscosity case they are almost straight lines; in other words the fluid moves almost as if it was a rigid body. On the other hand, when the viscosity is small, a thin layer forms at the wall in which the fluid moves and the velocity in the core of the domain is vanishingly small. This layer is referred to as an oscillatory boundary layer. The thickness of the oscillatory boundary layer at the wall is of order $\delta \sim \sqrt{(\mu/\rho\omega)}$. This means that similar results could have been obtained by keeping fixed the viscosity of the fluid and changing the frequency of oscillations. In fact, the problem is governed by a single dimensionless parameter α, the Womersley number, defined as $\alpha = \sqrt{((\rho R^2 \omega)/\mu)}$, which can be physically interpreted as the ratio R/δ, between the radius of the sphere

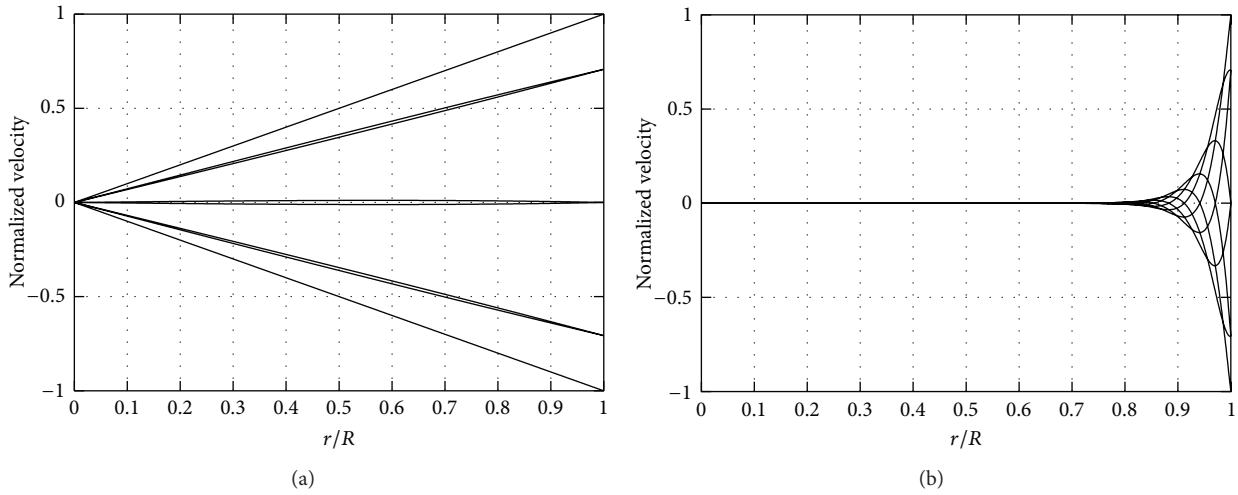

Figure 2: Velocity profiles in radial direction. $r = 0$ corresponds to the centre of the sphere and $r = 1$ corresponds to the location of the wall. The velocity is normalized with the maximum velocity at the wall. In both figures we assumed that the sphere contains purely viscous fluids and that the frequency of rotations is equal to 20 rad/s. (a) Silicon oil, $\mu = 0.96$ Pa·s; (b) water, $\mu = 0.001$ Pa·s.

and the thickness of the oscillatory boundary layer. Flows characterized by the same value of the Womersley number have identical velocity profiles.

In purely viscous fluids, whatever the value of the viscosity, the maximum of the velocity is invariably attained at the wall ($r = R$). We note that the real healthy vitreous is a viscoelastic fluid [18, 19], that is, a fluid in which the state of stress depends on the history of deformation. In other words viscoelastic fluids have a "fading" memory. Figure 6 in the paper by Meskauskas et al. [11] is the equivalent of Figure 2 of the present paper but is obtained taking into account the viscoelasticity of the fluid and adopting values of the vitreous properties obtained in [19] from ex vivo experiments on porcine eyes. The velocity profiles show striking qualitative differences with respect to those obtained for purely viscous fluids (Figure 2 of this paper). In particular, in the case of a viscoelastic fluid, the maximum velocity can be attained in the core of the domain and not at the wall. This phenomenon is due to a resonant excitation of vitreous motion. When resonance occurs, large values of the stress are attained on the boundary of the domain, that is, on the retina.

In Figure 3 we show how, in a viscous fluid, the maximum shear stress at the wall changes with fluid viscosity. This figure is equivalent to Figure A.2 in the paper by Abouali et al. [15]. Since the shear stress depends linearly on the viscosity of the fluid and also on the spatial derivatives of the velocity profile, predicting if the stress will increase or decrease with the viscosity is not obvious. In fact, Figures 2(a) and 2(b) show that as the viscosity decreases the derivative of the velocity at the wall increases. The results reported in Figure 3 show that the maximum shear stress at the wall increases nonlinearly with the viscosity and attains an asymptotic value for very viscous fluids. This maximum asymptotic value can be shown to be $A\rho\omega^2R^2/5$ (see also [15]). This implies that the adoption of high viscosity fluids as vitreous substitutes induces the generation of larger mechanical stresses on the retina. In the figure we report with vertical lines the cases corresponding

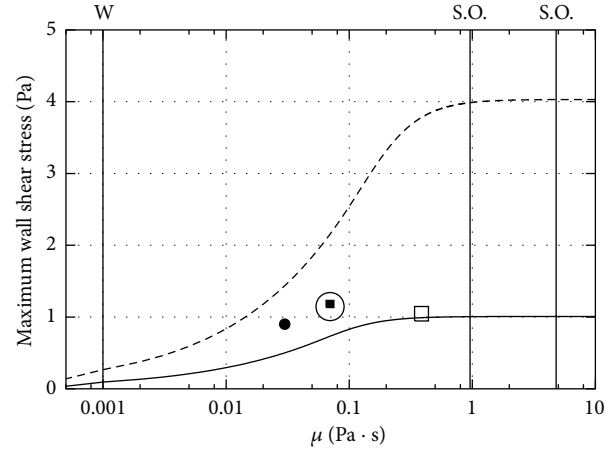

Figure 3: Dependency of the maximum shear stress at the wall on the viscosity in the case of a purely viscous fluid. The two curves correspond to two different values of the frequency of eye rotations (dashed line 20 rad/s; solid line 10 rad/s; A = 20 deg = $\pi/9$ rad). W: water; S.O.: silicon oils ($\rho = 960$ Kg/m^3, $\mu = 0.96$ Pa·s, and $\mu = 4.8$ Pa·s). In the figure we also report with symbols the values of the maximum wall shear stress obtained in the case of a viscoelastic fluid and adopt the rheological properties measured in [18, 19]. Solid square: complex viscosity $\mu^* = 0.39 - i$ Pa·s, $\omega = 10$ rad/s [18]; empty square: $\mu^* = 0.07 - 0.28i$ Pa·s, $\omega = 10$ rad/s [18]; solid circle: $\mu^* = 0.07 - 0.28i$ Pa·s, $\omega = 12.57$ rad/s [19]; and empty circle: $\mu^* = 0.03 - 0.064i$ Pa·s, $\omega = 12.57$ rad/s [19].

to water and to two often used silicon oils (0.96 and 4.8 Pa·s) [17]. It appears that in the cases of the two oils the maximum stress on the retina is an order of magnitude higher than in the case of water. However, the differences between the two oils are small since, in both cases, the value of the maximum stress on retina is almost equal to the maximum possible asymptotic value.

Finally, we report in Figure 3 also points corresponding to the viscoelastic case, adopting for the rheological properties

of the vitreous the values measured in [18, 19]. In these cases there is also an elastic component of the stress, the effect of which is to slightly increase the maximum wall shear stress with respect to the purely viscous case.

3.2. The Effect of the Existence of a Thin Layer of Aqueous between the Retina and the Vitreous Substitute. In the previous section we have discussed how the stress on the retina depends on the viscosity of a vitreous substitute, under the assumption that the fluid completely fills the vitreous chamber. In particular, we have shown that the mechanical actions on the retina grow with increasing fluid viscosity. In reality the situation is more complicated than this because, owing to the hydrophobic nature of vitreous substitutes, a thin layer of aqueous may form between the retina and the vitreous substitute.

We therefore now consider how the scenario described in the previous section is modified when we account for the presence of a thin layer of aqueous close to the retina.

In Figures 4(a) and 4(b) we show azimuthal velocity profiles on the equatorial plane at different times. The position of the interface between the two fluids is shown in the figure with a vertical solid line. The velocity profiles are continuous across the interface between the two fluids, but their slope is not. This is due to differences between the two fluids viscosities (we assumed in the figure $\mu_a = 10^{-3}$ Pa·s for the aqueous and $\mu_{vs} = 1$ Pa·s for the vitreous substitute, e.g., a silicon oil). Figures 4(a) and 4(b) differ because a different thickness d of the aqueous layer has been assumed. In the first case (Figure 4(a)) we consider a thickness of the aqueous layer smaller than the thickness δ of the boundary layer that would form at the wall if the aqueous was completely filling the vitreous chamber ($d < \delta$). In this case the motion of the wall is also felt in the vitreous substitute, which moves with a significant velocity. On the other hand, when $d > \delta$, most of the motion keeps confined within the aqueous layer and the velocity in vitreous substitute is very small (Figure 4(b)). In other words in the latter case the vitreous substitute barely feels the motion of the wall.

This has important implications for the wall shear stress at the wall, as it is shown in Figure 5. In the figure we plot the maximum stress at the wall versus the thickness of the aqueous layer. For the sake of clarity, we use dimensionless variables. The stress is normalized with the stress that would be obtained at the wall if the vitreous substitute was completely filling the domain. The thickness of the layer d is scaled with δ, computed as $\sqrt{(\mu/\rho\omega)}$ and using the viscosity of the aqueous. When d/δ tends to zero, the scaled stress obviously tends to 1 (vitreous substitute alone) and the stress on the wall is maximum. However, the figure shows that it is sufficient for a thin layer of aqueous to be present to make the maximum shear stress at the wall drop significantly. When $d/\delta \approx 1$ or greater, the presence of the vitreous substitute is not felt by the wall and the stress drops to the value it would attain in the presence of aqueous alone. This simple model highlights the importance of accounting for the possible presence of the thin layer of aqueous at the wall in the calculation of the stress on the retina.

3.3. Stability of the Interface between Aqueous and Vitreous Substitute. The presence of an aqueous layer separating the vitreous substitute from the retina was shown in the previous section to have an important effect on the shear stress on the retina. It is also known that one of the main complications after injection of long-term vitreous replacement fluids (particularly silicon oils) is the possible occurrence of emulsification. This implies that the oil-aqueous interface might break, eventually leading to the formation of oil droplets dispersed in the aqueous. There are several possible causes of generation of an emulsion, with one of them being introduction of mechanical energy into the system that breaks down the oil aqueous interface [20]. Many authors have hypothesized that shear stresses at the tamponade fluid-aqueous interface generated during eye rotations play a crucial role in the generation of an emulsion [21, 22].

In order to investigate the feasibility of this assumption and determine which parameters play a role in the breakdown of the interface, we present in this section results from an idealized, yet informative, theoretical model. As discussed in Section 2 we assume that the aqueous layer in contact with the retina is much smaller than the radius of the eye and we neglect the curvature of the eye wall, treating the problem as two-dimensional (see Figure 1(c)). We perturb the flat configuration of the interface between the two fluids with a sinusoidal wave and investigate whether the amplitude of this wave grows or decays in time, with the aim of identifying threshold conditions for instability as the values of the controlling parameters are changed.

The problem of the stability of the interface is governed by the four dimensionless parameters introduced and described in the appendices. Here we discuss the role of two of them: $m = \mu_{vs}/\mu_a$, which is the ratio between the viscosities of the two fluids, and $S = \sigma/(\rho d U^2)$, which represents a dimensionless surface tension at the interface, where σ denotes the dimensional surface tension between the two fluids, ρ denotes fluid density, d is the thickness of the aqueous layer, and U is the maximum wall velocity. We note that, for the sake of simplicity, we neglect possible differences between the densities of the two fluids, thus effectively neglecting the role of gravity. The other dimensionless parameters that govern the stability problem are set to values that are reasonable for real eye rotations.

Our stability analysis shows that very long waves on the interface are invariably unstable during certain phases of the oscillation cycle. In other words the amplitude of very long disturbances always grows in time. We note that in the absence of an interface this stability problem consists in the stability of the so-called "Stokes boundary layer," that is, the flow of a single fluid over an oscillating wall. This problem has been largely studied in the literature [23] and it is known to be stable in the range of parameters considered here. Therefore, we can conclude that the instability mechanism is indeed related to the existence of the interface. Very long waves might not be able to form within the eye globe, owing to the three-dimensionality of the domain (they will not effectively fit in the eye). Short waves, on the other hand, are stabilized by the surface tension acting on the interface. In Figures 6(a) and

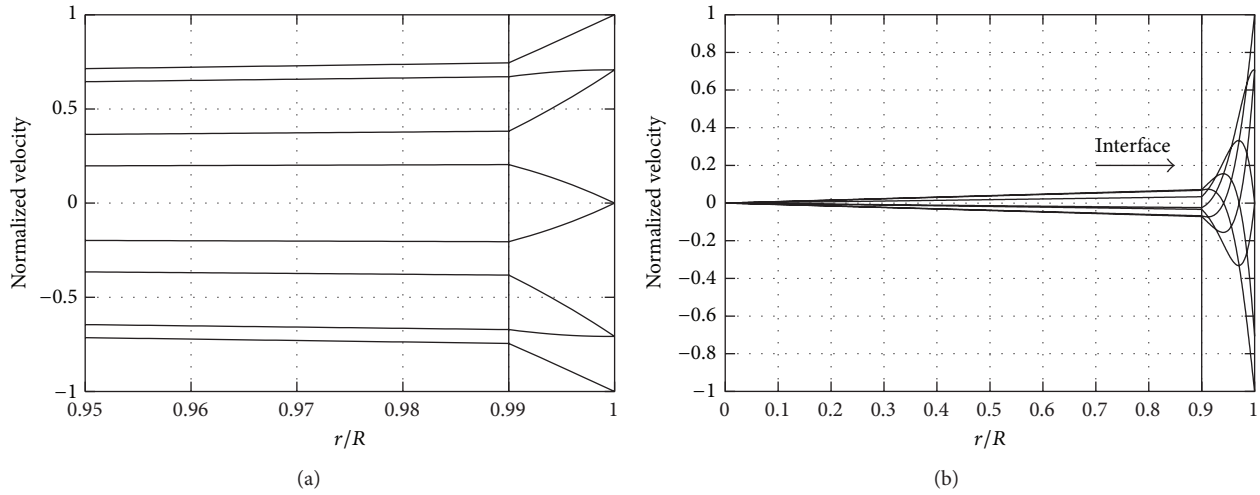

Figure 4: Velocity profiles in radial direction in the case in which the vitreous chamber contains two immiscible fluids. $r = 0$ corresponds to the centre of the sphere and $r = 1$ corresponds to the location of the wall. The velocity is normalized with the maximum velocity at the wall. The frequency of rotations is equal to 10 rad/s. Vitreous substitute $\mu = 1$ Pa·s; water, $\mu = 0.001$ Pa·s. (a) $d = 0.01R$ and (b) $d = 0.1R$.

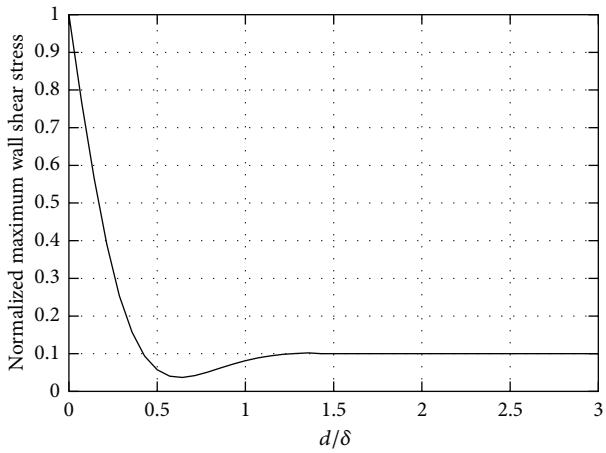

Figure 5: Maximum stress at the wall versus the thickness of the aqueous layer. The stress is normalized to 1, and the thickness of the layer d is scaled with δ, computed using the viscosity of water. Vitreous substitute $\mu = 0.96$ Pa·s; water, $\mu = 0.001$ Pa·s.

6(b) we show how the length of the shortest unstable wave depends on the controlling parameters. In particular we focus on the role of the two dimensionless parameters S and m.

Figure 6(a) shows that, as the value of the (dimensionless) surface tension decreases, instability progressively affects shorter perturbations. This can be interpreted as follows. When the surface tension decreases, the interface effectively becomes more unstable, since even relatively short waves are predicted to be unstable and thus their amplitude is expected to grow in time. The stabilizing role of the surface tension too is not surprising in the light of results from stability analyses performed on similar problems [24].

In Figure 6(b) we show the effect of changing the ratio m between the viscosities of the two fluids. Note that the viscosity of silicon oils is much larger than that of water. The figure shows that as m increases the system becomes more stable, again meaning with this statement that only very long waves are expected to possibly grow in time. Conversely, for relatively small values of m progressively shorter waves are found to be unstable.

4. Conclusions

In the present paper we have discussed theoretical results from three different idealized mathematical models that, in our view, help in understanding some of the basic features of the fluid mechanics of vitreous substitutes in the eye. We have focused our attention on the flow generated in the vitreous chamber by rotations of the eye globe, which is by far the most important mechanism generating fluid motion.

We first have considered the case in which the whole vitreous chamber is filled with a single fluid and have modelled the chamber as a rigid sphere, performing sinusoidal small amplitude torsional oscillations, similar to what was done by previous authors [10, 11]. We have shown that, when the fluid is purely viscous, the maximum velocity is invariably attained at the sphere wall and the velocity at the centre of the domain is zero. In the limit of very large fluid viscosity the velocity profiles are approximately straight lines and the fluid moves almost as a rigid body. In the opposite limit of low viscosity, an oscillatory boundary layer forms at the wall and the fluid velocity in the core of the vitreous chamber is almost zero. We have shown that the maximum wall shear stress on the retina grows with increasing viscosity of the fluid in a highly nonlinear way and reaches an asymptotic value in the limit of high viscosity fluids, which is easily predicted analytically. This is relevant for the choice of vitreous replacement fluids. In fact the model shows that if the vitreous is replaced with a highly viscous fluid, mechanical actions of the retina should be expected to increase. This is, for instance, the case with silicon oils. In the clinical practice silicon oils with a viscosity

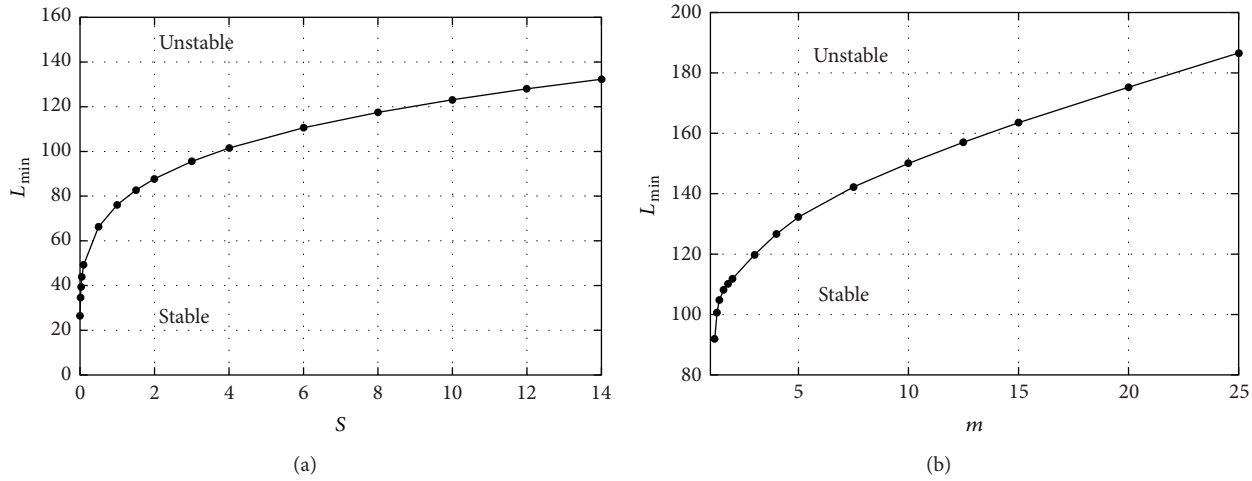

FIGURE 6: Length of the shortest unstable perturbation L_{min}, scaled with the thickness of the aqueous layer d versus S (a) and m (b). $R = 12$ and $\omega = 0.003$ ($m = 5$ (a) and $S = 14$ (b)).

of 1000 centistokes or 5000 centistokes are typically adopted. We remark that in both cases the viscosity is so large that the maximum values of the shear stress at the retina are close to its maximum possible asymptotic values. This means that, in terms of mechanical stresses on the retina, the two oils are equivalent to each other.

We have also briefly recalled how flow characteristics change when a viscoelastic fluid fills the vitreous chamber. The real healthy vitreous has viscoelastic properties, and there is a large body of research devoted to the identification of vitreous replacement fluids with viscoelastic properties. We have recalled that the motion of a viscoelastic fluid can be resonantly excited by eye rotations and, if this happens, large values of the shear stress are expected to develop on the retina. This has important implications for the choice of the ideal properties of vitreous substitutes. Soman and Banerjee [25] and Swindle and Ravi (2007) [26] review all materials currently in use, discuss their advantages and disadvantages, and list the characteristics of an ideal vitreous substitute. In their papers it is mentioned that the ideal substitute should have a large enough elastic component, so as to avoid excessive flow within the vitreous chamber. However, the possible occurrence of resonance as a risk factor for generating large mechanical stresses on the retina is disregarded.

In the second part of the paper we considered the effect of a thin layer of aqueous separating the vitreous substitute from the retina. Since vitreous substitutes are normally hydrophobic fluids and complete filling of the vitreous chamber can be hardly obtained, a layer of aqueous in correspondence with the retina is likely to form. We have shown that, when this is the case, the maximum stress on the retina can be significantly reduced, even if the viscosity of the vitreous replacement fluid is very large. Therefore, the possible existence of an aqueous layer should be accounted for when estimating the mechanical stresses on the retina after injection of a vitreous substitute.

The presence of an aqueous layer and, consequently, of an interface between the aqueous and the vitreous substitute also has a crucial effect in the possible development of an emulsion, which is one of the main drawbacks associated with the use of silicon oils. Making use of a simple mathematical model we have studied the stability of the aqueous-vitreous substitute interface. The results show that the interface becomes more unstable if the surface tension decreases and it becomes more stable if the viscosity of the vitreous substitute is higher. Both results are in agreement with clinical observations. In fact there is evidence that the tendency to emulsification is significantly enhanced by the presence of surfactants that decrease the surface tension between the two fluids [27]. Moreover, clinical experience shows that highly viscous vitreous substitutes are more resistant to emulsification than less viscous ones [28–30]. Obviously, our model only represents in a highly idealized fashion the real behaviour of the aqueous-vitreous substitute interface in the vitreous chamber during eye rotations and we are perfectly aware that reality is much more complex than we have assumed. However, to our best knowledge this is the first attempt to study the instability processes that might lead to the formation of an emulsion in the vitreous chamber and we believe that stability analyses such as the one proposed here can significantly contribute to highlighting the basic physical mechanisms taking place and to guiding the interpretation of more realistic models, as indeed it has been the case in many other physical contexts.

Appendices

A. Model 1

We consider a hollow rigid sphere with radius R performing periodic torsional oscillations of amplitude A and frequency ω about an axis passing through its centre (see Figure 1(a)).

The angular displacement β of the sphere in time is described by the following time law:

$$\beta(t) = -A\cos(\omega t), \tag{A.1}$$

with t time. We assume that the amplitude of oscillations is small ($A \ll 1$).

The motion of a viscous fluid within the sphere is governed by the Navier-Stokes equations and the continuity equation, which read

$$\frac{\partial \mathbf{u}}{\partial t} + (\mathbf{u}\cdot\nabla)\,\mathbf{u} + \frac{1}{\rho}\nabla p - \frac{\mu}{\rho}\nabla^2\mathbf{u} = 0, \tag{A.2a}$$

$$\nabla\cdot\mathbf{u} = 0, \tag{A.2b}$$

subject to the following boundary conditions:

$$u = 0 \qquad (r = R) \tag{A.3a}$$

$$v = 0 \qquad (r = R) \tag{A.3b}$$

$$w = A\omega R\sin(\omega t) \qquad (r = R) \tag{A.3c}$$

$$\text{regularity conditions} \quad (r = 0), \tag{A.3d}$$

where u, v, and w represent the radial, zenithal, and azimuthal components of the velocity, p is pressure, ρ is density, and μ is the dynamic viscosity of the fluid.

Taking advantage of the assumption of small amplitude eye rotations ($A \ll 1$) the above equations can be linearized and solved in closed form. The velocity is purely azimuthal and the solution reads

$$u = v = 0,$$

$$w = -\frac{iA\omega}{2}\left(\frac{R}{r}\right)^2 \frac{R\sin(kr/R) - kr\cos(kr/R)}{\sin k - k\cos k} e^{i\omega t}\sin\theta + \text{c.c.},$$

$$p = \text{const.} \tag{A.4}$$

In the above expression c.c. denotes the complex conjugate, θ is the zenithal coordinate ($\theta = 0$; π identifies the axis of rotation), and

$$k = \frac{\sqrt{2}}{2}\alpha(1 - i), \tag{A.5a}$$

$$\alpha = \sqrt{\frac{\rho\omega R^2}{\mu}}, \tag{A.5b}$$

where α is a dimensionless number named the Womersley number. The corresponding solution for the wall shear stress is

$$\tau = -\frac{\rho A}{2}(\omega R)^2\left(\frac{1}{1 - k\cot k} - \frac{3}{k^2}\right)\sin\theta e^{i\omega t} + \text{c.c.} \tag{A.6}$$

and the maximum of τ is located on the equatorial plane $\theta = \pi/2$. The maximum wall shear stress over a period of oscillation and over space grows with the fluid viscosity ν and reaches the following limiting value $\tau_{\max}$ as $\nu \to \infty$ (with $\nu = \mu/\rho$ being the kinematic viscosity of the fluid):

$$\tau_{\max} = \frac{\rho A}{5}(\omega R)^2. \tag{A.7}$$

The solution for the motion of a viscoelastic fluid is obtained by introducing a complex viscosity (i.e., a complex Womersley number in (A.5a)); see [10, 11] for further details.

B. Model 2

We now take into account the presence of a thin layer of aqueous between the retina and the vitreous substitute fluid. We assume that the two fluids have the same density ρ but different viscosities (μ_a for the aqueous and μ_{vs} for the vitreous substitute). For the sake of simplicity we assume that the aqueous layer is arranged concentrically with respect to the vitreous substitute, as shown in Figure 1(b), so that the aqueous layer thickness is constant and equal to d.

The problem is still governed by the Navier-Stokes equations for the two fluids and, at the interface between the fluids, we impose the continuity of the velocity and the dynamic boundary condition. Assuming again that the sphere rotates according to (A.1) and that $A \ll 1$ the solution can be found analytically and reads

$$u_a = 0 \tag{B.1a}$$

$$v_a = 0 \tag{B.1b}$$

$$u_{vs} = 0 \tag{B.1c}$$

$$v_{vs} = 0 \tag{B.1d}$$

$$w_{vs} = c_1 A\omega\left(\frac{R}{k_{vs}r}\right)^2\left[R\sin\left(\frac{k_{vs}r}{R}\right) - k_{vs}r\cos\left(\frac{k_{vs}r}{R}\right)\right] \times e^{i\omega t}\sin\theta + \text{c.c.} \tag{B.1e}$$

$$w_a = A\omega\left(\frac{R}{k_a r}\right)^2\left\{c_2\left[R\sin\left(\frac{k_a r}{R}\right) - k_a r\cos\left(\frac{k_a r}{R}\right)\right] + c_3\left[R\cos\left(\frac{k_a r}{R}\right) + k_a r\sin\left(\frac{k_a r}{R}\right)\right]\right\} \times e^{i\omega t}\sin\theta + \text{c.c.}, \tag{B.1f}$$

where the subscripts a and vs denote the aqueous and the vitreous substitute, respectively. Moreover, the constants c_1, c_2, and c_3 are determined by the boundary conditions and k_a and k_{vs} are given by (A.5a) and (A.5b) using the viscosity of the aqueous and the vitreous substitute, respectively.

The wall shear stress on the equatorial plane is equal to

$$\tau|_{\theta=\pi/2} = A\mu_a\omega\left[\left(1-\frac{3}{k_a^2}\right)(c_2\sin k_a + c_3\cos k_a) + \frac{3}{k_a^2}(c_2\cos k_a + c_3\sin k_a)\right]e^{i\omega t} + \text{c.c.} \tag{B.2}$$

C. Model 3

We now wish to study the stability of the interface between the aqueous layer and the vitreous substitute. For simplicity we assume that the thickness d of the aqueous layer is much smaller than the radius of the sphere R and, as a first approach to the problem, we neglect the effect of wall curvature and consider a two-dimensional problem in the (x, y) plane (see Figure 1(c)). Thus we consider two immiscible fluids occupying the regions of space $0 \le y < d$ and $y > d$, respectively, with kinematic viscosities ν_a and ν_{vs}, and again assume that the two fluids have the same density. The flow is induced by periodic motion of the rigid wall, located at $y = 0$, with amplitude A and frequency ω.

We work in terms of the following dimensionless variables (denoted by superscript stars):

$$(x^*, y^*) = \frac{(\mathbf{x},\mathbf{y})}{d}, \qquad \mathbf{u}_i^* = \frac{\mathbf{u}_i}{U}, \qquad p_i^* = \frac{p_i}{\rho_1 U^2}, \qquad t^* = \frac{U}{d}t, \tag{C.1}$$

where U is the maximum wall velocity and the subscript i denotes either the aqueous ($i = a$) or the vitreous substitute ($i = vs$). By scaling the governing equations we introduce the following dimensionless parameters:

$$m = \frac{\mu_{vs}}{\mu_a}, \tag{C.2a}$$

$$R = \frac{Ud}{\nu_a}, \tag{C.2b}$$

$$S = \frac{\sigma}{\rho d U^2}, \tag{C.2c}$$

$$\omega^* = \frac{d}{U}\omega, \tag{C.2d}$$

where m represents the ratio between the fluid kinematic viscosities, R is the Reynolds number of the flow (based on the aqueous viscosity), S is a dimensionless surface tension (where σ is the dimensional surface tension on the interface), and ω^* is a dimensionless frequency.

We decompose the flow in a basic state and infinitesimally small perturbation as follows:

$$\mathbf{u}_i^* = \mathbf{U}_i^* + \overline{\mathbf{u}}_i^*, \tag{C.3a}$$

$$p_i^* = P_i^* + \overline{p}_i^*, \tag{C.3b}$$

where capital letters indicate the basic flow and small letters with a bar refer to perturbation quantities.

The basic flow is unidirectional (in the x-direction) and can be solved in closed form. We do not report the details here for the sake of space.

For the stability analysis we consider two-dimensional perturbations $\overline{\mathbf{u}}^* = (\overline{u}_x^*, \overline{u}_y^*, 0)$. This allows us to introduce the stream function ψ, defined as

$$u_{xi}^* = \frac{\partial\overline{\psi}_i}{\partial y}, \tag{C.4a}$$

$$u_{yi}^* = -\frac{\partial\overline{\psi}_i}{\partial x}. \tag{C.4b}$$

We adopt the quasi-steady approach; that is, we assume that perturbations evolve on a time scale that is much smaller than the characteristic time scale of the basic flow. This implies that we study the stability of a "frozen" basic flow at time τ, with $0 \le \tau < 2\pi/\omega$. The suitability of this approach can be verified a posteriori by checking the relative magnitude of the time scale of perturbations with respect to that of the basic flow.

Taking advantage of the assumed infinite extension of the domain in the x-direction we expand the unknowns in Fourier modes as follows:

$$\overline{\psi}_i = e^{i\alpha(x-\Omega t)}\psi_i(y,\tau) + \text{c.c.}, \tag{C.5}$$

where α is the dimensionless wavenumber and Ω denotes the complex eigenvalue of the system, whose real part represents the phase speed of perturbations and whose imaginary part represents the growth rate. Moreover, let $\overline{\eta}^*$ denote the dimensionless perturbation of the interface position, measured in units of d. We impose that

$$\overline{\eta}^* = \eta(t)\, e^{i\alpha(x-\Omega t)} + \text{c.c.} \tag{C.6}$$

The final system of the equations for the perturbation evolution is given by two Orr-Sommerfeld equations, one for each fluid, together with suitable boundary conditions [31]. The system can be written as a generalized eigenvalue problem:

$$\mathbf{A}\mathbf{v} = \Omega\mathbf{B}\mathbf{v}. \tag{C.7}$$

If $\text{Im}(\Omega) < 0$, the system is linearly stable; if, on the other hand, $\text{Im}(\Omega) > 0$, then the system is linearly unstable. Zero values of the growth rate separate the space into stable and unstable subspaces. The system (C.7) is discretized employing a second-order finite-difference scheme with uniform spatial step and is efficiently solved using an inverse iteration algorithm.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Review Article

Some Physicochemical Remarks on Spontaneous Emulsification of Vitreal Tamponades

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The importance of gravitational instability in determining the emulsification of vitreal tamponades is discussed. Theoretical results and numerical simulations indicate that the spontaneous formation of water-silicon oil is a rare event and that the very low concentration of surface active agents cannot justify the systematic formation of emulsions. The gravitational instabilities seem to play the main role. Our theoretical results seem in agreement with the experimental evidences; furthermore they indicate a future research line for the improvement of endotamponades. Indeed, the use of biodegradable antifoam may avoid the formation of bubbles and delay the formation of emulsions.

1. Introduction

Intraocular tamponade agents have been used by vitreoretinal surgeons for a long time to repair retinal detachment, a potentially blinding condition with an incidence reported to be between 6.3 and 17.9 per 100000 [1, 2]. Traditional tamponade agents include gases and silicone oils that, owing to their lower specific gravity, provide good support for breaks or holes located in the upper retina [3]. For retinal holes in the lower retina, tamponades which are heavier than water offer a more logical approach. Among them, perfluorocarbon (PFCL) liquids have an important role for intraoperative manipulation of retina but may induce retinal degeneration after long-term use [4]. Similarly, semifluorinated alkanes such as perfluorohexyloctane (F6H8) are associated with early and extensive emulsification and are therefore not used as long-standing tamponade agents. Conversely, heavy silicone oils, also called fluorosilicones, obtained by mixing silicone oil with semifluorinated alkanes, are well tolerated and offer a satisfactory support for the inferior retina.

Both silicones and fluorosilicones emulsify after incorporation into the eye [5]. However, from the thermodynamic point of view, spontaneous emulsification can only occur under specific conditions depending on the chemical composition of phases and the presence of surface active agents (*surfactants*) [6–8]. What is the mechanism of formation of emulsions in the vitreous cavity? Which are the surfactants in the eye? Herein we focus mainly on the chemical-physical properties of the tamponades to address these questions.

2. Chemical Structure and Surface Properties

The surface properties of silicones (or more exactly organosiloxane polymers), closely related to their unique chemistry, are responsible for many of their applications. The

polydimethylsiloxanes (PDMS) are the most common and possess the most interesting surface properties [9, 10].

The general structure of these colorless liquids insoluble in water is $(CH_3)_3SiO[(CH_3)_2SiO]_nSi(CH_3)_3$, with n approximately 0 to 2500. From comparison with other polymers, one deduces that the surface activity of PDMS approximates that of a relatively close-packed array of methyl groups. These properties are also characteristic of organic polymers, which are however handicapped by thermal and oxidative instability [11]. The fluorocarbons, characterized by lower surface energy than PDMS, have a high interfacial tension in both aqueous and organic solvent systems. In both systems it has been observed that methylsilicones were less emulsified than fluorosilicones of same viscosity, suggesting that the smaller density difference between silicones and intraocular fluid makes intermixing with water more difficult as compared with fluorosilicones [12].

3. Emulsification Formation

Generally an emulsion is defined as two immiscible liquids wherein droplets of one phase (*the dispersed phase*) are spread in a *continuum* of another phase (*the continuous phase*) [13–15]. When silicone oil is introduced in the eye, two basic forms of emulsions are possible. The first is a silicone oil-in-water (o/w) emulsion, in which silicone droplets are dispersed within a continuum of water. The second is a water-in-silicone emulsion (w/o), where water droplets are dispersed in a continuum of silicone. Davis and Rideal suggested that both types of emulsions are formed during the emulsification process, but only the one with the lower coalescence rate survives [16]. Indeed, if the initial concentration of drops is the same for both types of emulsions the coalescence rate ν_1 for type o/w, ν_2 for type w/o, and their corresponding interfacial film lifetimes, τ_1 and τ_2, are inversely proportional:

$$\frac{\nu_1}{\nu_2} = \frac{\tau_2}{\tau_1}. \tag{1}$$

By evaluating τ_1 and τ_2 using the lubrication's theory one proves that the emulsion, where the surfactant is soluble in the continuous phase, will coalesce much more slowly and thus it will survive [16]. In the vitreous cavity silicone oil is in the presence of vitreous liquid; that is to say, a biphasic system is created. The water promotes the formation of w/o emulsions. On the other hand, however, in the vitreous cavity there are also compounds such as phosphatidylcholine and proteins, which form o/w emulsions. The rate of formation of emulsions is proportional to the concentrations of surfactants. Indeed, it was observed that high level of cholesterol in the eye is associated to high rate of emulsions of the type w/o emulsions [17].

4. Free Energy of Emulsion Formation

In order to allow emulsification to occur, a work to increase the interfacial area between two liquids has to be done. Such a process is accompanied by change in free energy of formation:

$$\Delta G^{\text{form}} = \gamma \Delta A - T\Delta S^{\text{conf}}, \tag{2}$$

where γ is the mean interfacial tension, $\gamma\Delta A$ is the work done to increase the interfacial area of ΔA, T is the absolute temperature, and ΔS^{conf} is the entropy change due to the different system configuration. The emulsification process is spontaneous if $\Delta G^{\text{form}} < 0$. This can be achieved only if the work done on the system (in absolute terms) is less than the entropic contribute. This result can be achieved in two ways: by increasing ΔA or by reducing γ. The first is generally obtained by blowing mechanical energy in the system, while the second by means of surfactants which reduce the surface tension. Since mechanical energy blow in the eye is a nonsense, only the second way seems to be possible. Thus the presence of a mixture of surfactants could generate an ultralow (or transiently negative) interfacial tension so that the work, to create the new surface, becomes comparable or even lower than the configurational entropy. In this case the variation of free energy of formation would be zero or negative, and the process would appear to be spontaneous. A rough estimate of the chance that a low interfacial tension in the eye is sufficient to cause spontaneous emulsification can be obtained by calculating the two different terms of (2). Indeed, according to Tadros and Vincent [18], the configurational entropy can be estimated by

$$\Delta S^{\text{conf}} = -nk_B \left[\ln\phi - \frac{1-\phi}{\phi}\ln(1-\phi)\right], \tag{3}$$

where k_B is the Boltzmann constant, n is the droplets number, and ϕ is the volume fraction of the dispersed phase. On the other hand, when n droplets of radius R are formed, the surface increase is $\Delta A = n4\pi R^2$; thus (2) and (3) allow determining the emulsion spontaneity as a function of volume fraction of the dispersed phase, when the interfacial tension γ and the average radius R are known. For in water-emulsions we assume an average radius of 5 μm and calculated the free energy change per droplet as a function of the volume fraction and for various values of interfacial tension.

From Figure 1 it is evident that droplets formation with a mean radius of 5 μm is spontaneous only for interfacial tensions very low, of the order of 10^{-12} Nm^{-1}. In fact, a value of only 10^{-10} Nm^{-1} suffices to make the free energy positive. Such very low values are not achievable, ruling out the possibility that an ultralow interfacial tension is responsible for spontaneous emulsification of liquid tamponades. It is important to note that such a conclusion is valid for any type of liquid tamponade independently of its density or viscosity.

5. Surfactant Role

Generally emulsions formed in the eye have large size; to understand this aspect from physical-chemical point of view, we assume that the disperse phase is a large drop of prolate spheroidal shape [19–21]. The equilibrium geometry of the

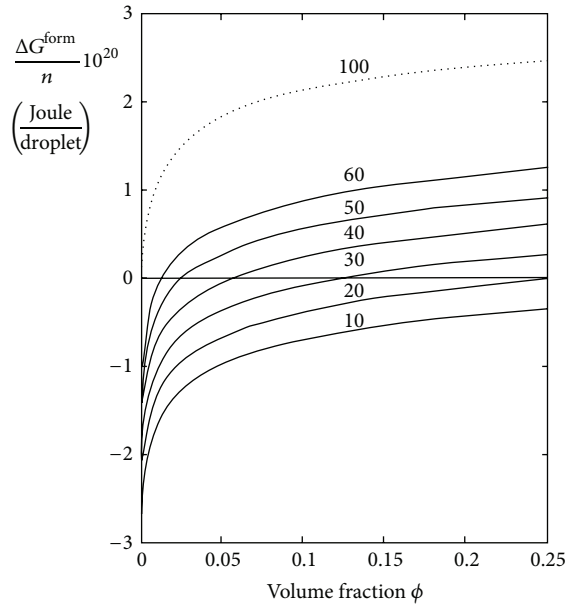

FIGURE 1: Change in free energy for the formation of n water droplets in a heterogeneous system water-silicone oil at 37°C, as a function of volume fraction of droplets of radius $R = 5\ \mu$m.

two phases is dictated by the pressures in the two phases which are related by Laplace equation:

$$\Delta p = \gamma \left(H_1 + H_2\right), \tag{4}$$

where Δp is the difference in pressure between inside and outside of the drop and H_1 and H_2 are the principal curvatures [22, 23]. In the case of a spherical drop $H_1 = H_2 = H$. A large drop can be broken up into many small drops if it is strongly deformed with great values of Δp. But, as one can see from (4), a spherical drop has only one curvature while a prolate spheroid (or even a generic form) has two curvatures so that the stress necessary to deform a small drop is higher than that required to deform a large one. In addition, since the stress is not transmitted directly to the drops but to the liquid surrounding the drops, the energy required to produce the deformation is even higher. However, the surfactant ability to lower the interfacial tension depends on its concentration at the water-tamponade interface as well as on the energetic interactions of the surfactants with the surrounding phases. Although the amount of surfactants present in the eye is not sufficient to disperse the water phase into small droplets, the presence of such substances is of fundamental importance for the stability of the system. Depending on their individual rate of interfacial adsorption as well as their amphiphilicity, different surfactants lower the interfacial tension to a different extent during emulsion formation, thereby affecting the final size distribution of the emulsion droplets. There are obvious differences between the surface properties of a low-molecular-weight surfactant and biomolecules. In small molecules the amphiphilic character of the molecular structure is easily delineated. This simple structure allows the molecule to adopt a low-energy conformation at the interface and its small size leads to high packing density. The structure of a protein emulsifier is obviously more complicated than that of a low-molecular-weight surfactant and can less readily be described by the idealized head-tail model. Hydrophobic groups, consisting of nonpolar amino acids, are distributed throughout the protein molecule, and their ability to access a nonpolar phase at an interface can require complex rearrangements of the native protein. In addition, emulsion formation is directly affected by emulsifier concentration because this concentration determines the surface excess of surfactant and hence the degree to which the interfacial tension is lowered. Another important role of the surfactant is its effect on the interfacial dilatational modulus [24]. During emulsification there is an increase in the interfacial area A and this causes a reduction in the surface excess. The equilibrium is restored by adsorption of surfactant from bulk, but this takes variable times, depending on surfactant concentration. The presence of more than one surfactant molecule at the interface tends to increase the interfacial dilatational modulus. Surfactants may vary in surface activity and this regulates their distribution at the interface. Indeed, surfactants with the lowest γ tend to predominate at the interface, but if present at low concentrations, it may take long time to reach the lowest value. In the vitreous the protein concentration is very low, so that very long times are expected in order to start the process.

6. Hydrodynamic Aspects

Thermodynamic results suggest that spontaneous emulsification process cannot be attributed to the interfacial tension. As a consequence emulsions formation is controlled almost entirely by hydrodynamics factors. Following a vitrectomy intervention only 80–90% of the vitreous is removed; therefore the injection of silicone will form a two-phase system. Such a system is initially gravitationally stable; that is, the heavier fluid is below the lighter one; however, the eye and head movements can reverse this situation. Since head movements are much faster than the readaptation of the fluids in the eye, a gravitational instability is generated (i.e., the heavy fluid may temporarily top the light one) triggering a finger-like convective motion [25, 26]. Such instability receives its energy from the work done by the normal component of gravity at the interface. The major part of this energy is used to overcome the restoring effect of the interfacial tension and dissipation; the remainder is converted into kinetic energy. For the sake of simplicity, let us first consider an extreme type of stratification, namely, a two-layer system (Figure 2), in which initially a lighter layer of silicon floats over another heavier water layer (Figure 2(a)). The density profile (Figure 2(c)) along a vertical axis crossing the interface (for the sake of simplicity is assumed to be flat) is always stable. A head movement leads the eye in the instable configuration (Figure 2(b)). The corresponding density profile (Figure 2(d)) exhibits a *fall* in the point where silicone is sandwiched between two layers of water. This fall becomes an *attractor* for the water (heavy liquid) that acquires greater kinetic energy and the surface area of

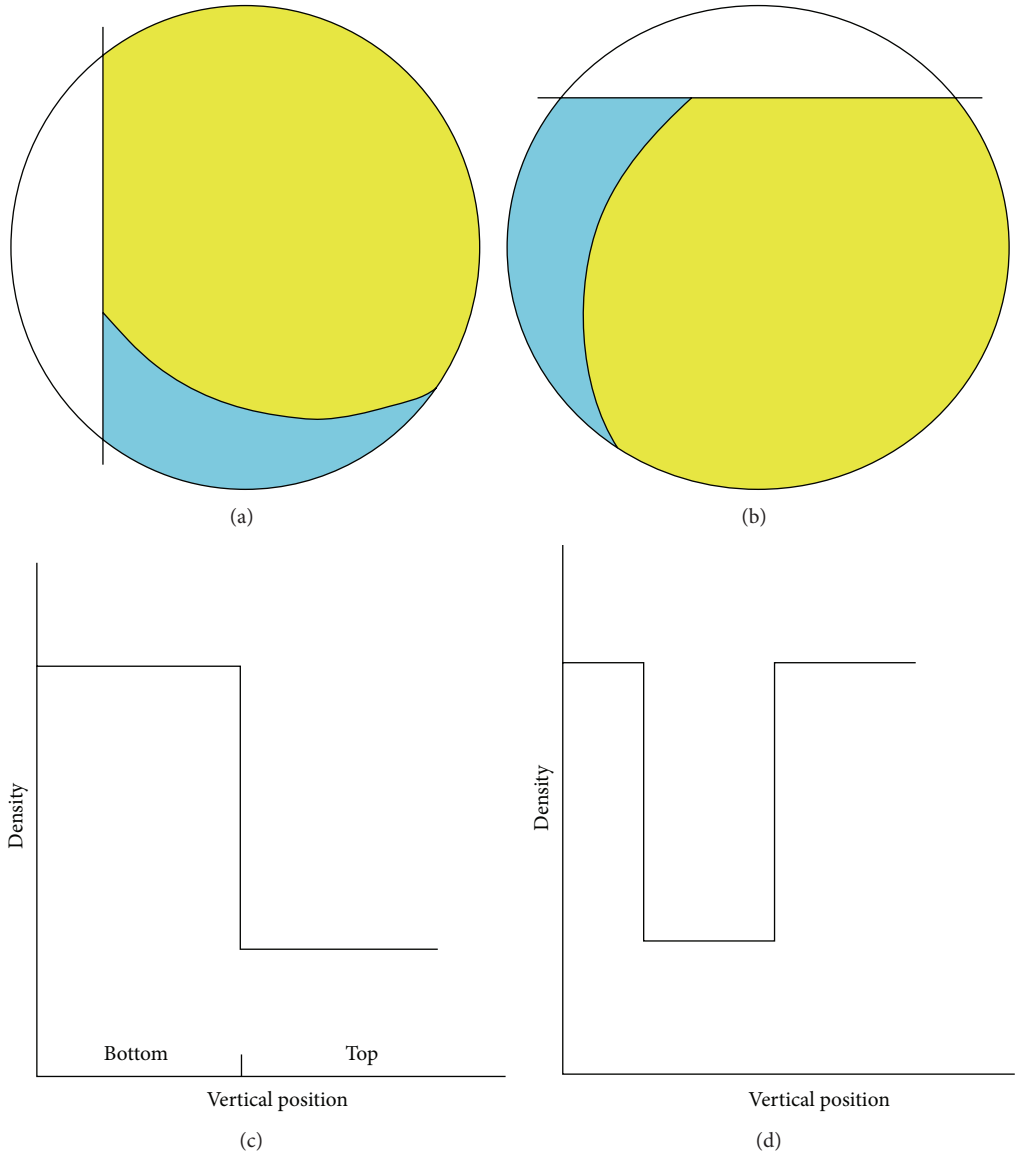

Figure 2: Schematic representation of the eye after vitrectomy and gravitational instability induced by the movement of the head. The blue and yellow colors indicate water silicone, respectively. In the graphs below each "eye" represents density profiles measured along a vertical axis.

water/silicone increases. Of course, the fall does not instantly produce the emulsion, which depends on the time of permanence in that configuration, on the density and viscosity differences between the phases, and on the interfacial tension.

Formation of emulsions may also be favored by a continuous circulation of aqueous humor produced by the ciliary body and drained through the usual routes of outflow. Aqueous humor flow is tangent to the interface water-tamponade and this may induce the deformation of the interface. Indeed, physical principles tell us that gravity waves can propagate on the interface separating these two layers, but if the layers flow at different rate (i.e., when a shear is present), these waves may grow in time and lead to overturning in the vicinity of the interface. These breaking internal waves generate mixing over a height a little shorter than their wavelength (*Kelvin-Helmhotz instability*) [27]. Viscosity-induced instability finds its origin in a viscosity difference between the fluids, creating a jump in the basic-state velocity profile at the interface. Gravity-induced instability originates at the interface and receives its energy from the work done by the component of gravity in the direction of the primary flow in contrast to Rayleigh-Taylor instability, which is driven by the component of gravity perpendicular to the interface. It should be clear, however, that the effect of viscosity jump and effect of density are *coupled*; that is, it is not possible to separate viscosity-induced from gravity-induced instability, in as much as they are different manifestations of the same physical phenomenon. In which way can gravitational instability trigger

the process of emulsification? A possible explanation is the formation of the interfacial tension gradients which result in *Marangoni effect* [28]. If the interface is locally curved, the concave side of the phase provides the surfactant and the curved part will have a higher interfacial tension, since it receives the smallest quantity of surfactant molecules per unit surface area. Hence interfacial transport of surfactant and a flow of liquid dragged towards the point of the strongest curvature will occur leading to an instable situation. A special discussion deserves temperature. Indeed, in recent years it was shown that, during the vitrectomy surgery, the temperature varies by several degrees [29, 30]. This may produce a gradient of density and viscosity to trigger a gravitational instability, *Benard-Rayleig instability* [31]. Since the convection flow has to vanish at the interface between adjacent *rolls*, the emulsion at the interface, and therefore the interface itself, rises at the coalescence velocity. If the temperature gradient is too large, the hydrodynamic torque exerted by counterpropagating flows meeting at an interface exceeds the gravitational restoring torque and destabilizes the interface.

7. Looking the Future

Intravitreous injection of silicone is considered useful for desperate cases of retinal detachment in which more convectional procedures have failed. Vitrectomy with silicone oil removal is also a preferred choice when dealing with retinal detachments occurring because of penetrating traumas especially for breaks which are too posterior to be adequately covered by an explant. The removal of silicon is performed when the silicone oil has completed its function to reattach the retina, usually after 3–6 months. However, there are many elements that speed up or delay the silicone removal (eye pressure, cataracts, vitreoretinal proliferation, and emulsification) [32]. These issues associated with silicone have stimulated the development of new blends using combinations of silicone oil and other liquids. Heidenkummer et al. investigated the emulsification rate of eight silicone oils with specific physicochemical features [33]. They observed that high contents of hydroxyl end groups enhanced silicone-oil emulsification to a greater extent than did phenyl side groups [33]. Their conclusion is in agreement with our theoretical remarks. Indeed, hydroxyl end groups decrease the silicone oil hydrophobicity, then bind more strongly water molecules reducing the interfacial turbulence. In short, it reduced the starting rate of instability. More recently, Caramoy et al. [34] studied the viscoelastic behavior of silicone oils and concluded that blends of silicone oil and high molecular mass silicone oil can be used as endotamponade in vitreoretinal surgery. These novel materials have the same viscosity of silicone oils but a lower tendency to emulsification. Once again, the cause is not attributable to the interfacial tension but the local elasticity. This in turn is due to dilatational elasticity, namely, a hydrodynamic property. In recent years, research is moving towards blends of high molecular weight silicones. Combining two liquids, the solution takes advantage of the high density of silicone blend but it can be challenging to remove. Currently, it is being removed using strong active aspiration through a long 18-gauge needle just above the optic disc, which increases the risk of iatrogenic damage to the optic nerve. Understanding what are the conditions that stabilize the system means to find the conditions to avoid the formation of foam. In the future, we will try to use a biodegradable antifoam to reduce the formation of emulsions without losing the advantage of a low molecular mass silicone oil.

8. Conclusion

We propose that gravitational instabilities play the main role for the formation of emulsions in vitrectomized eyes filled with liquid tamponades. The instability is induced by tangential disturbances originated at the interface and is driven by the rate at which work is done by the velocity and stress disturbances in the direction of primary flow. Theoretical remarks performed herein have shown that the spontaneous emulsification of silicone oil is not due to lowering of the surface tension but due to a hydrodynamic instability. Our theoretical results seem in line with the experimental evidences; furthermore they indicate a future research line for the improvement of endotamponades. Indeed, the use of biodegradable antifoam may avoid the formation of bubbles and delay the formation of emulsions.

Conflict of Interests

None of the authors have a propriety financial interest in the development or marketing of any of the products mentioned in the paper.

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Review Article

Heavy Silicone Oil and Intraocular Inflammation

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In the past two decades, many advances have been made in vitrectomy instrumentation, surgical techniques, and the use of different tamponade agents. These agents serve close retinal breaks, confine eventual retinal redetachment, and prevent proliferative vitreoretinopathy (PVR). Long-acting gases and silicone oil are effective internal tamponade agents; however, because their specific gravity is lower than that of the vitreous fluid, they may provide adequate support for the superior retina but lack efficacy for the inferior retina, especially when the fill is subtotal. Thus, a specific role may exist for an internal tamponade agent with a higher specific gravity, such as heavy silicone oils (HSOs), Densiron 68, Oxane HD, HWS 45-300, HWS 46-3000, and HeavySil. Some clinical evidence seems to presume that heavy tamponades are more prone to intraocular inflammation than standard silicone if they remain in the eye for several months. In this review, we discuss the fundamental clinical and biochemical/molecular mechanisms involved in the inflammatory response after the use of heavy tamponade: toxicity due to impurities or instability of the agent, direct toxicity and immunogenicity, oil emulsification, and mechanical injury due to gravity. The physical and chemical properties of various HSOs and their efficacy and safety profiles are also described.

1. Introduction

The introduction of silicone oil (polydimethylsiloxane, PDMS) to retinal detachment surgery in the early 1980s was one of the main steps in the effective treatment of this pathology [1–4]. In the last three decades, vitreoretinal surgery combined with PDMS tamponade has become the widespread treatment for complicated cases of retinal detachment caused by a proliferative process. Silicone application mainly serves two functions. The first is the displacement of the retina toward the eye-wall by its surface tension effect and volume displacement, and the second, to a lesser degree, is the tamponade of the superior retina by its flotation force.

More than 30 years of clinical use has demonstrated that the tamponade effect of PDMS is usually sufficient, provided that the retina is completely mobile and provided that no new membranes develop. Moreover, the stability and immunological tolerability of PDMS make it relatively safe as a long-term internal tamponade. Histological examination of the human retina after more than 3 years of PDMS endotamponade did not show significant morphological alterations [5]. Intraretinal or intracellular deposits suggestive of silicone have been observed in attached retinas only if subretinal silicone deposition occurred in accidental situations [5].

However, PDMS and long-acting gases provide good support only for the superior retina and lack efficacy for the inferior retina, especially when the fill is subtotal. This makes these tamponade agents less useful for closing inferior retinal breaks and for defending them from the proliferative vitreoretinopathy (PVR) that usually begins in the inferior

quadrants. Placing an agent that is heavier than water in contact with the retina should reduce the redetachment rate and the rate of inferior PVR.

In the past two decades, clinicians and researchers have attempted to identify internal tamponades that are heavier than water and have good tolerability. The first heavy tamponade used was fluorinated silicone oil or fluorosilicone (FSiO), but its high rate of complications such as early emulsification and development of intraocular inflammation and PVR limited its use [6]. A second group of heavy internal tamponades, the perfluorocarbon liquids (PFCLs), was studied for prolonged postoperative endotamponade at the end of the 1980s. These are fully fluorinated alkane compounds with a high specific gravity. However, these compounds turned out to be unsuitable long-term internal tamponade because of the mechanical damage on the retina and the tendency for droplet dispersion [7–9]. Presently, these compounds are widely used as intraoperative tools, but not as vitreous substitutes.

A third group of substances, liquid semifluorinated alkanes (SFAs), appeared to have the potential to act as heavy internal tamponade agents [10]; in particular, perfluorohexyloctane (F6H8) seemed to be well tolerated in long-term animal studies [11]. In clinical practice, the use of F6H8 provided adequate reattachment rates and few signs of retinal damage; however, it was associated with a high rate of postsurgical inflammation and an early rate of emulsification of droplets into the entire eye [12].

SFAs have the ability to bring the silicone oil into solution, creating a fourth category of heavy tamponades, the heavy silicone oils (HSOs). HSOs are admixtures of different concentrations of highly viscous PDMS and SFAs, combining the advantages of increased gravity and high viscosity. Some of these mixtures were more tolerated by ocular tissues compared to SFAs, and these mixtures have been successfully investigated as long-term endotamponades. However, in some clinical situations, the combination of two or more tamponade agents is suspected to increase postsurgical inflammation.

Two compounds belonging to the HSO group are available for clinical use: Densiron 68 (Fluoron: a combination of F8H8 and silicone oil) and Oxane HD (Bausch and Lomb: a combination of olefins RMN3 and silicone oil). A third compound, HWS 46-3000, appeared to be well tolerated, but it is not yet available in common practice.

In this review, we describe the current knowledge on HSOs and heavy tamponades and discuss the fundamental clinical and biochemical/molecular events involved in the ocular inflammation induced by these compounds.

1.1. Physical Properties of an Optimal Heavy Tamponade. The essential attribute of the PDMS is its ability to keep the retina in contact with the pigment epithelium by the hydraulic force of its volume displacement, thereby alleviating the tractions. The efficacy of an internal tamponade depends on its ability to make contact with the internal surface of the retina.

The PDMS cannot flatten the retina because it has a weak flotation force; rather, it exerts a tamponade effect mainly by immobilizing the retina and reducing fluid circulation. Thus, the tamponade effect of the injected PDMS is modest and is not comparable to that of air or gas. A layer of fluid between the retina and the silicone bubble is always present, and closed contact between the oil and retina is not possible. However, the stabilization of the eye for a long period after surgery is the main advantage of silicone oil compared to gas.

PVR is an exaggerated wound-healing phenomenon in which inflammation, proliferation, and remodeling lead to a retinal scar [13]. At the end of surgery, the meniscus of fluid that remains between the endotamponade and the retina is a milieu of rich proinflammatory cytokines and growth factors that promote PVR development, and this is the main cause of failure after retinal detachment surgery.

With conventional "light" endotamponades (either gas or PDMS), the PVR is located in the inferior quadrants where the remnant fluid is displaced in almost all cases. In cases of inferior breaks, the contact between an agent that is heavier than water and the inferior retina can prevent the passage of aqueous through the hole and displace water upwards. An ideal heavy tamponade agent should possess the following qualities: optical clarity, no effects on the eye's refractive state, no toxic effects on eye structures, no effects on eye pressure, no cataractogenic effects, and the ability to inhibit inflammation, cellular migration, and glial proliferation [14]. Moreover, the following physical properties regulate endotamponade effectiveness: the difference in the specific gravity of the agent and the aqueous (buoyancy), the interfacial tension, and the viscosity [15]. Unfortunately, all of the presently used agents have both advantages and disadvantages related to their different properties.

The specific gravity (the difference between the specific gravity of the agent and water) determines whether the tamponade will sink or float in water and the shape of the intraocular bubble. The specific gravity and the interfacial tension determine the effectiveness of an internal tamponade in the short term. The viscosity of the material is crucial for maintaining its integrity, thus reducing dispersion in the long term. In contrast to PDMS (specific gravity, 0.97 g/cm^3), the high specific gravities of perfluorodecalin (1.93 g/cm^3) and F6H8 (1.35 g/cm^3) allow these substances to stay perfectly in contact with the lower retina. These compounds are able to flatten the retina because of their strong sinking force; they fit perfectly over all of the irregularities of the posterior pole and the recesses of the indents, and no fluid remains between the inferior retina and the tamponade agent. However, the specific gravity of these agents is probably too high, and the absence of water between the agent and the inferior retina produces a mechanical or metabolic negative effect that impairs retinal function [16]. The lower specific gravities of "lighter" heavy tamponades, such as Oxane HD (specific gravity, 1.02 g/cm^3) and Densiron 68 (1.06 g/cm^3) minimize these effects. Thus, these compounds should be less toxic, although this reduces their tamponade effects, especially in the presence of a retinal indents [17].

Further, an effective tamponade must have a high interfacial tension against water in order to push the retina toward the eye-wall. Gas or air has the highest interfacial tension against water (approximately 80 mN/m), whereas

PFCLs and silicone oil derivatives (PDMS or HSO) have a lower tamponade capability because of their lower interfacial tension against water (around 40–45 mN/m or 35 mN/m, resp.).

According to Archimedes' principles, the tamponade force that presses against the retina depends on the gravity of a submerged bubble, namely, buoyancy. When in contact with water, the bubble of a light or heavy silicone oil is rounded because of its small "pressing" force. In an eye that is almost completely filled with a tamponade, this substance is in contact with only a portion of the retina (superior or inferior, depending on the gravity), while it forms a convex meniscus on the opposite side that is not in contact with the retina. The shape of this meniscus is more or less convex, depending on the physical characteristics (gravity, buoyancy, and superficial tension) of the substance; in general, a flat meniscus is a characteristic of a good endotamponade agent. For example, gas or air has a flat meniscus, while PDMS and HSO have a convex meniscus, and it seems that the Densiron 68 meniscus is less convex than the Oxane HD meniscus.

In clinical practice, it remains unclear whether the differences between Densiron 68 and Oxane HD are significant. The essential role of any vitreous substitute is presumably its ability to fill the eye and maintain the retina in contact with the pigment epithelium rather than to flatten it [18].

Emulsification is a frequent complication associated with the use of heavy internal tamponade [19]. This phenomenon is influenced by many factors including the interfacial tension, the viscosity of the oil, and the presence of impurities such as low-molecular-weight siloxanes and catalytic remnants [15].

The viscosity rate is the main factor influencing emulsification; a reduction in viscosity reduces the mechanical energy needed to disperse a large bubble in small droplets. In theory, an intraocular tamponade should be highly viscous, thus reducing the tendency to emulsify and to disperse into small bubbles that can cross retinal breaks or the zonula to the anterior segment, causing inflammation or glaucoma [20]. Silicone oil, which has high viscosity (5000 mPas), is more stable and tends to have less dispersion; therefore, it is associated with a lower rate of complications related to emulsification compared to the less viscous PDMS (1000 mPas) [21].

In the clinical practice, however, the PDMS is usually removed after 3-4 months, and such a difference in dispersion may be not significant in this time interval. The high viscosity of 5000 mPas PDMS increases the difficulties associated with handling the substance. A PDMS of 1000 Cs can be introduced and removed much more easily than a PDMS of 5000 Cs; thus, the former is largely utilized by most vitreoretinal ophthalmologists. Moreover, with the advent of minimally invasive surgery (23–25 gauge), the use of a less viscous silicone oil is preferable in order to save time during its introduction and its passage through the small gauge system. Therefore, obtaining an HSO of low viscosity that does not generate the phenomena of emulsification would be desirable.

Heavy tamponades have lower viscosity than PDMS: F6H8 and the other SFAs have a viscosity of 2.5–3 mPas, close to that of water (1 mPas). These compounds are easy to handle, but they tend to emulsify very early after surgery. Dispersion was described in 30% to 100% of cases treated after a few weeks with F6H8, depending on the time to removal. The mixture of SFA with a PDMS that has a viscosity of 1000 mPas can inhibit dispersion by F6H8, but this mixture was found to be unstable, depending on the temperature and movement of the eyes [22, 23].

The mixtures of an SFA and a PDMS with a viscosity greater than 5000 mPas, forming the HSO compounds, seem to be more stable. HSO compounds have higher viscosity than pure FSA: approximately 1400 mPas for Densiron 68 and approximately 3800 mPas for Oxane HD. Although this quality slows the emulsification rate, it influences their handiness during removal [24].

The amount of emulsification of heavy tamponades is, among other factors, time-dependent. Thus, the tendency to emulsify is the main factor that influences the time to removal of these tamponades.

This factor is crucial for stabilizing the retina for the time that is necessary for PVR to develop (usually 4–6 weeks). The better tolerance of the new HSOs allows these substances to remain for up to 3-4 months without detrimental effects [25].

1.2. Immune Response and the Proinflammatory Nature of HSOs. The inflammatory response after prolonged retinal detachment and after vitreoretinal surgery peaks in the development of PVR, which occurs when the retinal cells are exposed to the inflammatory milieu in the vitreous humor [26]. The "PVR soup" consists of the aqueous humor containing growth factors and cytokines [27]; it tends to settle at the level of the inferior retina and posterior pole because of gravity [28]. This situation is common in complicated retinal detachment, but it is amplified after invasive surgery and by the use of intraocular tamponades that float over a subtle film of liquid where the inflammatory cytokines and growth factors reach the critical concentration over the inferior retina.

The accumulation of the PVR soup beneath the inferior meniscus of the PDMS or gas exposes the inferior retina (in the orthostatic position) and the posterior pole (in the supine position) to factors that may generate epiretinal membranes. Heavy tamponades theoretically possess the quality to displace this inflammatory environment away from the inferior retina and the posterior pole [29]. With a heavy tamponade, the head movements during common daily postures should frequently displace the liquid meniscus from the upper retina to the posterior capsule of the lens. In contrast, with PDMS, head movements frequently displace the liquid from the inferior retina to the posterior pole, increasing the risk of damaging the macula. However, PDMS has been used for more than three decades and is appreciated for its stability and immunological tolerability, which make it safe for use as a long-term internal tamponade. The same level of safety has not yet been achieved by any of the heavy tamponades used up to now, especially for their physical and immunological interaction with ocular tissues.

Many authors have noted that heavy tamponades are more prone to causing intraocular inflammation compared to standard silicone if they remain for several months in the eye. It is difficult and often impossible to distinguish between inflammation caused by the tamponade and the

inflammatory reaction that is associated with the underlying complicated retinal disease. High inflammation can be commonly expected after a complicated retinal detachment surgery, and this is not related to the tamponade used. Fibrin formation, corneal edema, and cataract progression are frequent complications related to surgical trauma or to the ocular disease itself (i.e., in cases of retinal detachment after an ocular injury). Moreover, severe reproliferation is the major reason for anatomical and functional failure, and it can be seen with or without the use of heavy tamponades.

However, detecting any possible adverse inflammatory event related to the physical characteristics of any endotamponade agent is crucial because it could modify or amplify the wound-healing response and stimulate PVR, which is the primary reason for visual loss and poor visual outcome.

Four mechanisms are involved in the genesis of the inflammatory response: toxicity due to impurities or the instability of the agent, direct toxicity and immunogenicity, oil emulsification, and mechanical injury due to gravity [30].

1.3. Toxicity due to Impurities or the Instability of the Agents. PDMS and FSiO contain impurities like linear and cyclic low-molecular-weight components (LMWCs), ionic compounds, and compounds with cleavable fluoride that are thought to cause ocular toxicity [31]. LMWCs (less than 2,500 Da) have high volatility and may diffuse as vaporized molecules into the surrounding tissues, where they can produce toxic effects. The vaporized siloxanes can also condense and become silicone oil droplets in areas of temperature change, such as near the iris or in the anterior chamber, or in presence of polarized molecules in the anterior chamber fluid. Further, the inactivated catalysts remaining in the silicone oil may be toxic.

Severe inflammation and corneal edema can be induced when small species of linear and cyclic LMWCs of endotamponades are injected into the anterior chambers of animals. The ocular responses to the single species of the LMWCs increase as the molecular weights decrease. However, unpurified PDMS and FSiO, as well as purified oils (via solvent fractionation), usually do not cause significant adverse ocular responses, presumably because the amounts of LMWCs (especially the smallest species) in the oils are relatively small.

Using gas chromatography, several authors analyzed the PDMS and FSiO recovered from rabbits and human vitreous cavities up to 2 years after injection and discovered that LMWCs may diffuse from the oils into the ocular tissues [32]. Although the long-term effect of LMWCs in the intraocular PDMS and FSiO has not been determined, the diffusion of LMWCs into ocular tissues may be related to the chronic ocular toxicity of the oils. In addition, postoperative emulsification of silicone is related to the number of low-molecular-weight polymer chains [32].

In HSOs, the semifluorinated alkanes are embedded in silicone oil molecules that may theoretically contain LMWCs. However, the companies that produce Densiron 68 and Oxane HD stated that these agents are 100% pure preparations and that they do not contain low-molecular siloxanes and other impurities.

The biocompatibility of the SFAs and their admixtures with PDMS (the HSO) depends on the lipophilic behavior and on the molecular dimension of the semifluorinated alkanes. Because cell membranes and other physiological borders are composed of lipophilic substances, it is possible that they could be damaged or solubilized into the silicone bubble at certain temperatures [10–12]. The composition of the HSO may vary with time and temperature and from contact with other chemical agents. For example, the higher temperature of the anterior chamber might separate the F6H8 and PDMS in some situations.

Further, the stability of the combination of two different agents may cause unexpected ocular toxicity. The interaction between F6H8 and other substances like PFCLs, PDMS remnants, or the cortical humor vitreous and humor acqueous may alter the stability between the two compounds and the properties of HSOs. The decomposition of these substances was shown to cause intraocular inflammation or phenomena like "sticky silicone oil" [33, 34]. It was shown that F6H8 might react with remnants of the humor vitreous and humor acqueous either in the vitreous base or in the posterior pole, creating whitish epiretinal membranes [35].

Even if an apparently complete exchange of the PFCL with air is assumed, a thin layer of the PFCL may remain on the retinal surface and in ciliary bodies; these remnants can be found in droplets in many patients months or years after the surgery at the follow-up visits [36].

The interaction between the HSO and the volatile remnants of the PFCL or vitreous remnants may generate drops of sticky silicone, a sort of "glued oil," attached on the retinal surface and, in the worst cases, on the macula. PFCL remnants were found in high concentrations in the sticky samples of several patients [33]. Contamination of the tamponade with the heavy liquids used during intraoperative manipulations is also suspected to cause granulomatous uveitis with the use of Oxane HD [37]. For these reasons, it is recommended that a PFCL-air exchange be performed before injecting any HSO in order to avoid direct contact between the PFCL and HSO, thus preventing unpredictable side effects.

The biocompatibility of the SFA and their admixtures with PDMS (the HSO) is dependent on the lipophilic behavior and on the molecular dimension of the semifluorinated alkanes. Because cell membranes and other physiological borders are composed of lipophilic substances, it is possible that they could be damaged or solubilized into the silicone bubble at certain temperatures.

1.4. Direct Immunogenicity and Toxicity of the Compounds. The early clinical reports of some heavy tamponades showed a relatively high rate of intraocular inflammation. A fibrinoid reaction and even retinal necrosis associated with the use of high-density fluorosilicone oils as well as semifluorinated alkanes such as F6H8 and their oligomers have been reported [12, 35, 38–40].

In particular, F6H8 is suspected to increase the wound-healing reaction and to cause granulomatous reactions, fibrinoid reactions, and retropupillary membrane formation. The direct immunogenicity of this compound has been demonstrated by the finding of a granulomatous reaction with epithelioid cells containing minute drops of F6H8 [37].

The introduction of HSO reduced the rate of intraocular inflammation compared to previous reports. However, several cases of fibrin formation and unusual anterior chamber inflammation were reported either with Oxane HD or with Densiron 68 [37, 41]. An abnormal inflammatory reaction was not found in any patients treated with HWS 46-3000 [42].

The chronic presence of an intraocular endotamponade may also indirectly cause some form of toxicity. An endotamponade that remains in the vitreous cavity for several months may absorb endogenous substances from the ocular tissues or exogenous substances via the blood stream. The analysis of PDMS and FSiO extracted after several months of intraocular placement demonstrated the presence of cholesterol, retinol, and lipophilic acids that were extracted from the retinal cells or from the blood. Further, depending on their molecular dimensions and temperatures, SFAs may extract cholesterol from ocular plasma membranes that are damaged or are solubilized into the silicone bubble [10]. These findings suggest that intravitreal endotamponades containing PDMS or SFAs are not completely inert and may extract cellular components or accumulate substances not normally present in the vitreous cavity, and these substances may have a cytotoxic effect over time [43, 44].

1.5. Emulsification. Heavy tamponades with a viscosity that is lower than that of silicone oil are more prone to emulsification compared to standard silicone oil, which in turn gives rise to inflammation. The dispersion and diffusion of a tamponade agent in the aqueous are responsible for the subsequent formation of an emulsion of droplets or "fish eggs" [45]. Emulsification is probably either the effect or the cause of intraocular inflammation, quite apart from the fact that individual agents might be a stimulant for inflammatory reaction. Intraocular inflammation promotes early emulsification of the endotamponade, while the diffusion of foreign molecules from the endotamponade promotes further inflammation.

Minute bubbles of oil are suspected to trigger inflammatory cell chemotaxis and phagocytosis, which stimulate a foreign body-type reaction [46]. However, it is not clear whether the size of the bubble or the combination of the vesicle shape with a specific stabilizing surfactant activates neutrophils or stimulates phagocytosis by monocytes [47].

Dispersion also depends on the underfilling of the tamponade after surgery especially in large-volume eyes and if severe postoperative inflammation coexists. Silicone oils are composed of polymers and hence show the characteristics of non-Newtonian fluids, which means that the viscosity changes along with the share rate. Saccadic and pursuit movements of the eyes and of the head may cause intraocular fluid currents that exert shear stress on the silicone bubble surface. Therefore, the shear force or the lateral attrition, created by rotatory movements, exceeds the surface tension of the bubble, creating a dispersion of small fractions of the tamponade in small bubbles.

Because the viscosity of silicone oil is determined by its molecular weight, low viscosity silicone emulsifies more easily. Differences in the rates of emulsification are not due to differences in surface tension because surface tension changes minimally with increasing viscosity. Different samples of silicone oil with the same viscosity may be composed of a narrow band of different molecular weight chains containing only a few short chains, whereas another sample of the same viscosity may be composed of a wider range of molecular weight chains with more short-chain molecules capable of emulsification. The homogeneity of the silicone components and the low concentration of the LMWCs are important factors for avoiding toxicity and emulsification.

While emulsification is transitory in the first phase, it becomes permanent in the presence of blood components and inflammatory proteins that act as surfactants [47]. Red blood cell membranes, plasma lipoproteins, and HDL-apolipoproteins support silicone oil emulsification [48]. Further, vigorous physical activity with the tamponade in situ is reported as a possible cause of dispersion, opacification of the endotamponade, and intraocular inflammation [35]. Finally, the contact of silicone oil with any type of substance during a direct exchange may increase emulsification [49].

The first agents used as heavy tamponades (FSi, PFCL, and F6H8) have low viscosity and fast intraocular emulsification; however, the resistance to extensional deformation and therefore the extensional viscosity of F6H8 may be increased by mixing a certain amount of very long-chain silicone molecules into the heavy tamponade. This maintains the specific weight at a value greater than 1 and increases the resistance to emulsification.

Rachel et al. studied a combination of high-molecular-weight (423 kDa) PDMS and silicone oil 1000 at 5% and 10% w/w concentrations in order to increase the emulsification resistance of the tamponade agents while maintaining ease of injection and removal [50].

HSOs are derived from a mixture of a highly viscous PDMS (more than 5000 mPas) and different semifluorinated alkanes (F6H8, F4H5, and F4H6) or a similar substance (RMN-3), and these have a lower tendency to create dispersion and emulsion. However, the concentration of the two components may vary with time and temperature, and the possible chemical decomposition of HSO has been reported, where the heavier component tends to settle over time in the inferior part of the bubble, separating it from PDMS. Thus, the specific gravity of HSO in the eye may become heterogeneous over time with the oil because the SFA dissociates from the silicone oil, thereby producing droplets of PDMS and droplets of SFA. This dissociation may result in an anterior uveal reaction [51, 52]. The iris pigment could be absorbed by HSO droplets in some cases, leading to iris depigmentation [52].

In an in vitro model, Caramoy et al. demonstrated that increasing the extensional viscosity by the addition of small amounts of very long-chain silicone molecules significantly influenced the reduction of the emulsification for 1000 cSt silicone oil (Siluron 2000) and for 1000 cSt silicone oil with an admixture of F6H8 (Densiron 68 HV) [53]. These findings are expected to be investigated further in an in vivo model.

1.6. Effect of Gravity in Long-Term Vitreous Tamponade. Previous reports showed that PFCL agents (perfluorodecalin,

perfluoroperhydrophenanthrene, and perfluorooctane) are clinically tolerated in the eyes for only a few days (5–7 days) [54–57]. Mechanical pressure on the retina may be partly responsible for the changes observed in the retina when PFCL agents are used. These considerations are mainly dependent on experiments and histological evaluations conducted in animal models. A few weeks of endotamponade with PFCL may cause the following ultrastructural changes in the inferior retina of rabbits: narrowing of the outer plexiform layer, ultrastructural distortions of the photoreceptor outer segments, and migration of the receptor cell nuclei to the photoreceptor layer [8, 9, 58]. These changes may represent a mechanical rather than toxic effect; in fact, similar changes have been reported in the superior retina in silicone-filled eyes. The specific gravity of PFCL ranges from between 1.7 g/cm^3 and more than 2.0 g/cm^3. The histologic changes in the retina may be partly attributed to the dystrophic effect of the "heavy" liquids that press the inferior retina. However, it was noted that the retinal damage was more evident in the external layers rather than in the inner retinal layers that are in direct contact with the heavy substance. A mechanism of damage different from a simple mechanical interaction was assumed.

Recent observations indicate that PFCL toxicity is not primarily due to the high specific gravity or possible chemical impurities but rather due to their inability to dissolve ions. Gravity might not be causally linked to retinal damage that may rather depend on a metabolic disturbance. OCT measurements indicate that PFCLs, including the semifluorocarbon PFH with low specific gravity, replace most of the aqueous sink volume available for potassium (K^+) siphoning. Thus, impairment of retinal K^+ clearance may be an important mechanism of PFCL-induced retinal injury.

These observations explained the morphological alteration reported regarding Müller cells. Müller cells have been shown to develop features of reactive gliosis including hypertrophy, expression of glial fibrillary acidic protein, and drop-like protrusions between the inner segments of the photoreceptors. Müller cells may be directly injured by the elevated [K^+], thus causing subsequent atrophy of the photoreceptors that occupy the external retinal layers. HSO is less efficient compared to PFCLs and SFAs at remaining in contact with the retina and is unable to fit into small recesses; however, this relatively poor contact allows a thin film of aqueous to remain in contact with the retinal surface, and this is important for retinal cell survival and for potassium siphoning by retinal Müller cells [16].

2. Internal Tamponade Agents

2.1. Fluorosilicone. Fluorinated silicone oil (trifluoropropylmethylsiloxane or fluorosilicone-FsiO), which has a density of 1.30 g/cm^3, was the first heavy tamponade used. Clinically, it was marked by immediate, albeit transient, iritis. The ocular toxicity of fluorinated silicone oils was attributed to their low-molecular-weight components and to their high dispersion rate [31, 32]. In animal models, FsiO fluorosilicone caused inflammatory responses that exceeded those observed with PDMS [6]. This agent is thought to promote PVR in the longer term, with an epiretinal membrane forming around the oil bubble. Histologically, these membranes showed foreign body reactions [59].

A copolymer of PDMS and FsiO was evaluated in order to avoid the anatomical damages caused by PFCLs with the aim of decreasing the specific gravity (density, 1.16 g/cm^3) of the tamponade [60].

The atrophic retinal changes were much less than those observed with the heavier perfluorotetradecahydrophenanthrene (density, 2.03 g/cm^3). However, thinning of the outer plexiform layer in rabbit retina was still observed after 6–8 weeks and small droplets ingested by mononuclear cells were found in the vitreous cavity or preretina after 4–6 months [61, 62].

2.2. Perfluorohexyloctane (F6H8). Perfluorohexyloctane (F6H8) is the most extensively investigated agent belonging to a group of fluorinated hydrocarbons: the semifluorinated alkanes (SFA) [10]. These agents have specific gravities greater than those of water, but slightly lower than those of perfluorooctane (1.35 g/cm^3), and their surface tension and interfacial tension against water are equal to those of perfluorocarbon liquids (45.3 mN/m).

F6H8 is chemically and physically inert because of the strength of its hydrocarbon (C–H) and fluorocarbon (C–F) bonds. The fluorocarbon moiety is lipophobic, while the hydrocarbon moiety is lipophilic; thus, the SFAs are amphiphilic molecules that are soluble in both silicone oils and perfluorocarbon liquids but are insoluble in water.

F6H8 is a biocompatible compound that was investigated as a candidate for blood substitutes [63]. F6H8 was well tolerated for three months in rabbit eyes [11], and it was introduced initially as a solvent for silicone oil to remove silicone oil remnants from intraocular surfaces [64, 65]. Further, F6H8 was investigated as an intraoperative tool and as a long-term tamponade in several small case series [12, 66]. Its low density and viscosity (2.5 mPas) reduced the risk of mechanical retinal damage, but it promoted dispersion and the phenomena of emulsification in the eye in up to 100% of all treated cases [67].

According to some authors, the ability of this compound to generate inflammatory responses is mostly due to its propensity to disperse and to form small, emulsified droplets. Minute bubbles of oil subsequently trigger chemotaxis of inflammatory cells and phagocytosis [46, 47]. Despite good results with the use of F6H8 in animal models and in some small case series [11], studies conducted in vitro and in vivo showed evidence that F6H8 had proinflammatory activity. In preclinical studies, blood-retinal barrier breakdown associated with local vasoconstriction, hypertrophy of Müller cells, and vacuolization of the inner retinal surface were observed in rabbit retinas after 6 weeks of tamponade [68].

An evaluation using the live/dead assay on cultured ocular cells that were incubated with F6H8 for up to 5 days showed a significant reduction of vital EPR cells. Due to its lipophilicity, F6H8 seemed to be able to interact with cell membranes, causing a change in the adherence of the cells to extracellular matrix [69].

Some evidence for an irritating effect has been observed in clinical pilot studies using F6H8 as a retinal tamponade. In some cases, retrolental, epiretinal, and simil-PVR membranes were associated with its use as a prolonged tamponade. These membranes were similar to the classical PVR membrane histologically, but they also exhibited dense macrophagic infiltration and foreign body reactions. Further, they contained vacuolated and pigmented CD68-positive cells, exhibiting a macrophagic and EPR phenotype. These observations supported possible differentiation of the EPR cells in response to the proinflammatory stimulus induced by F6H8 [35].

The presence of intracellular droplets of F6H8 in the vacuolated cells suggested that the contact with the oil in the form of microemulsion causes activation of the monocyte-macrophage population. This finding indicated that the inflammatory reaction was enhanced by droplets of a certain vesicle size. In an in vitro study, however, the inflammatory response appeared only when the vesicles interacted with specific artificial, but not natural surfactants [46].

From the clinic-pathological point of view, the inflammatory reaction leads to the formation of epiretinal membranes that sometimes extend to the posterior surface of the lens. The difference between these membranes and the classical ones encountered in PVR is greater infiltration of leukocytes, which appear to be mostly CD68-macrophages, or rather RPE cells, which have "transdifferentiated" to a macrophage-like phenotype [47]. Epithelioid cells, which are typical of a granulomatous reaction, were found in some specimens, suggesting that emulsified F6H8 could result in the release of growth-promoting factors for macrophages.

Regarding the development of retrolental membranes, it is known that silicone oil usually causes cataract formation because it interferes with the metabolism of posterior capsule epithelial cells [70].

The microscopic examination of lens capsule in eyes after F6H8 tamponade demonstrated the presence of macrophages adhering to the lens capsule with epithelioid cells and with fibroblastic differentiation, thus adding a probable inflammatory genesis to cataract formation [47].

2.3. Other Perfluoroalkanes Oligomers: Perfluorobutylpentane (F4H5), Perfluorobutylhexane (F4H6), and Perfluorobutyloctane (F4H8). A recent study by Mackiewicz et al. conducted on rabbits showed that the use of different semifluorinated alkanes leads to quite different immunologic reactions. Whereas F6H8 (perfluoroexyloctane) and F4H5 (perfluorobutylpentane) were well tolerated, F4H6 (perfluorobutylhexane) and F4H8 (perfluorobutyloctane) resulted in a severe inflammatory response, which appeared to be more pronounced when these substances were used in pure form rather than in an admixture with silicone oil. Microscopic investigation showed that the vitreous was replete with immune cells, mostly neutrophils.

Chemically, these tamponades are amphiphilic (either hydrophilic or lipophilic). The capacity to penetrate the cellular membranes depends on the lipophilic property, and this is directly proportional to the length of the alkylic chain. A minimal increase in the lipophilic properties of some semifluorinated alkanes may lead to their penetration into the cell membranes, causing cellular damage and complete disorganization of the retinal layers and lens structure [30].

However, experimental studies have produced a new biocompatible perfluoroalkane, F4H5 (perfluorobutylpentane). The combination of F4H5 with PDMS 100.000 mPas gave rise to a new HSO, HWS 46-3000. This oil is very viscous (3109 mPas); it did not show a tendency to emulsify in clinical trials, and it is well tolerated. However, its high viscosity limits its use because the removal of this oil is reportedly difficult and time-consuming [42].

2.4. Heavy Silicone Oils

2.4.1. Oxane HD. Oxane HD (Bausch and Lomb, Toulouse, France) is a mixture of 5700 mPas PDMS and RMN-3 (perfluorooctyl-5-methyl-hex-2-ene), a mixed fluorinated and hydrocarbonated olefin. The surface tension and interfacial tension of this agent against water are similar to those of perfluorocarbon liquids (41 mN/m), and its specific gravity is only slightly greater than that of water (1.02 g/cm^3). Its high viscosity (3800 mPas) reduces the risk of early emulsification. The rate of inflammatory reactions related to the use of Oxane HD was reported to be from 3% to 37% of treated patients (Table 1).

The immunogenicity of Oxane HD was investigated in a recent study in which immunohistochemistry was performed on epiretinal membranes formed in redetached retinas under this HSO [80]. Using monoclonal antibodies against retinal pigment epithelium cells, glia, macrophages, and T-lymphocytes, the inflammatory cell population was found to be similar to that obtained with conventional silicone oils; however, several aspects emerged that were attributed to a reaction against a foreign body. CD68-positive macrophages and epithelioid cells containing phagocytosed silicone oil were found in the area adjacent to the fibrocellular component of the membrane.

Another study that investigated intraocular inflammation following endotamponade with Oxane HD showed that 37% of treated patients presented with a severe inflammatory reaction that assumed the characteristics of a granulomatous anterior uveitis [37]. Seven patients in this series developed pigmented endothelial precipitates, flare, and cellularity of the aqueous humor. In contrast to what has been shown in other studies, the uveitic reaction did not regress after the administration of topical corticosteroids and was reversible only after tamponade removal. The immune reaction was attributed to a granulomatous type IV reaction, in which an immune complex of insoluble antigens can cause T-lymphocyte-mediated reaction.

The high percentage of intraocular inflammation in this series was probably due to the intraoperative contact between the Oxane HD and the PFCL. In fact, other authors did not report this phenomenon. Thus, a direct exchange between PFCL and Oxane HD has been contraindicated, and a PFCL-air exchange is recommended before injecting the HSO.

Several case series performing this maneuver did not report uncommon posterior chamber reactions; thereby it was concluded that Oxane HD is well tolerated by the

Table 1: Ocular complications after HSOs use in CRT.

Author, year (reference)	Tamponade	*N*	Pathology	Time to removal	Follow-up	Complications	Conclusions
Wolf et al. 2003 [71]	Oxane HD	33	Complicated RRD of inferior quadrants	Within 3 months	12–16 months	Rise in IOP (18%) Pupillary block (6%) Marked AC inflammation (3%) Retinal hemorrhages (6%)	Complications are similar to those reported with conventional silicone oil
Theelen et al. 2004 [37]	Oxane HD	19	Complicated RRD of inferior quadrants	1–4 months	2–4 months after tamponade removal	Keratic precipitates, pigmented clumps, and anterior chamber cellular reaction (37%) Emulsification (11%)	Inflammatory response resembling granulomatous uveitis; it is likely that Oxane HD is an immunogenic agent
Wong et al. 2005 [41]	Densiron 68	42	Complicated RRD of inferior or posterior quadrants	10–16 weeks	>3 months after tamponade removal	Cataract progression (100%) Rise in IOP (8%) Moderate AC inflammation (8%)	We neither observed clinically significant dispersion nor found any inflammation more than we would except from routine vitreoretinal surgery
Rizzo et al. 2006 [72]	Oxane HD	28	Complicated RRD	45–96 days	6 months after tamponade removal	Cataract progression (38%) Rise in IOP (14%) Tamponade in AC (4%) Membrane formation (54%)	Good intraocular tolerance with few minor complications
Sandner and Engelmann 2006 [73]	Densiron 68	48	Complicated RRD	27–4000 days	103 days after tamponade removal	Dispersion (16%) Emulsification (15%) Hypotony (2%) Ocular hypotension (13%) Glaucoma (10%) Cataract progression (50%) Moderate AC inflammation (21%) Sterile hypopyon (4%)	Compared with conventional silicone oil, a temporary inflammation and early emulsification developed more frequently with Densiron 68
Cheung et al. 2007 [74]	Oxane HD	12	RD secondary to myopic macular hole	3-4 months	9–15 months	Transient rise in IOP (42%) Mild oil emulsification and transient peripheral choroidal detachment (8%)	
Rizzo et al. 2007 [42]	HWS 46-3000	32	Complicated RRD of inferior or posterior quadrants	3 months	6 months after tamponade removal	Early posterior subcapsular cataract (100%) Epiretinal membranes (9%) Rise in IOP (0.3%)	No evidence of emulsification and intraocular inflammation
Sandner et al. 2007 [25]	Densiron 68	12	Complicated primary RRD	33–126 days	400 days after tamponade removal	Emulsification (17%) Ocular hypotension (8%) Glaucoma (17%) Cataract progression (100%) Moderate AC inflammation (33%) Suspected intraretinal gliosis (25%)	
Berker et al. 2007 [75]	Oxane HD	21	Complicated primary RRD	3 months	11.5 months	Rise in IOP (14%) Cataract progression and PVR (19%) Dispersion (9.5%) Rubeosis iridis (14%) Vitreous hemorrhage and optic atrophy (5%) Ocular pain and photophobia (100%)	Its complications were acceptable, and mostly due to its physical properties

Table 1: Continued.

Author, year (reference)	Tamponade	*N*	Pathology	Time to removal	Follow-up	Complications	Conclusions
Boscia et al. 2008 [76]	Oxane HD	10				Posterior capsular opacification (22%) ERM (30%)	
Romano et al. 2008 [77]	Densiron 68	41	Complicated RRD of inferior quadrants	3 months	6 months	AC shallowing (5%) Emulsification (5%) Posterior synechiae (5%) Cataract progression (54%) Rise in IOP (2.4%) PVR (2%)	Analyzing the observed side effects in our series, we found no presence of clinically significant emulsified Densiron 68 or intraocular inflammation
Majid et al. 2008 [78]	Densiron 68	40	Complicated or primary RRD	9–14 weeks	6–12 months after tamponade removal	Emulsification (20%) Fibrinous uveitis (5%) ERM (12%) Cataract progression CMO (8%)	Emulsified Densiron may have contributed to significant intraocular inflammation, ERM formation, and CMO. This has potentially significant implications on the indications for Densiron-68 use.
Auriol et al. 2008 [79]	Densiron 68	27	Complicated primary RRD	14 weeks	6 months	AC inflammation with fibrin accumulation (41%) Sterile hypopyon (1%) PC inflammation with preretinal membranes without traction (0.3%) Hyphema and endothelial corneal dystrophy (1%) Rise in IOP (25%) Emulsification with pseudohypopyon (1%)	Special attention must be paid to unusual adverse effects like inflammatory reactions and fibrin accumulation in the anterior chamber.
Wickham et al. 2010 [80]	Oxane HD	18	Complicated RRD of inferior quadrants	3 months	6 months	Postoperative PVR (28%) Hypotony (17%) Uveitis (11%) Rise in IOP (22.2%) Glaucoma (6%)	Histopathological analysis showed that the structure and associated inflammatory response of membranes were similar to those observed following the use of conventional oils
Meng et al. 2010 [81]	Oxane HD	40	Complicated RRD	Mean 87.9 days	Mean 438.1 days after tamponade removal	Mild-to-moderate AC inflammation (45%) Fibrin accumulation (40%) Temporary pupillary synechiae (15%) Rise in IOP (17.5%) Emulsification and dispersion (22.5%) Cataract progression (77.8%) ERM (30%)	Oxane HD showed an encouraging anatomical and functional success rate and good intraocular tolerance, with a few complications in complicated RD patients
Li et al. 2010 [82]	Densiron 68	21	Complicated primary RRD	1–3 months	15 months	Mild-to-moderate AC inflammation (24%) Severe intraocular inflammatory reaction (10%) Emulsification (24%) and pseudohypopyon (10%) Early posterior capsular cataract (24%) Choroidal detachment/ocular hypotension (5%) Rise in IOP (20%) Pupillary block (5%) Transient corneal edema (5%)	Vitreoretinal surgery with temporary Densiron 68 intraocular tamponade appears to increase anatomical success, while giving rise to minimal complications, in selected cases of complicated RD and PVR

Table 1: Continued.

Author, year (reference)	Tamponade	*N*	Pathology	Time to removal	Follow-up	Complications	Conclusions
Li et al. 2010 [83]	Densiron 68	27	Complicated RRD of inferior or posterior quadrants	3 months	15 months	Cataract progression (25%) or early posterior capsular opacification (26%) Intraocular inflammation (22%) Corneal edema and rubeosis iridis (7%) Emulsification and dispersion (19%) Rise in IOP (19%) Intraocular hemorrhage (4%) Choroidal detachment/ocular hypotension (11%) Pupillary block (4%) PVR (15%) and ERM (7%)	Postoperative complications did not increase significantly in the vitreoretinal surgery with temporary Densiron 68 intraocular tamponade
Ang et al. 2010 [84]	Oxane HD	18	Complicated RRD of inferior quadrants	Mean 27 weeks	Mean 66 weeks	Posterior capsular opacification (22%) Severe intraocular inflammation (6%) Pseudohypopyon (6%) Emulsification (33%) Rise in IOP (11%) ERM (28%)	The relatively high rate of emulsification and increased risk of intraocular complication when compared to other reported series is less promising and warrants further evaluation
Rizzo et al. 2011 [85]	HWS-45 3000	10	Complicated RRD of inferior quadrants	2 months	6 months after tamponade removal	Tiny droplets in CA (30%) Mild inflammatory reaction (40%)	HWS-45 3000 appears to be a well-tolerated heavy oil suitable for the treatment of complicated inferior retinal detachment
Romano et al. 2013 [86]	HeavySil (HSIL)	31	Complicated RRD of inferior quadrants	1 month	2 months after tamponade removal	Emulsification in AC (19%) Mild/severe intraocular inflammation (9.6%) Cataract formation (71%) Sticky oil formation (9.6%) Posterior synechiae (3.2%)	HeavySil is a safe and effective tamponade agent for the treatment of complicated RD; no major complication in terms of corneal damage, hypotension or hypertension, or postoperative proliferation was observed
Kocak and Koc 2013 [87]	Densiron 68	31	Complicated RRD of inferior quadrants	3 months	6 months after tamponade removal	Rise in IOP (25%) Cataract progression (80%) AC inflammation with fibrin accumulation (3%) PVR (17%) and ERM (6%)	Densiron 68 does not have higher complication rates than conventional silicone oil

eye for up to 3 months of the endotamponade period [71, 72, 74].

2.4.2. Densiron 68. Densiron 68 (Fluoron, Neu Ulm, Germany) is an admixture of F6H8 (30.5%) and PDMS 5000 mPas (69.5%); thereby, the viscosity was increased to 1387 mPas. This translates into a reduced ability for dispersion and emulsification, consequently reducing irritability to ocular structures [41].

Hence, compared with F6H8 alone, Densiron 68 is associated with significantly less inflammatory side effects [24] (Table 1). A comparison of Densiron 68 with 1000 mPas PDMS demonstrated that Densiron 68 does not have a higher rate of postoperative inflammation in the middle period [87].

Moreover, in cases likely to develop PVR, Densiron 68 was demonstrated to be useful for avoiding repeated surgeries with scleral buckle usage [77, 87]. A common finding was a mild-to-moderate anterior chamber reaction [25, 73, 82]. This inflammatory reaction was sometimes associated with the development of fibrous membranes, the appearance of keratic precipitates, and cataract formation with inflammatory precipitation on the lens. Posterior capsular opacification could be caused by an increased cellular infiltration as a reaction to emulsified tamponade [73, 82].

The percentage of patients who developed significant postoperative inflammation varies greatly in different studies, depending mostly on the tamponade period. The probability of having complications increases if prolonged retention of this agent is required.

A high rate of inflammatory reactions (40.7%) was recorded in a study in which Densiron 68 remained for more than 6 months [79]. In this retrospective study, an inflammatory reaction that was sometimes associated with fibrin exudation or with the appearance of a sterile hypopyon was detected in 11 patients out of 29 affected by complicated inferior retinal detachment.

Due to its low viscosity, Densiron 68 also appears to be correlated with a high rate of dispersion and emulsification in droplets, which in turn precipitates inflammation if a long tamponade period is required [82, 88, 89].

2.4.3. HeavySil (HSIL). HeavySil (ALCHIMIA srl, Padua, Italy) is made from the combination of high purity 75% silicone oil 5000 cSt (polydimethylsiloxane) and 25% perfluoroalkyloxyoctane ($C_{11}H_{11}F_{13}O$); it has a density of 1032 and a viscosity of 1500 cSt. Its stability and high affinity for silicone oil are due to the presence of a partially fluorinated ether instead of an alkane.

In a prospective, noncomparative interventional study on 31 consecutive eyes, Romano et al. investigated the anatomic and functional results and complications of this ocular tamponade. They found that HSIL is a safe and effective tamponade agent for the treatment of complicated RD; the main complications were cataract formation (71%), emulsification (19%), sticky oil formation (9.6%), and severe intraocular inflammation (3.2%) (Table 1).

One of the coauthors (B. Parolini) reviewed retrospectively 13 eyes of 13 patients with retinal detachment complicated with inferior PVR, treated using HeavySil 1500 as tamponade. All surgeries were performed with standard three-port 20-gauge pars plana vitrectomy. Additional surgical procedures such as membrane peeling and relaxing retinotomy were performed when necessary to allow retinal reattachment. Retinal breaks were treated by endophotocoagulation. In patients with preexisting endotamponade, the silicone oil was removed first. All patients were pseudophakic and underwent already at least one previous vitreoretinal surgery. Three patients were lost at 16-month follow-up. After tamponade with HeavySil, retina appeared to be attached in 9 cases over 10 (90%). Only one patient developed an IOP increase that was successfully treated with topical therapy. Another patient presented with emulsification in anterior chamber. Persistent subretinal fluid was never detected after surgery. Mean best corrected visual acuity was 2.1 ± 0.2 logMar preoperatively and 0.9 ± 0.1 logMar postoperatively. Three cases developed severe retinal inflammation 2 weeks after Heavysil 1500 tamponade. All three patients presented with optic disc swelling and retinal edema with diffuse narrowing of arteries and veins (Figure 1). One patient developed pain and the other two developed significant discomfort. Another case showed retinal inflammation with features resembling herpes retinitis, although virology was negative. In all cases, oil removal was performed within 1 week after the occurrence of retinal inflammation. The appearance of the fundus slightly improved within 2 weeks after oil removal. Silicone oil was analysed in these three cases with cytology and only in one case inflammatory cells were found. During oil-removal surgery, the sticky oil phenomenon appeared in one case. A retinal tissue sample was collected for histology examination; however, the result showed nonspecific signs of inflammation (Figures 2, 3, and 4). In this particular group visual acuity remained very low after surgery even if retinal reattachment was reached in all patients. The cause for final low vision was cystoid edema in one patient and persistent macular hole and retinal thinning in the other two. It is difficult and often impossible to distinguish between problems caused by the tamponade and those that are associated with the underlying complicated retinal disease. In these three cases the timing of acute appearance of inflammation and retinitis was considered significant and differed from other more chronic and subtle signs of silicone related inflammatory reactions. Our case series, with all the limitations due to the retrospective examination of data, shows a significant rate of severe acute retinal inflammation when using HeavySil (70%). Larger prospective clinical trials will be needed in order to define the safety of this new heavy tamponade.

2.5. HWS 46-3000 and HWS 45-3000. HWS 46-3000 and HWS 45-3000 are admixtures of 45% silicone oil 100,000 and 55% perfluorobutylhexane (F4H6) and perfluorobutylpentane (F5H6), respectively. Of the three new generation tamponades, HWS 46-3000 is the heaviest and has the greatest viscosity (3.109 mPas). In Rizzo's pilot study of a case series of 32 patients published in 2003, the major side effect detected was the development of early posterior subcapsular cataract (100%); intraocular inflammation and emulsification were not observed (Table 1). Rizzo et al. postulated that the low rate of postsurgical reproliferation and epiretinal

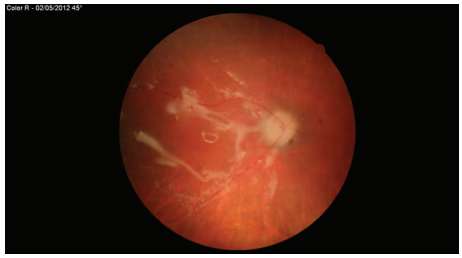

Figure 1: Optic disc swelling in presence of heavySil tamponade.

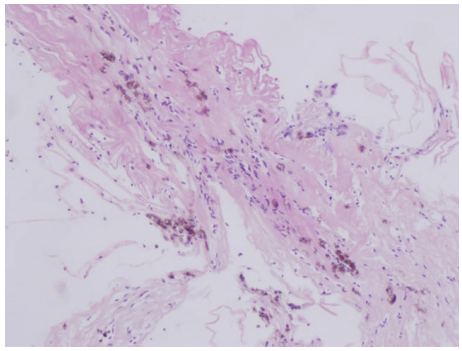

Figure 2: Small specimen of peripheral retinal biopsy showing convoluted basal lamina and retinal microvasculature (arterioles, venules, and intervening capillaries) with prominent reactive endothelium and multiple clusters of pigmented macrophages.

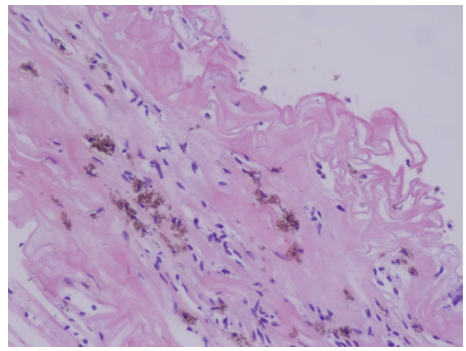

Figure 3: Convoluted basal lamina and retinal microvasculature with reactive endothelium and many pigmented macrophages.

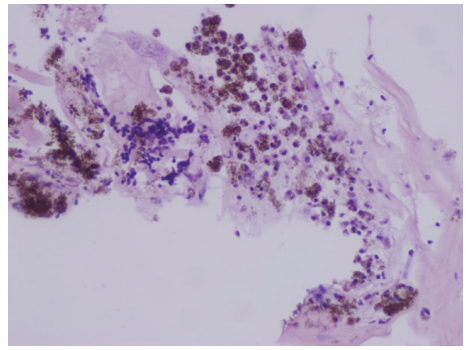

Figure 4: Large aggregates of pigmented macrophages with interdispersed not pigmented histiocytes on the left perivascular lymphoid infiltrate.

membranes formation (9%) was due to adequate contact with the buffering of the retina, reducing the infiltration of the PVR soup. HWS 45-3000 has a density of 1.118 and a viscosity of 2.903 mPas. In 2010, Rizzo et al. did not observe significant emulsification or a significant inflammatory reaction with this agent.

3. Conclusions

The treatment of complex retinal detachments using internal tamponade agents produces successful restoration of vision in many cases. However, the recurrence rates for complicated retinal detachment are as high as 20–25%, and this rate increases in the presence of PVR [4–13]. Although vitreoretinal techniques have been improved over the past years, the rate of PVR has not decreased considerably [90].

PDMS or gas exposes the inferior retina (in the orthostatic position) and the posterior pole (in the supine position) to proinflammatory growth factors and cytokines that may generate epiretinal membranes. Compared to PDMS, heavy tamponades theoretically possess the quality to provide better protection to the posterior pole from PVR [29].

With a heavy tamponade, the head movements during common daily postures are expected to displace the liquid meniscus from the upper retina to the posterior capsule of the lens frequently. In contrast, with PDMS, head movements frequently displace the liquid from the inferior retina to the posterior pole, increasing the risk of damaging the macula. Further, when postoperative posturing is more important, such as in cases of posterior breaks, macular hole in highly myopic eyes, or inferior retinectomies, heavy tamponades are advantageous, especially for patients with orthopedic disability or mental retardation and for children [91, 92].

The hypothetical advantage of using a HSO is that the physical separation of the "PVR soup" from the effector cells (retinal pigment epithelial cells, Müller cells, and fibroblasts of the inferior breaks) inhibits or mitigates fibroplasia. The most important presumed advantage for HSO compared to PDMS is a lower redetachment rate after endotamponade removal and a lower rate of macular redetachments.

However, the preliminary results of a recent multicentric randomized trial failed to demonstrate the real superiority of HSO in comparison with standard PDMS in eyes with proliferative PVR of the lower retina [93].

Regarding final acuity, HSO was neither inferior nor superior to PDMS in almost all clinical series. Further, the rate of PVR in HSO-treated patients was not inferior to that registered for PDMS-treated patients; rather, HSO caused a shift of the PVR to the upper retina above the horizontal meridian [93]. To prevent this complication, several authors proposed performing a prophylactic superior laser photocoagulation, while others suggested a shorter endotamponade period with subsequent silicone oil use [25, 73].

The presence of a subtle meniscus of fluid around bubbles with a specific gravity very close to that of water is probably

the main reason for the diffusion of growth factors and cytokines from the inferior breaks to the upper retina, which generates epiretinal proliferation. On the other hand, this subtle meniscus of fluid is essential for the correct K^+ siphoning of the Müller cells and is necessary for avoiding the functional damage due to the excessive drying of the retinal surface that has been reported for heavier agents or for gas [94–96].

The rates of complications, such an inflammatory reaction, macular epiretinal membranes, IOP rise, cataract, and emulsification of HSOs, seemed to be similar to those in patients treated with PDMS in the middle period. This indicates that the intraocular behavior and tolerance of HSOs and PDMS would be similar if they remained in the eye for 3-4 months. This is an important safety result obtained for HSOs in comparison with all of the previously used heavy agents, because none of these agents could be utilized for such a long period without severe complications.

The clear advantages of using HSOs rather than PDMS are shortening of the surgical time, easy handling, and a reduction in the necessity for utilizing external buckles or macular indents. However, when using HSOs, a strict follow-up period is required and the timing of the endotamponade removal should be respected more strictly in comparison with PDMS. Intraocular inflammation is common if it remains for more than 6 months [79].

The real utility of the use of HSOs depends on the correct selection of the patients for treatment. In a number of situations, such as myopic macular holes with or without retinal detachment, myopic foveoschisis, penetrating ocular injuries with retinal detachment, and inferior giant retinal tears, treatment with a heavy substance is easier and should therefore be the first choice.

Moreover, HSOs offer new strategies for treating very complicated cases of retinal detachment caused by a proliferative process, such as alternating the tamponade agent in two different surgeries (i.e., first using an HSO and using PDMS or gas after a few months), or by combining in a single step the HSO with PDMS to reach a tamponade effect on both the upper and lower retina [97].

A mixed bubble of 70% Densiron 68 −30% PDMS has been recently used to obtain a "filling effect," suggesting that this strategy could minimize the stress produced by the tractional forces originating from eye movements. However, the results of using HSOs in many of these clinical situations have not yet been evaluated in extensive multicentric clinical trials.

In conclusion, the introduction of HSOs represents an improvement in vitreoretinal techniques because the intraocular tolerance of these agents is good for 3-4 months. Even if the goal to prevent PVR formation is not reached and the visual results obtained with HSOs are comparable and not superior to those obtained with the "old PDMS," these new agents represent a useful new surgical tool. In the same way that the small gauge vitrectomy represents an improvement over the "old" 20-gauge vitrectomy, the HSOs are better than the "old PDMS" in some clinical situations. Although both agents obtain comparable visual results, the new agent gives similar results while the procedures are performed more easily, with appreciable advantages for both the surgeon and the patient.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Review Article

Silicone Oil: Different Physical Proprieties and Clinical Applications

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Silicone oils are important tools in vitreoretinal surgery because they have the ability to displace aqueous humor from the retinal surface, maintaining the adhesion between retina and retinal pigment epithelium. To understand this capability, it is important to know the silicone oil characteristics. Herein, we report first on the main chemical-physical proprieties and then we review the clinical applications of the current silicone oil which is lighter than water with particular reference to their indications with small gauge vitrectomy. Finally, we describe the surgical techniques to inject and remove this type of silicone oil. In the summary of this paper, we explain why silicone oils are today increasingly used and why their introduction has improved the prognosis of several retinal diseases. In fact, having different types of silicone oils allows us to choose the appropriate endotamponade for every single case.

1. Introduction

Silicone oils are important tools in vitreoretinal surgery and their introduction has represented a pivotal moment in the management of ophthalmic surgery as they are equipped with a combination of chemical and physical properties that have propelled their surgical use [1]. Silicone oils are essentially used as intraocular tamponade thanks to their ability to maintain the adhesion between retina and retinal pigment epithelium (RPE).

The safe and effective use of tamponade substances means the knowledge of their physical and chemical properties because it is on the basis of this knowledge that surgeons have to decide what type of tamponade they should use.

2. Physical Properties of Tamponades and Clinical Consequences

To be effective as an internal tamponade, a silicone oil has to have the ability to displace aqueous humor from the retinal surface. The following 4 physical parameters influence this function [2].

(1) Specific Gravity (SG). This explains why an intraocular tamponade sinks or floats in aqueous humor. Any substances with an SG of 1 are neutrally buoyant in water, those with SG greater than 1 are denser than water and so will sink in it, and those with an SG of less than 1 are less dense than water and so will float. The specific gravity of aqueous humor and vitreous humor is a little higher than that of water (SD 1.00). Since the specific gravity of silicone oils in comparison is a little lower (0.97), they float in vitreous cavity.

(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' principle indicates that the upward buoyant force that is exerted on a body immersed in a fluid, whether fully or partially submerged, is equal to the weight of the fluid that the body displaces. Archimedes' principle is a fundamental physics law of fluid mechanics. Regarding the vitreous cavity, the 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 humor. The force is greatest with air or gas, as the specific gravity is very low at 0.001.

(3) Interfacial Tension. When two immiscible agents are used together (e.g., silicone oil and aqueous humor), the interaction that occurs at the surface of these substances involved is named interfacial tension. Interfacial tension is a physical rating of the difference between the intermolecular force of the two liquids and it is responsible for the shape of liquid bubbles. Therefore, a substance with a high interfacial tension will have a greater tendency to stay as one large bubble without dispersion into small bubbles. Gas or air has the highest interfacial tension against water (around 80 mN/m), whereas perfluorocarbon liquids (PFCLs) and silicone oils have a lower interfacial tension, around 40–45 mN/m and 35 mN/m, respectively.

(4) Viscosity. The viscosity is the physical property of a fluid which measures its resistance to gradual deformation by shear stress. 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. Silicone oils have a high viscosity (1.000–5.000 cs) and, once dispersed, the small droplets will tend to recoalesce back as a large bubble.

3. Chemical Properties

Silicone oil is a term generally used to describe a group of hydrophobic polymeric and monomeric compounds constituted of silicon-oxygen bonds and named organosiloxane [3]. Because of their viscosity and their ability to repel water, they are referred to as oils.

Silicone oils are constituted of a linear chain of siloxane repeating units (–Si–O) and a variety of side chains (radical side groups). Those used in ophthalmology have hydrocarbon radicals as radical side groups (e.g., methyl, phenyl, vinyl, and trifluoropropyl groups). These composts are attached to the silicon atom and it is possible to have many different combinations. Therefore, one silicon atom can bond two radical groups of the same type (e.g., dimethyl-siloxane) or two different groups (e.g., phenyl-methyl-siloxane).

The major differences among silicone oils depend on the molecular weight (MW), on the length of the linear chain, and on the chemical structure of radical side groups, radical end termination of the polymer chains, and the size distribution of the chain. Thus, each type of silicone oil has specific chemical and physical characteristics.

The viscosity of different types of silicone oil, which is expressed in centistokes ($1\,\text{cs} = 10^{-6}\,\text{m}^2/\text{s}$), arises from the molecular weight and from the length of the polymers: increasing a silicone oil's molecular weight results in an increased polymer chain length and consequently an increase in its viscosity. Silicone oils currently used have a viscosity ranging from 1.000 (MW 37 kDa) to 5.000 cs (MW 65 kDa).

In order to create a tamponade effect on the superior or inferior retina, silicone oils have the capability to be lighter or heavier than water and this property arises from the radical side groups. Herein, we review the major indications regarding the use of the first generation of silicone oils, which is named lighter than water. They are the most commonly used and are referred to as polydimethylsiloxane (PDMS). Their viscosity rating is between 1000 and 30.000 cs.

4. Physical Properties

The aim of the use of silicone oil as vitreous substitute is to provide short- to long-term tamponade of the retina. The dynamic of the silicone oil depends on the interaction between buoyancy, interfacial surface tension, and viscosity.

Buoyancy arises from the difference in specific gravity between aqueous (or vitreous) humor and the selected silicone oil. As we have seen at the beginning of this paper, the specific gravity determines whether a vitreous substitute will sink or float in aqueous humor. If compared with water (specific gravity of 1.00), the specific gravity of aqueous humor and vitreous humor is a little higher than this while the gravity of silicone oil is a little lower (0.97). Therefore, silicone oil floats inside the vitreous cavity and the upward force is defined as buoyancy. This force is highest at the apex and gradually decreases to zero at the horizontal meniscus. Consequently, tamponade force arises from the difference in density between aqueous humor, vitreous humor, and silicone oil bubble. However, the buoyancy does not act upon a single point but is spread over a limited area and, for this reason, it produces pressure (force/unit area) [3].

Surface tension is responsible for the shape of liquid droplets because it describes the forces that tend to keep a bubble whole. In general, for 1000 cs silicone oil, it is 40 mN/m (at 25°C) that is approximately one-third of that generated on an air bubble. There are several factors that may influence the surface tension of a silicone oil bubble once it is injected into the eye. First, the viscosity: the higher the viscosity, the higher the surface tension. This is one of the reasons why silicone oils with higher viscosity are considered to emulsify less frequently than silicone oils with lower viscosity. There are then many factors that may decrease the surface tension: viscoelastic solutions, blood, proteins, lipids, and ionized solutions (e.g., biological fluids) are factors that, if present in the vitreous cavity when a silicone oil is injected, can decrease the surface tension and therefore lead to emulsification.

5. Does Viscosity Make a Real Difference in Emulsification Rate?

A major permanent problem in the use of silicone oils as vitreous substitutes is their tendency to emulsify. Emulsification means the formation of small oil droplets at the interface between oil bubble and intraocular fluids or tissues and it causes a dispersion of these droplets into the aqueous humor and vitreous humor with consequently higher risk of proliferative vitreoretinopathy, failed retinal detachment,

inflammation, secondary glaucoma, and keratopathy, even after silicone oil removal [4, 5].

In fact, once coated by emulsifiers, the droplets remain dispersed, pass through retinal breaks or through the zonules into the anterior segment, and cause inflammation and activation of neutrophils [6].

The tendency to emulsify depends on several factors: interfacial surface tension, viscosity, chemical composition, content of low molecular weight (MW) siloxane compounds or other impurities, and absorption of various biological substances from intraocular fluids and tissues (named emulsifiers) have been studied and all of them can have a role in the emulsification process [3].

The presence of a low MW siloxane compounds is very critical. For a given viscosity, the silicone oil with the lowest MW average will emulsify faster, while a purified silicone oil with higher average MW will exhibit a better biocompatibility and a higher resistance to the emulsification and therefore the removal of low MW compounds during the purification process of a silicone oil is very important.

Since a silicone oil with a higher viscosity has a lower tendency to emulsify, many surgeons prefer these types of silicone oil, such as 5000 cs, especially when the oil is intended to serve as a prolonged or permanent tamponade. However, although there are several studies demonstrating in vitro that the increasing viscosity of silicone oil reduces the tendency to emulsify [7–9], the commercially available 1000 cs and 5000 cs silicone oils do not have a clinically significant difference in emulsification [10]. Despite their difference in viscosity, the 1000 cs and 5000 cs silicone oils have nearly the same behavior because in reality there are many other determinant factors influencing the tendency to emulsification: first, because, despite marked viscosity difference, the 1000 cs and the 5000 cs silicone oils have nearly the same surface tension (21.2 mN/m and 21.3 mN/m, resp.) [3]; second, because, although the commercially available preparations of 1000 cs and 5000 cs silicone oils have reached a high grade of purity to minimize the risk of silicone oil emulsification, the presence of impurities in the oil, such as low MW molecules, may still occur; third, because, once inside the vitreous cavity, silicone oil adsorbs biological solutes from ocular fluids, blood, or tissue such as lipoproteins, cholesterol, and retinol [2, 3]. Each of these components is an emulsifier because the contact of these substances with the silicone oil bubble decreases their surface tension and consequently increases the tendency to emulsify. Therefore, it is easy to understand why in cases of hemorrhages and inflammation or rather when the concentration of these emulsifiers is high the risk of silicone oil emulsification is higher.

Emulsification has been reported to occur after several months. In a study of 150 eyes, Federman and Schubert [5] found that emulsification of silicone oil occurred in 1% after 1 month, 11% at 3 months, 85% at 6 months, and 100% after 12 months. The emulsification seems to be therefore time dependent [11] and it has been speculated that it depends on a combination of the saccadic motion, the difference in density of intraocular fluids and silicone oil, and the gradual decrease of interfacial surface tension of the oil due to the adsorption of surface-active components from the intraocular fluids [3, 8, 9].

With the advent of the Micro-Incisional Vitreoretinal Surgery (MIVS) surgeons prefer less viscous silicone oils which can be introduced and removed more easily through the small instruments and cannulae. However, a more viscous silicone oil would be less likely to emulsify. For this reason, new silicone oils with an increasing extensional viscosity have been studied [12–15]. These types of silicone oils are obtained by the addition of a small amount (around 5–10%) of very-long-chain silicone molecules to a common silicone oil. The advantage of a silicone oil with an increasing extensional viscosity would seem to be an increased resistance to emulsification while maintaining a low viscosity and therefore an easier injection and removal with small gauge instrumentation with respect to single grade oils of the equivalent shear viscosity. To date, there are only few publications about the use of these new types of silicone oils and all of them are in vitro tests. The main concept raised from those tests is that silicone oil blends containing small percentages of a high molecular weight of the same chemical composition as the bulk oil are more resistant to emulsification and are easier to inject than single grade oils of the equivalent shear viscosity. However, there is only a case report on their clinical use by Maier et al. in which they reported two cases of early emulsification with a 2000 cs silicone oil (Siluron 2000, Fluoron, Neu-Ulm, Germany) [16]. Therefore, there is no evidence yet in the literature whether these new types of silicone oil show lower tendency to emulsify and therefore further clinical studies are needed.

6. Potential Complication Related to the Postoperative IOP Control

Since a variety of complications are possible in case of a vitreoretinal surgery, it is important to understand whether they are associated with the use of silicone oil or related to the underlying pathology and other aspects of surgical intervention.

One of the main issues regarding the use of silicone oils is the management of the postoperative IOP. In fact, a postoperative IOP rise is not uncommon after vitrectomy with silicone oil injection. In the Silicone Study a chronic elevated IOP has been reported in the 8% of eyes treated with conventional silicone oil at 36 months [17]. However, in the literature, the incidence ranges from 2 to 40% [10, 18]. The causes of raised IOP are multifactorial but, schematically, there are 3 types of mechanisms.

(1) Pupillary block glaucoma: it may develop at any time but it is more frequent in the early postoperative time (days to some weeks). Aphakic eyes have more risk compared to phakic/pseudophakic eyes. In either case, the block originates when aqueous humor cannot move in the anterior chamber due the presence of silicone oil bubble with consequent aqueous misdirection, shallow anterior chamber, and raised IOP. Therapy is to perform an inferior iridectomy (or

reopen it) with YAG laser or tPA injection. Otherwise, a second operation may be considered.

(2) Overfill of silicone oil: also this condition is more frequent in the early postoperative period and it is usually well treated with medical management. However, if the IOP remains too high, another operation with partial removal of silicone may be necessary.

(3) Chronic elevation of IOP: while the first two mechanisms were related to the presence of a whole silicone oil bubble, a chronic elevation of the IOP is usually related to a silicone emulsification and consequent migration of silicone oil drops into the anterior chamber angle. The emulsified droplets may obstruct the trabecular meshwork and develop a trabeculitis. For this reason, the therapy of this complication consists in topical or periocular steroids, conventional antiglaucoma drops, and, eventually, the removal of silicone oil with careful attention to remove emulsified droplets from the anterior chamber. Unfortunately, when the trabecular meshwork is permanently damaged, the IOP does not return into a normal range and therefore a glaucoma surgery may be required. In this regard, glaucoma drainage devices have been investigated for the treatment of refractory glaucoma. Ishida et al. found that the chronically raised IOP can be well controlled using the Ahmed glaucoma valve even if the presence of silicone oil was associated with an increased risk of surgical failure when compared with eyes that had not been treated with silicone oil [19]. However, in a case-control study by Wong et al., the authors found that the use of a heavy silicone oil (Densiron-68) was associated with a higher IOP in the early postoperative period when compared with a conventional silicone oil [20].

7. Indications for Silicone Oil Tamponade

The history of silicone oil in ophthalmic surgery is very short in comparison with gases. In the USA, in fact, silicone oil as intraocular tamponade has been approved by the Federal Drug Administration only in 1996. Since that date its use has increased very fast. The first indications were complicated retinal detachment due to PVR or viral retinitis, giant retinal tears, trauma, and severe proliferative diabetic retinopathy [21, 22]. New possible indications are now retinal detachment due to macular hole in highly myopic eye [23, 24], chronic and persistent macular hole, colobomatous retinal detachment [25], and chronic uveitis with hypotony [26]. In summary, every time a long-term tamponade is required. Silicone oil has in fact the important advantage of determining a long support until the recovery of the retina has occurred. In case of retinal detachment, we usually perform a silicone oil removal after 3–6 months because we believe this time is sufficient for the recovery of the eye with minimal risk for the development of a PVR.

Silicone oil is also the first choice for patients that have to fly or for patients that cannot maintain the correct postoperative positioning such as children or old patients.

The Silicone Oil Study, a prospective, multicentered, randomized, controlled clinical trial comparing silicone oil and long-acting gases in the management of eyes with severe PVR, concluded that silicone oils were superior to sulfur hexafluoride gas (SF6) and equivalent to perfluoropropane gas (C3F8). If we consider however certain subgroups, it appears clear that the use of silicone oil was better in case of relaxing retinotomy, severe anterior PVR, difficulty in maintaining the postoperative positioning, and the need to fly or travel to higher altitudes. On the contrary, the use of C3F8 had the relative indications for those cases with a poor iris diaphragm due to a high probability of corneal tamponade touch; superior retinal breaks on the posterior edge of a scleral buckle, because gas conforms better than silicone oil to the slope of the buckle; and the presence of a silicone intraocular lens with an open posterior capsule [27–29].

The rationale for silicone oil use in the management of PDR is the reduction in postoperative hemorrhages and the presence of a severe anterior segment neovascularization [30]. This is because silicone oil may prevent the flow of vasoproliferative factors into the anterior segment decreasing the risk of iris rubeosis and neovascular glaucoma. Obviously, we also use silicone oil after failure of conventional vitrectomy for PDR due to the development of PVR.

The use of silicone oil for macular hole repair is very controversial. We never use silicone oil as the first tamponade of an idiopathic macular hole, except in some particular cases. We prefer gas for many reasons. Gas has a higher superficial tension and better buoyancy and does not need a second surgery to remove it. This technique is well established nowadays and the success rate with the use of gas is very high [31]. We consider the use of silicone oil for selected and particular cases in the treatment of idiopathic macular holes when there are problems with the postoperative positioning, air travel is necessary, or one-eyed patient.

Before the advent of PFCLs, silicone oil has been used in the treatment of giant retinal tears both as intraocular tool and as postoperative tamponade. As an intraocular tool, silicone oil has been used to facilitate unfolding and flattening of retinal tears and retinal detachment. Today, we prefer for this purpose using PFCLs because they are easier to use and because they unfold and flatten the retina less traumatically. As permanent tamponade, silicone oils are indeed very useful. While gases may be used to repair a superior giant tear, in all other cases, we prefer silicone oil as intraocular tamponade until we believe the retina recovered.

The advent and the improvement of the vitreoretinal surgery have improved the prognosis of traumatized eye [32]. Silicone oils are used to minimize the risk of postoperative bleeding, maintain retina attached, and avoid phthisis in case of severely traumatized eyes. Often, several operations are needed to obtain a reasonable anatomical and functional outcome. After silicone oil removal, the high failure rate is generally due to the development of a retinal detachment and/or PVR that requires a new operation. In this regard, since it is believed that the proliferative process continues for a longer period of time than in eyes with nontraumatic retinal

detachment, especially in case of penetrating ocular trauma, it is recommended to leave silicone oil for several months.

8. Surgical Techniques

8.1. Silicone Oil Injection. Today, silicone oils are mainly used as intraocular tamponade because the recent introduction of PFCLs has decreased the use of silicone oils as intraoperative tool.

With the modern vitrectomy systems, the injection and the removal of silicone oils are performed using a syringe connected to a pump that is controlled by the surgeon with the foot-pedal. Since, 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 and due to the high viscosity and the high pressure that is required to infuse silicone oils into the vitreous cavity, special devices have been developed. The system is therefore made of a large syringe, an infusion line as short as possible, and nondistensible material. A large syringe is required because it has to handle the high infusion pressure, while a short infusion line is important to reduce the resistance during the injection and the removal. The use of a nondistensible material is important to avoid that, once the injection is stopped, undesired further injection occurs when the distended tube returns to its normal diameter, forcing more silicone into the eye [33].

There are 3 surgical techniques to inject silicone oils into the eye:

(i) fluid-silicone exchange,

(ii) air-silicone exchange,

(iii) perfluorocarbon liquid-silicone exchange (the so-called direct exchange).

We do not perform a fluid-silicone exchange because, due to the low surface tension, we believe that the risk is too high that silicone oil enters the subretinal space through retinal breaks. The choice of air, rather than perfluorocarbon liquid-silicone exchange, depends on two main reasons: the eventual presence of a retinotomy or an anterior break. If the break is in the mid periphery or at the posterior pole, we usually perform first a fluid-air exchange with internal drainage of subretinal fluid and then, once the retina is flattened under air, an air-silicone exchange. If a relaxing retinotomy has been applied or the retinal break is anterior, we prefer to perform a direct exchange between PFCL and silicone oil in order to avoid the slippage of the posterior edge of the tear. In this case, we connect the syringe to the infusion line and an extrusion needle is placed into the vitreous cavity. In this way, while the surgeon injects the silicone oil pushing the foot-pedal, either passive or active aspiration may be used to remove the PFCL. In case of 23- or 25-gauge vitrectomy systems, we set the machine with an aspiration rate from 0 to 30 mmHg and an infusion pressure rate from 0 to 28 Psi. It is important to not exceed 30 Psi to avoid the disconnection of the infusion line from the eye.

Regarding the management of the anterior segment, particular attention has to be drawn to aphakic patients. In these patients, an inferior peripheral iridectomy (IPI) is mandatory to avoid pupillary block secondary to the silicone oil filling. The IPI allows aqueous humor to pass under the silicone oil bubble and to enter into the anterior chamber without causing a pupillary block.

8.2. Silicone Oil Removal. Also, regarding silicone oil removal, there are several techniques. Some surgeons prefer to remove silicone oils using a two-port system, one for the infusion line and another one to aspirate the tamponade. Using this technique, it is also possible to passively remove silicone oil through a small cornea incision in aphakic eyes. At the end of the procedure, surgeons have to control whether retina is still attached using a binocular indirect ophthalmoscope. We do not use this technique anymore for several reasons: first, because it is impossible to have a direct control of the intraocular pressure and because it is impossible to be sure that the silicone oil has been removed completely. Finally, with this technique, it is impossible to remove the silicone oils which are heavier than water.

We therefore always perform a standard three-port pars plana vitrectomy also for silicone oil removal. We set the machine with an IOP at 20–25 mmHg and a vacuum rate from 0 to 650 mmHg. We currently use the new high-flow extraction sleeve by Alcon that significantly improves oil extraction compared with the old system, up to 5 times faster depending on the gauge. The sleeve consists of a silicone tube that is inserted on the head of the cannula (both 23- and 25-gauge) and allows the aspiration of the silicone oil through the cannula. To remove the sleeve from the cannula, it is enough to exert a tilt motion, taking care to keep the head of the cannula with a forceps (e.g., Bonn).

Once the silicone oil bubble has been removed, we perform several fluid-air exchanges in order to remove every small drop of silicone oil that remained inside the eye. In case of emulsified drops in the anterior chamber, their removal through a small corneal incision to minimize postoperative risk of complications such as silicone keratopathy and secondary glaucoma is mandatory.

In phakic eyes, the decision whether or not to remove the lens depends on the presence of a cataract and the patient's age. If there is a significant cataract, we usually remove the lens during vitreoretinal surgery. If the crystalline lens is clear, the decision arises from the age of the patient because in patients older than 50 years we prefer to remove the lens because the eye will develop a significant cataract few months after the surgery. In this case, we perform a combined phacoemulsification, posterior-chamber IOL implantation, and silicone oil removal.

9. Conclusions

Silicone oils are very useful surgical tools because they are able to simplify the surgical management of many vitreoretinal diseases. With the modern vitrectomy systems and the possibility to use such different tamponades, the prognosis of several diseases has improved. According to the vitreoretinal pathology, we can choose between a variety of silicone

tamponades and we can therefore select the best intraocular tamponade in relation to the underlying disease.

Depending on the situation and the duration of the tamponade, we can decide which of the various characteristics of an endotamponade would be the most important. Nevertheless, we have to keep in mind that there are some steps, such as complete removal of any traction, that are crucial for the success of the surgery.

The decision of silicone oil usage may be taken both before and during the operation. The first and more important parameter of choice is the time that is, in surgeon's opinion, requested for the tamponade. Before the operation, it is fundamental to take into consideration the type of vitreoretinal disease (e.g., is there a PVR? And is the risk of a surgical failure high?) and the postoperative position because if we know that it is impossible for the patient (e.g., children) to maintain a certain postoperative positioning, maybe it is better to choose silicone oil instead of another tamponade. However, even if we have not programmed the use of a permanent tamponade, it is possible to decide during the operation that silicone oil is needed. For example, the decision to perform a retinotomy or complications such as an intraocular bleeding can indicate the choice of silicone oil.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Review Article

Vitreous Tamponades in Highly Myopic Eyes

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The use of endotamponade agents has gained a major role in the management of macular complications of high myopia. Myopic foveoschisis and macular hole are the main macular complication of pathologic myopia, this growing condition that is a main cause of visual loss, especially in patients at a younger age. We discuss the physical properties and advantages and disadvantages of the main ocular tamponade agents used in the treatment of these diseases.

1. Introduction

Intraocular tamponade agents are used to prevent the flow of intraocular fluid through retinal breaks, maintaining a temporary retinal attachment and allowing a persistent chorioretinal adhesion to appear after retinopexy is applied (laser photocoagulation or cryotherapy). Different endotamponade agents have been classically used: room air, sulphur hexafluoride (SF_6), perfluoropropane (C_3F_8), and silicone oil. More recently, high-density or heavy silicone oils (HSO), a mixture of semifluorinated alkanes and silicone oil, have been described to provide tamponade to the inferior retina.

The effectiveness of a tamponade agent depends on its ability to maintain contact with the retina while displacing displacing the aqueous from the retinal surface. Several physical parameters, such as specific gravity, buoyancy, interfacial tension, and viscosity, influence this property [1].

The use of internal tamponades, specially gas agents, requires postoperative positioning in order not only to achieve good postoperative apposition between the bubble and the retina but also to avoid postoperative complications. Poor compliance with head positioning may potentially reduce the anatomical success rate.

High myopia, defined as a refractive error of >−6,00 D and an axial length of >26 mm [2], is a growing condition in developed countries, especially in Asia. These eyes can develop specific pathologies, such as myopic foveoschisis and retinal detachment (RD) secondary to macular hole (MH), that may need the use of an internal tamponade. Other common complications, such as rhegmatogenous RD due to peripheral retinal pathology, can also appear more frequently.

2. Indications of Endotamponade Use in High Myopic-Related Pathology

2.1. Retinal Detachment Secondary to Macular Hole. RD secondary to MH in highly myopic eyes is a challenging condition and one of the most difficult retinal detachments to treat. There is no clear understanding of the pathogenesis of myopic MH and RD, but anteroposterior and tangential traction from the posterior cortical vitreous, similar to idiopathic MH, have been suggested as the main causative factors [3]. Posterior staphyloma, causing inverse traction of the macula, and poor retinal adhesion secondary to retinal pigment epithelium (RPE) atrophy have also been described in the development of this condition [4].

Several treatment options have been proposed and, before the advent of pars plana vitrectomy (PPV), episcleral macular buckling alone was the standard of care in this situation. More recent approaches include the injection of an expansible gas bubble with or without PPV. Internal limiting membrane

(ILM) peeling has also been implemented in the surgical procedure of these eyes in the last years.

Some authors have reported good outcomes after a more conservative approach, such as pneumatic retinopexy [5–7]. This surgical technique consists of injecting a gas bubble in the vitreous cavity, as internal tamponade, and prone position of the patient. In some cases, subretinal fluid is released through a sclerotomy [5, 6]. The best results reported with this technique are with RD involving only the posterior pole, provided that vitreous traction is absent [6]. Nevertheless, these studies were carried out before the optical coherence tomography (OCT) era, thus, making it difficult to assess the macular status of the patients. More recently, Ripandelli et al. reported a high retinal reattachment rate in a group of patients with RD due to MH and complete posterior vitreous detachment, treated with external drainage, pneumatic retinopexy, and transpupillary diode laser [7]. The treatment consisted of an injection of 1.5 to 2.5 cm^3 of sterile 18% SF_6into the vitreous cavity via the pars plana under topical anaesthesia and face-down positioning for less than 7 days.

Li et al. performed a prospective study comparing the efficacy of simple intravitreal gas injection versus PPV combined with intraocular gas tamponade, for the treatment of RD secondary to MH in high myopia [8]. PPV with C_3F_8 endotamponade resulted in a higher anatomical success rate than intravitreal C_3F_8 gas injection alone. Though being inferior, pneumatic retinopexy resulted in 59.8% success rate after 6 months, therefore providing a good economic option in some cases. The authors reported no intra- or postoperative complications with pneumatic retinopexy. No retinopexy to the MH rim was used and, though patients underwent regularly OCT examinations, the MH closure was not reported.

PPV with the use of an endotamponade agent is the most commonly used technique for the management of RD secondary to MH in highly myopic eyes [3, 4, 9–16]. It is controversial, though, whether any of the available internal tamponades are associated with a higher retinal reattachment rate. What seems clear is that initial reattachment, within the first surgery, is correlated with a better final visual outcome [4].

Unfortunately, there are no randomized clinical trials comparing which tamponade agent yields the best outcome in these patients. Some authors have retrospectively compared different gas endotamponade agents with contradictory results. Uemoto et al. reported a higher rate of retinal reattachment and MH closure with C_3F_8 compared to SF_6 gas [9]. Nakanishi et al. did not observe significant differences between types of gas tamponade. Interestingly, both studies are retrospective, and it is difficult to determine whether the duration of the gas tamponade may influence the surgical outcome [4].

The rationale for using a longer-action endotamponade in highly myopic eyes with MH and RD is to increase retinal reattachment rate and final visual outcome. This is based on the idea that shorter-acting gas does not provide a long-enough tamponade effect to allow for a glial reaction responsible for the closure of the MH and posterior retinal reattachment. This is especially relevant in highly myopic eyes, where the chorioretinal adhesion may not be as firm as it would be in patients with a healthy retinal pigment epithelium [9].

The repair of RD resulting from a posterior staphyloma-associated MH in highly myopic eyes may need more prolonged internal tamponade, as that given by silicone oil, in order to achieve MH closure and subretinal fluid reabsorption. Silicone oil in this situation shows additional advantages: shorter duration of prone positioning, faster visual rehabilitation, and easier follow-up of the retina and MH by the ophthalmologist [14]. Additionally, high myopic patients may benefit from the hyperopic shift induced by the refractive index of the silicone oil [17].

Scholda et al. reported a reattachment rate of 100% in eleven patients using silicone oil (5,000 centistokes (cSt)). The authors argued that silicone oil served as an inductor scaffold for glial closure of the causative macular hole. No additional manoeuvre was performed and the internal retina was left untouched. They did not remove the subretinal fluid through the macular hole. However, in this study, the authors did not use an OCT to assess the status of the macula after the surgery [13]. It is mandatory to achieve a complete closure of the macular hole in order to avoid recurrent retinal redetachment. OCT helps to predict anatomic and functional outcomes of highly myopic eyes having macular hole-related retinal detachment.

Silicone oil removal can be performed when MH closure is confirmed by OCT, while, in eyes with nonclosed MH, silicone oil removal may lead to a recurrent retinal redetachment [18].

2.1.1. Myopic Posterior Staphyloma. Despite the documented advantages favouring silicone endotamponade, a recent study comparing silicone oil tamponade with C_3F_8 reported better results when C_3F_8 tamponade was employed. The initial rate of MH closure was 94% in the C_3F_8 group and 54% in the silicone oil group [19]. The authors point to the tendency for silicone oil to bridge across the margins of the staphyloma as one of the causes for higher rate of failure in the silicone group. It is well accepted that silicone oil bubble does not fit well into small recesses, such as the retina under the scleral buckling indentation, as well as into posterior staphyloma [20]. Interestingly, all subjects with initial anatomical failure achieved stable retinal reattachment after being reoperated with vitrectomy and HSO tamponade. Unfortunately, this is a small retrospective series and no definite conclusions can be established [19]. According to Nakanishi et al., the depth of posterior staphyloma may be associated with MH closure and RD reattachment rates, as it is difficult for the tamponade to fit into this area [4]. This is secondary to the buoyancy of silicone oil (specific gravity of 0.97 gr/mL) that is not enough to fit the posterior staphyloma, where there is practically no tamponade effect of the silicone oil. This raises an interesting question: why does MH in the presence of posterior staphyloma in highly myopic eyes close with silicone oil tamponade? Being a hydrophobic fluid, a thin layer of aqueous separates the silicone oil bubble from the retina. This is more evident in the presence of a posterior

staphyloma in highly myopic eyes, where silicone oil does fit well and probably leaves a pocket of aqueous fluid. Fluid filled retinal areas experience negligible shear forces [21]. Besides, this compartmentalized fluid is scarcely influenced by ocular movements, and therefore fluid current is very low, generating even a lower shear retinal stress. This, in turn, may allow the MH to close and the RD to reattach.

2.1.2. Is Prone Positioning Always Needed? The role of postoperative posturing after vitreoretinal surgery is still controversial, as there is insufficient scientific evidence of whether it has a direct relationship with surgical outcome [14, 21]. A recent noncomparative study showed a high retinal reattachment rate performing PPV with internal limiting membrane peeling and silicone oil tamponade without any postoperative position restriction [14, 15]. Nevertheless, nonposturing surgery critically relies on the tamponade fill of the eye, especially in the early postoperative time [22]. This is even more important when silicone oil is used, because the typical round shape of the bubble it forms needs almost complete fill to make an effective contact with the retina. Complete vitrectomy and the greatest percentage of fill are always advisable to achieve maximal tamponade effect. It is important to note that tamponade efficiency does not depend on the size of the eye [22].

In the case of MH in highly myopic eyes treated with silicone oil as endotamponade, there should be no theoretical difference in whether standard or heavy silicone oil is used and whether the patient maintains a strict head posturing after the surgery, because it is a matter of low shear stress that closes the MH.

2.1.3. Heavy Silicone Oils (HSO). New HSO are mixtures of silicone oil with semifluorinated alkanes that combine a good tolerance with a satisfactory inferior tamponade. Oxane HD (Bausch & Lomb Inc., Waterford, Ireland) and Densiron (Fluoron GmbH. Neu-Ulm, Germany) were developed as vitreous substitutes to provide better inferior tamponade in cases of complicated retinal detachments with inferior breaks and proliferative vitreoretinopathy. HSO have a higher specific weight than water, which enables effective tamponade of the inferior retina, allowing the patient to adopt a supine posture postoperatively.

There are 2 studies comparing standard silicone oil and Densiron in highly myopic eyes with MH RD with different results. Avitabile et al. reported a better anatomical success rate with Densiron than 1000 cSt silicone oil [3]. Retinal redetachment after initial surgery with endotamponade in situ occurred more frequently in eyes filled with standard silicone oil, as all the eyes filled with Densiron had attached retinas. This finding was the same after removal of the silicone oil. In this study, patients did not get a significant visual improvement despite anatomical success probably due to the damage induced by the laser burns around the macular hole. In contrast, Mete et al., in a retrospective study, showed no statistically significant difference in retinal reattachment rate between eyes treated with standard silicone oil and Densiron [16].

Other authors have shown good results after using the combination of HSO and standard silicone oil in the treatment of RD with breaks and proliferative vitreoretinopathy involving the upper and lower quadrants [23].

2.1.4. Disadvantages of Silicone Oil Endotamponade. One of the main downsides of using silicone oil as an ocular tamponade is the need for a second surgery to remove the oil. Another issue associated with silicone oil is intraocular pressure problems, sometimes related to oil emulsification [14]. Silicone oil viscosity has been classically proposed as the main factor affecting its emulsification. More recently, though, complete eye cavity fill and the presence of a scleral buckling have been described as factors even more important than viscosity influencing silicone oil emulsification. The presence of an encircling scleral element prevents emulsification by reducing the velocity of the oil inside the eye and therefore the shear force that generates emulsification [24]. Tamponade effectiveness of silicone oil is directly associated with the emulsification of this intraocular agent.

Comparing significant emulsification (e.g., abundant droplets of silicone oil in the anterior chamber or in the angle) of different types of silicone, Avitabile et al. found that, within 12 weeks of surgery, it was present in 30% of myopic eyes in the 1000 cSt silicone group and in 13% of the Densiron group. Minor dispersion of oil was also more frequently detected in the silicone group [3].

Other side effects described with either standard silicone oil or HSO are corneal opacity, corneal decompensation, and cataract formation. Others more specifically associated with Densiron are pseudohypopyon, due to intense emulsification, and chronic hypotony [25]. Inflammatory response may be another concern when using silicone oil. In a study comparing HSO with 1000 cSt silicone oil, Densiron showed a more proinflammatory profile [3]. Up to 40% of myopic eyes with retinal detachment treated with PPV and Densiron tamponade showed signs of inflammation, such as fibrin accumulation, keratopathy, or anterior chamber reaction. This inflammatory reaction was more frequent and intense than that seen in eyes treated with standard silicone oil. Interestingly, when managed with topical steroid therapy, they needed almost 1 week of treatment to control the inflammatory signs whereas eyes treated with standard oil responded in few days.

Unresponsive granulomatous inflammation, which usually resolves after HSO removal, has been reported with the use of HSO [26]. However, as suggested by Cheung et al., this finding might be secondary to the direct perfluorocarbon-HSO exchange [15]. Similarly, Veckeneer et al. have described an abnormal silicone oil adherence to the retina at the time of removal, related to the use of perfluorocarbon [27]. Other authors have confirmed these findings in vitro and related the "sticky oil" formation to the variation in temperature of the oil [28].

Sudden visual loss after silicone oil removal has been reported by several authors. Visual acuity drop can be severe and irreversible. It is not associated with other complications and it may happen after macula on retinal detachment.

Fundus examination, fluorescein angiography, and OCT findings are usually unaltered, and only electroretinogram testing shows a different range of abnormalities, usually a severe macular dysfunction. There are several theories, but exact pathogenesis is unclear [29, 30].

2.2. Myopic Foveoschisis. Foveoschisis, in the presence of posterior staphyloma, is a major cause of visual impairment in highly myopic eyes. This condition has also been called macular retinoschisis, posterior retinoschisis, foveal retinoschisis, or shallow detachment of the macula, and its prevalence has been reported in up to 34% of eyes with pathologic myopia [31]. Foveal detachment is frequently associated, between 32% and 72% of the cases [32], complicating the situation and giving a lower visual acuity to the patient.

The pathogenesis of myopic foveoschisis and foveal detachment still remains unclear. Different factors have been related to its progression, but vitreous and epiretinal traction of residual vitreous cortex in the presence of a posterior staphyloma has been postulated as the main one. Other factors, such as poor elasticity or excessive rigidity of the ILM, stiffness of retinal vessels, progressive posterior staphyloma, and choroidal atrophy, may also play a relevant role in the pathogenesis [31, 33–37].

Some authors believe that this condition is not a true retinoschisis, with separation between retinal layers, but instead a form of retinal oedema secondary to vitreoretinal traction, and they have named it myopic traction maculopathy [38].

Natural course of myopic foveoschisis is variable, but it can remain stable for many years, without significant variation in visual acuity, with changes only appearing slowly over time [39, 40]. There is a report of spontaneous anatomical reattachment and visual improvement after posterior vitreous separation [41]. Nevertheless, other authors have described this condition as the initial step to the onset of a MH or a RD, in almost 50% of the patients [31, 33, 36, 39, 42, 43].

PPV, with or without ILM peeling, is widely accepted as the standard of care for macular schisis in high myopia [44–46]. Nevertheless, complications can occur, especially in patients with pathologic myopia: vitreous or macular haemorrhage, macular hole, ocular hypertension, and retinal breaks with or without retinal detachment. Furthermore, visual improvement is not always achieved after the macula has been reattached.

Other less invasive alternatives have been described. Anatomical success can be accomplished after gas tamponade without vitrectomy, although it may occur after a prolonged time period and multiple gas injections [32]. An intravitreal injection of C_3F_8, followed by prone positioning for 5–7 days, initially resolved 50% of cases with additional cases being resolved after repeated injections. According to the authors, this procedure is not suitable for cases with obvious central vitreomacular traction [32].

2.2.1. Is Intraocular Tamponade Always Necessary? Some studies have also questioned the necessity of using gas tamponade in patients who undergo PPV for myopic foveoschisis. Several authors have found that PPV with ILM peeling without gas tamponade results in resolution of foveoschisis and foveal reattachment, with an improvement in best-corrected visual acuity (BCVA) [38, 47]. The rationale behind this management is that the simple release of vitreoretinal traction without using any tamponade can slowly reverse macular distortion and lead to stable retinal anatomy restoration [38]. Additionally, this approach would be more favourable for the patient, as it would not require any postoperative positioning.

There are no accepted and universal criteria for vitreoretinal surgeons of when to use an intraocular tamponade in myopic foveoschisis. For Zheng et al., in a retrospective study, the criteria for using C_3F_8 or balance-salt solution (BSS) at the end of the PPV were exclusively based on the surgeon's experience and the feeling of where "macular region looked mobile and detached during posterior vitreous removal and ILM peeling" [33]. These authors showed a significant higher visual improvement when gas tamponade was used (logMAR BCVA change 0.58 ± 0.44) compared to the BSS group (logMAR BCVA change 0.25 ± 0.34). It is important to highlight that the presence of foveal detachment and duration of symptoms were not taken in account. Besides, final visual acuity could depend on the dye used for ILM peeling and time of incubation of the dye.

Uemoto et al. support the fact that long-acting gas endotamponade, like C_3F_8, even gives a better outcome than SF6, in the management of this condition [9].

By contrary, Kumagai et al. did not find a significant correlation between gas endotamponade use and final BCVA, in cases of myopic foveoschisis treated with PPV and ILM peeling [35]. Eyes treated with gas, though, showed a tendency to have better visual outcome. For these authors, the presence of a foveal detachment, in the preoperative period, was the best predictor for a better final BCVA [35].

2.2.2. Does Intraocular Tamponade Induce Macular Holes in Eyes with Myopic Foveoschisis? Several studies have pointed out the potential relationship between intravitreal tamponade and the creation of a MH, in cases of foveoschisis with foveal detachment in highly myopic eyes. Hirakata and Hida suggested that intravitreal gas might push the subretinal fluid inside the limited space under the foveal detachment toward the thin fovea, breaking this weak point and creating a MH [36]. These authors described a postoperative MH in 19% of eyes treated with endotamponade, all of which had a concomitant foveal detachment.

In a retrospective study, Kim et al. described the development of a MH in 22% of patients with foveoschisis and foveal detachment when gas tamponade was used, but no cases of MH were found in the group without tamponade [34]. On the contrary, Kumagai et al. described no cases of MH or other complications, in a retrospective study with 34 highly myopic eyes, after PPV, ILM peeling, and SF_6 endotamponade [35]. Other authors have shown similar results using C_3F_8 [33]. Interestingly, Panozzo and Mercanti showed 25% of patients with myopic foveoschisis who developed a MH after PPV, when no endotamponade agent was used [38].

Studies on this topic reveal contradictory results and are mostly retrospective. Besides, ILM peeling was performed in many of the cases. This may be a potential confounding factor for the appearance of a MH, because this technique, although it has proven its effectiveness, can induce MH in eyes with very thin foveola [34, 37]. Supporting this idea, Shimada et al. reported 0% MH formation rate after fovea-sparing ILM peeling compared to 16.7% of MH in the conventional ILM peeling group, for the treatment of myopic traction maculopathy [48]. It is also important to note that myopic eyes are more prone to MH, even when PPV is not performed. MH has been described in almost 20% of fellow eyes in patients with myopic foveoschisis and foveal detachment [36].

It is not totally clear how a bubble of intraocular gas can improve anatomical restoration in myopic foveoschisis. Several factors have been related to its mechanism of action. Firstly, the gas bubble can induce displacement of outer layer detachments, by making RPE and retina together. Facedown positioning could enhance this. Once the subretinal fluid is spread out of the subfoveal area by the bubble of gas, healthier RPE cells can more easily pump it out [8, 32, 49]. Other authors suggest that the gas bubble generates a dry environment in the macular area, which has the potential effect of accelerating the reabsorption of residual fluid in the retina. This, in turn, may benefit the delivery of oxygen and metabolites to the outer retina [8, 33, 37]. But the mechanical effect of the gas bubble can last for a maximum of 1 or 2 months, until it has been totally reabsorbed. Resolution of foveoschisis, in many cases, can easily take more than this time, making it more difficult to understand the precise mechanism of action of the gas [34].

In eyes with myopic foveoschisis in which PPV is not performed, the gas bubble may act differently. The intraocular agent may work by stretching the posterior vitreous hyaloid and weakening the vitreoretinal adhesion.

2.2.3. Is Anatomical Resolution Faster with Gas Tamponade? Several studies have found that gas tamponade leads to faster anatomical resolution of myopic foveoschisis, compared to not using a gas tamponade [33, 34]. Kim et al. showed that the mean time for resolution was 2.25 months (range: 1–3) for the gas treated group, whereas it was 4.50 months (range: 2–8) for the group without tamponade [34]. Similarly, Panozzo et al, in a noncomparative study, described a slow process of anatomical recovery (mean: 4.4 months; range: 1–12 months) [38]. The time needed for anatomical resolution for Zheng et al. was obviously longer in the BSS group (without tamponade) [33].

3. Conclusion

High myopia macular complications are an increasing cause of visual loss. New diagnostic technologies have greatly increased our understanding of these pathologies and help to plan the surgical approach that yields the best postoperative result. The use of endotamponade agents plays a definite role in the surgical management of these patients, especially with myopic foveoschisis and RD secondary to myopic MH. Comprehensive knowledge of the physical properties, indications and potential complications of the different available tamponade agents will help us to improve the care of our highly myopic patients.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Research Article

Analysis of the Time and Location of the Silicone Oil Emulsification by Spectral-Domain Optical Coherence Tomography after Silicone Oil Tamponade

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Purpose. To estimate localization and the period up to the appearance of small hyperreflective round-shaped droplets using spectral-domain optical coherence tomography (SD-OCT) after pars plana vitrectomy with silicone oil tamponade. *Methods*. A retrospective observational study included 24 patients who had undergone pars plana vitrectomy with silicone oil tamponade for proliferative vitreoretinopathy (PVR) retinal detachment. SD-OCT analysis was performed 1, 3, and 6 months after surgery. We characterized the emulsified silicone oil in the SD-OCT as the small hyperreflective round-shaped droplets. *Results*. In SD-OCT examination, none of the patients had hyperreflective round-shaped droplets visible one month after vitrectomy with silicone oil tamponade. The hyperreflective droplets were found three months after surgery—in one patient above the optic nerve and in five patients intraretinally (in the cystoid spaces). Six months after vitrectomy, the hyperreflective round-shaped droplets were still present in the aforementioned patients' eyes and additionally in 3 eyes above the optic disc. *Conclusions*. Hyperreflective round-shaped droplets were found in a SD-OCT examination 3 months after silicone oil tamponade. The authors suggest that they are most likely the emulsified silicone oil droplets. The authors hypothesize that emulsification and migration of silicone oil begin within 3 months after surgery.

1. Introduction

Emulsified silicone oil can penetrate into structures of the eye such as the retina, trabecular meshwork, anterior segment, and optic nerve in patients who were treated with silicone oil tamponade for various vitreoretinal procedures [1–4]. Histopathological examination confirmed that the oil droplets become toxic to the penetrated ocular structures and may result in loss of visual acuity [1, 5, 6].

However, we still know very little about the time when silicone oil becomes emulsificated and its eventual migration to the retina. To date, few reports have shown the presence of emulsified silicone oil droplets intraretinally, subretinally, and beneath the epiretinal membranes in *in vivo* studies, which is optical coherence tomography [7, 8]. However, these studies were only stating its presence while nothing is mentioned about the time in which emulsification and migration of silicone oil occurred.

The purpose of this study is to analyze, in the spectral-domain optical coherence tomography (SD-OCT) examination, the time in which the hyperreflective round-shaped droplets appear after pars plana vitrectomy with silicone oil tamponade. In addition, we also describe the possible localization of the hyperreflective droplets.

2. Material and Methods

A retrospective observational study included 24 patients who had undergone pars plana vitrectomy with 1000-centistoke silicone oil (Dorc, Zuidland, The Netherlands) tamponade for proliferative vitreoretinopathy (PVR) retinal detachment. Six

Table 1: Descriptive statistics for age, intraocular pressure (mmHg), and logMAR values at baseline and at final examination, taking place after 6 months, in 24 examined patients.

	M*	Me†	SD‡	SE**	95% CI††	CV‡‡	Min.–Max.	*P* value***
Patients' age (years)	66.92	64.00	10.87	2.22	62.33–71.51	16.24%	46–90	
Intraocular pressure (mmHg)								
At baseline	13.04	14.00	2.91	0.59	11.81–14.27	22.32%	8–19	
At final exam	15.17	16.00	4.59	0.94	13.23–17.11	30.29%	5–21	
LogMAR								
At baseline	5.12	5.76	1.94	0.40	4.30–5.94	37.84%	2.30–6.91	<0.001
At final exam	2.53	2.65	1.13	0.23	2.06–3.01	44.46%	0.92–4.61	

*M: mean value.
†Me: median value.
‡SD: standard deviation.
**SE: standard error.
††95% CI: 95% confidence interval.
‡‡CV: coefficient of variation.
***The Wilcoxon test was performed.

Table 2: Descriptive statistics for age, intraocular pressure (mmHg), and logMAR values in eight patients with hyperreflective round-shaped droplets during the follow-up SD-OCT examination.

	M*	Me†	SD‡	SE**	95% CI††	CV‡‡	Min.–Max.
Patients' age (years)	64.25	63.50	9.22	3.26	56.54–71.96	14.36%	46–75
Intraocular pressure (mmHg)							
At baseline	13.13	14.00	1.55	0.55	11.83–14.42	11.83%	11–15
At final exam	17.50	18.00	2.88	1.02	15.09–19.91	16.45%	12–21
LogMAR							
At baseline	4.69	4.95	2.38	0.84	2.70–6.68	50.72%	2.30–6.91
At final exam	2.06	1.96	0.94	0.33	1.27–2.84	45.52%	0.92–3.22

*M: mean value.
†Me: median value.
‡SD: standard deviation.
**SE: standard error.
††95% CI: 95% confidence interval.
‡‡CV: coefficient of variation.

patients (6 eyes) additionally underwent 180-degree retinectomy. In 18 patients (18 eyes), internal limiting membrane (ILM) peeling was performed. At the time of surgery, 12 patients were pseudophakic (PCIOL). We performed phacoemulsification with intraocular lens implantation in 12 eyes as a combined procedure with vitrectomy. Four patients have, additionally, diabetes mellitus, nonetheless without evidence of diabetic retinopathy. All retinal surgeries were performed by a single surgeon (D.O.) in local anesthesia.

Patients were excluded if they had undergone a previous vitreoretinal surgery with silicone oil tamponade, silicone oil tamponade of less than 6 months, or different type of silicone oil or had diabetic retinopathy, poor SD-OCT scan quality, or high myopia exceeding −6,0 diopters.

All patients were interviewed and underwent ophthalmologic examinations prior to treatment and 1, 3, and 6 months after vitrectomy with silicone oil tamponade. Examinations included BCVA using standard Snellen eye charts, intraocular pressure, anterior segment, and fundus examination with Volk 78D and 90D lenses (Volk Optical Inc., Mentor, OH, USA). SD-OCT analysis (Spectralis; Heidelberg Engineering, Heidelberg, Germany) was performed 1, 3, and 6 months after surgery. In each patient we performed horizontal line scan through the fovea and 19 B-scans on an area of 4.5×6 mm were done. We compared the results analyzed and performed by 2 ophthalmologists (D.O., I.L.O) and the results were not different.

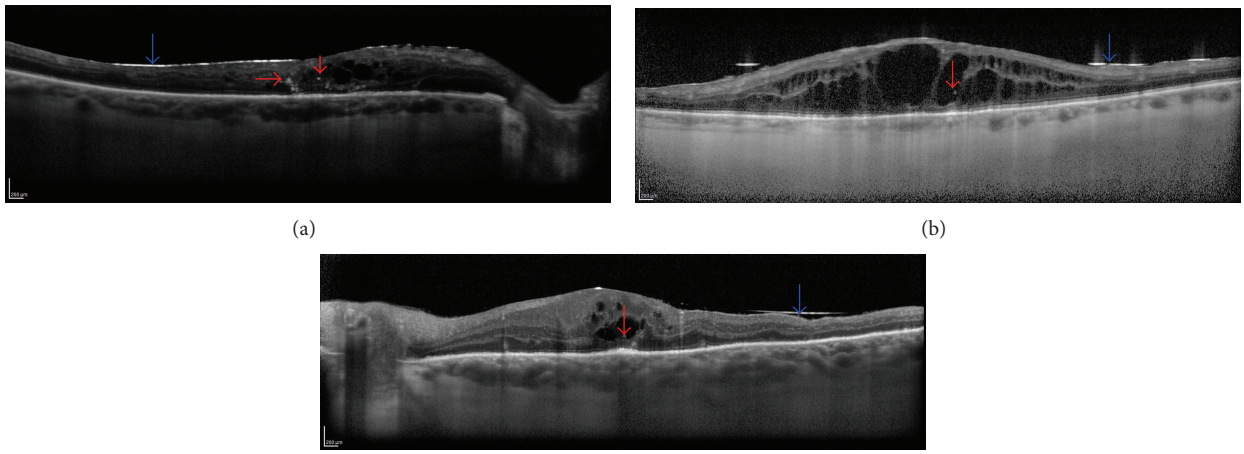
We characterized the emulsified silicone oil in SD-OCT as the small hyperreflective round-shaped droplets according to the Errera paper [8].

Statistical analyses were carried out using the Pearson product-moment correlation coefficient, Cochran's Q test, Fisher's exact test, Wilcoxon signed-rank test, and logistic regression. All the statistical procedures were conducted by means of Stata 12.1 Special Edition (StataCorp LP, College Station, Texas, USA). The significance level was set to be $P < 0.05$.

3. Results

The mean age of the 24 patients is 66.92 ± 10.87 years. The mean LogMAR visual acuity before vitrectomy with silicone oil tamponade was 5.12 ± 1.94.

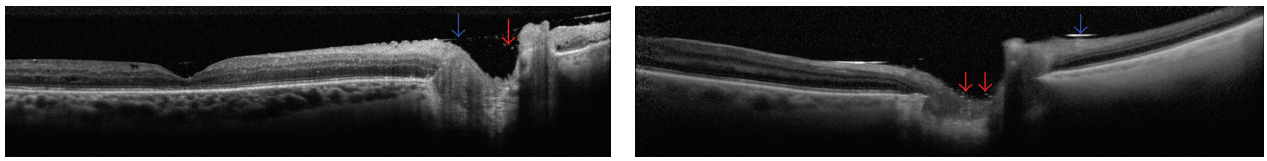
Anatomic success (complete retinal attachment) was noted in all cases. During the last follow-up examination, the retina was still attached in all eyes. The mean LogMAR visual acuity at the final follow-up visit was 2.53 ± 1.13



(a) (b)

(c)

Figure 1: Spectral-domain optical coherence tomography (SD-OCT) showing hyperreflective droplets of emulsified silicone oil visible intraretinally—in the cystoid spaces (red arrows) in 3 cases after vitrectomy with silicone oil tamponade (blue arrow) ((a)–(c)).



(a) (b)

Figure 2: SD-OCT showing hyperreflective round-shaped droplets (red arrow) between the visible hyperreflective line of silicone oil (blue arrow) and the optic nerve in 2 cases ((a)-(b)).

(Tables 1 and 2). We noted postoperative intraocular pressure (IOP) over 21 mmHg in 7 eyes, all of them receiving topical antiglaucomatous therapy. The IOP was normal in all of these patients at all follow-up visits and all of them still required the same antiglaucomatous drops.

In SD-OCT examination, none of the examined patients had hyperreflective round-shaped droplets visible one month after vitrectomy with silicone oil tamponade. The hyperreflective droplets of emulsified silicone oil were found three months after surgery; in one patient the droplets were detected between the visible hyperreflective line of silicone oil and the optic nerve; in five participants the emulsified silicone oil was found intraretinally (in the cystoid spaces) (Figure 1). Six months after vitrectomy, the hyperreflective round-shaped droplets were still present in the aforementioned patients' eyes and additionally in 3 study participants between the hyperreflective line of silicone oil and the optic disc (Figure 2). Table 3 records detailed information about each patient with visible hyperreflective round-shaped droplets in SD-OCT examination. Importantly, 11 patients presented cystoid macular edema (CME) at baseline and during the follow-up examinations. In 2 patients epiretinal membrane was found in the follow-up study 3 months after surgery (in these patients ILM peeling was not performed).

The persistence of the hyperreflective, tiny, round-shaped droplets of emulsified silicone oil between its hyperreflective line and the optic nerve was conditioned by the examined patients' age; the discussed droplets of emulsified silicone oil were significantly more frequent in younger participants of the study ($P = 0.014$), prevalence of glaucoma patients ($P = 0.002$), absence of CME ($P = 0.034$), and implementation of ILM peeling procedure ($P < 0.001$). The persistence of the droplets of emulsified silicone oil in the intraretinal area (in the cystoid spaces) was statistically determined only by the occurrence of CME ($P = 0.020$).

4. Discussion

In this study we submit that the SD-OCT examination can show the localization and allow detection of the time when small hyperreflective round-shaped droplets, which may be defined as emulsified silicone oil, appear.

Silicone oil has been used as an intraocular tamponade for many years and is considered to be relatively safe. However, its toxicity to the retina or the optic nerve has also been reported [4, 5].

The presence of intraretinal silicone oil emulsification in optical coherence tomography has been described in only a few articles [7, 8]. Errera et al. analyzed a few eyes in SD-OCT in which they demonstrated tiny hyperreflective spherical bodies intraretinally and underneath epiretinal membrane in eyes with silicone oil tamponade. They showed, on the basis of their observation, that these areas are most likely emulsified

Table 3: Detailed information about each patient with hyperreflective round-shaped droplets found in the SD-OCT examination in follow-up study.

Age (years)	DM	Retinectomy	Glaucoma	CME	ILM peeling	Location of SO 1 month postop.	Location of SO 3 months postop.	Location of SO 6 months postop.
73	−	+	+	+	+	−	Intraret.	Optic nerve, intraret.
71	−	+	+	+	−	−	Intraret.	Intraret.
75	−	−	+	+	+	−	Intraret.	Intraret.
64	−	−	−	−	+	−	—	Optic nerve
46	−	−	−	+	−	−	Intraret.	Intraret.
63	−	+	+	+	+	−	Intraret.	Intraret.
60	−	−	+	+	+	−	—	Optic nerve
62	−	−	+	−	+	−	Optic nerve	Optic nerve

DM: diabetes mellitus; CME: cystoid macular edema; ILM: internal limiting membrane; SO: silicone oil; postop.: postoperatively; intraret.: intraretinally.

silicone oil. We are finding similar areas in our study and also assumed that this may be emulsified silicone oil.

The duration in which the emulsification of silicone oil occurred and the mechanism of penetration into the retina are still unclear [7, 9, 10]. Some authors demonstrated the presence of silicone oil intraretinally only in the eyes in which retinal architecture was compromised in patients with retinotomy or the presence of oil subretinally [1, 11]. Errera et al. also demonstrate the presence of emulsified silicone oil droplets intraretinally in eyes in which retinotomy was not performed and in eyes without silicone oil under the retina. In our study, hyperreflective tiny droplets were shown intraretinally in 3 patients after retinectomy, but in 2 patients the retina architecture was intact.

In each of the 5 patients diagnosed with cystoid macular edema, the hyperreflective areas were shown at the edges of cystoid spaces. Errera et al. also noted the presence of tiny hyperreflective spherical bodies in cystoid spaces and on the edges of retinotomy sides, where retina was also with edema. Inflammation and long-lasting retinal detachment can cause retinal edema. In immunochemistry examinations, some authors found intraretinal macrophages containing phagocytosed silicone oil. Perhaps the extension of retinal layers in macular edema may lead to the penetration of macrophages with small droplets of emulsified silicone oil into the external and internal layers of the retina.

According to some authors, intact inner limiting membrane may be a barrier to the penetration of oil into the retina [7, 12]. On the other hand, ILM peeling is regarded as prophylaxis of epiretinal membrane formation [13]. In 18 patients who underwent ILM peeling, only 3 had hyperreflective droplets of emulsified silicone oil inside the retina. In contrast, in 2 patients with epiretinal membranes we did not find hyperreflective droplets in SD-OCT examinations. Analyzing the previous histological examinations, it may be noted that emulsified silicone oil is often present on or beneath the epiretinal membranes [1, 14]. In the SD-OCT study, Errera et al. demonstrated spherical hyperreflective bodies (emulsified silicone oil) underneath epiretinal membranes in 7 patients. They also showed that, in 60% of cases, patients with hyperreflective droplets intraretinally corresponded with the epiretinal membrane. Also, Wickham et al. found that, in all eyes with silicone oil inside the retina, the epiretinal membrane is present. It follows that emulsified silicone oil has a strong affinity to the epiretinal membranes.

Emulsification of silicone oil and migration into the eye structures may occur at different times after vitrectomy with silicone oil tamponade. So far, there are no studies that show the time in which the emulsified silicone oil can penetrate into the human retina. Ohira el al. showed that emulsified silicone oil injected into rabbit's eyes migrated to the inner retinal layers after 1 week [10]. The migration of emulsified silicone oil was also described by the same author in the short time observation from anterior chamber of rabbit [15]. On the other hand, in a histopathologic study, the mean duration of silicone oil tamponade before enucleation was 5 years [1]. Errera et al. only demonstrated emulsified silicone oil in the SD-OCT study, but we do not know since when there was emulsification of oil in the eye [8]. In our study we found hyperreflective tiny droplets visible in high resolution SD-OCT 3 months after silicone oil tamponade. So, we can therefore hypothesize that emulsification and migration of silicone oil occurred after 3 months. Actually, the SD-OCT could give us *in vivo* high resolution cross-sectional images of the retina and also give us more information of the location and time of silicone emulsification.

There are several limitations to this study. Our study has a small sample size. We cannot definitively determine that the hyperreflective round-shaped droplets are emulsified silicone oil. In our opinion, the hypothesis concerning hyperreflective structures as emulsified silicone oil cannot be definitively confirmed without histopathological examinations.

We hypothesize that hyperreflective round-shaped droplets found in SD-OCT correspond with emulsified silicone oil. The authors hypothesize that emulsification and migration of silicone oil begin within 3 months after surgery.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Review Article

Vitreous Substitutes: The Present and the Future

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Vitreoretinal surgery has advanced in numerous directions during recent years. The removal of the vitreous body is one of the main characteristics of this surgical procedure. Several molecules have been tested in the past to fill the vitreous cavity and to mimic its functions. We here review the currently available vitreous substitutes, focusing on their molecular properties and functions, together with their adverse effects. Afterwards we describe the characteristics of the ideal vitreous substitute. The challenges facing every ophthalmology researcher are to reach a long-term intraocular permanence of vitreous substitute with total inertness of the molecule injected and the control of inflammatory reactions. We report new polymers with gelification characteristics and smart hydrogels representing the future of vitreoretinal surgery. Finally, we describe the current studies on vitreous regeneration and cell cultures to create new intraocular gels with optimal biocompatibility and rheological properties.

1. Introduction

In recent times vitreoretinal surgery has made important progress regarding instruments, drugs, and materials [1, 2]. Numerous pathologies, such as retinal detachment, diabetic retinopathy, and proliferative vitreoretinopathy, require partial or total vitreous removal [3]. Presently, temporary and permanent intraocular vitreal substitutes mainly have a structural function to ensure retinal adherence following cryo or laser retinopexy for the necessary time, to control intraocular hemorrhages, and to maintain intraocular pressure. Future polymers will interact with intraocular anatomy and physiology, as well as intraocular drug distribution [4]. One of the main challenges is the control of inflammatory and immune-system reactions that modify the stability of the vitreous substitute and the integrity and functionality of intraocular structures [5].

In this review, we examine the characteristics of the vitreous, the advantages and disadvantages of presently available tamponades, the characteristics of several vitreal substitutes studied some years ago but actually not used for several reasons, and new substances for vitreous substitution that are under research.

2. Characteristics of the Vitreous

The vitreous body appears as a gelatinous structure (98-99% water) filling the space between the lens and the retina, the so-called vitreous chamber. The molecular structure of the vitreous is composed mainly of hyaluronic acid and different types of collagen that create the gelatinous structure. Water is present on a bounded form to the glycosaminoglycans for about 15–20%; this ensures the stability of the vitreal

Table 1: Biochemical composition of the vitreous.

Subgroups	Molecule	Action
Protein	Albumin (40%)	
	Iron binding protein (30%) like transferrin	Protective effect to reduce iron toxicity
	Collagens	Structure of the vitreous
	Type II (60–70%)	
	Type IX (25%)	
	Type V/IX (10–25%)	
	Type IV (<10%)	
Glycosaminoglycan	Hyaluronic acid (66–115 microgram/mL concentration)	Determine the vitreous body viscosity
	Chondroitin sulfate	Major component of extracellular matrix
	Versican	
	Type IX collagen	
	Heparan sulfate	It maintains adequate spacing between the collagen fibrils
Metabolites	Glucose	To support the enzymatic activity
	Lactic acid	
	Ascorbic acid	Neovascularization inhibitor Increase proliferation of hyalocytes Potent antioxidant
	Amino acids	Metabolic cells maintenance
	Fatty acids unsaturated (50–55%)	Metabolic cells maintenance
	Prostaglandins (100 picogram/mL)	Cells regulation
	PGE2	Cells regulation
	PGF2alpha	Cells regulation
	Prostacyclin	Cells regulation
	Thromboxane	Cells regulation
Cells	Hyalocytes	Vitreous matrix creation and maintenance
	Fibrocytes/fibroblasts	Vitreous matrix creation and maintenance
	Macrophages	Cells and matrix regulation and degradation
	Enzymes and metabolic activity: ACE	Cells regulation

Table 2: Physical characteristics of the vitreous.

Physical characteristics of the vitreous	
Weight	4 g
Density	1.0053–1.008 g/cm^3
Refractive index	1.3345–1.3348
Viscosity	300–2000 cP
pH	7.0–7.4

structure. Table 1 shows various molecules contained in the normal vitreous body.

Vitreous physical characteristics need to be well known in order to recognize its active role in ocular physiology, as shown in Table 2 [6]. The vitreous appears as a complex structure with its own viscoelastic properties due to a high hyaluronic acid concentration that maintains and absorbs the stress and strain of the bulb during its continuous movement during the day. The collagen-glycosaminoglycan and water frame ensure the transparency of the media, also acting as support for the vision and accommodation mechanism.

Its anatomical structure has been long studied, with recognition of its modifications due to physiological aging or pathological processes [7, 8]. The gelatinous structure is denser adjacent to the posterior hyaloid membrane (vitreous cortex) and more at the ora serrata.

The presence of active molecules allows control over inflammation, proliferation, and neovascularization, acting as a barrier to infection (bacterial not viral) [5, 9]. Finally, the vitreous body revealed its role as a repository: oxygen and nutrient as well as drugs transportation inside the eye follow definite diffusion and releasing processes [10]. These facts justify the role of the vitreous body not only as a filling substance but also as an element that has an active function on the physiology eye [11].

2.1. Ideal Vitreous Substitute. Since 1960, clinical and bioengineering researches have tried to find a substance that might replicate either the molecular structure of the vitreous or the physical characteristics of this gelatinous substance [12, 13]. In vitro or in vivo testing allowed evaluating not only the physical and biological parameters required to satisfy

Table 3: Characteristics of the ideal vitreous substitute.

The ideal vitreous substitute
Mimic the native vitreous
Be easily manipulable during surgery
Have similar viscoelastic proprieties
Be clear and transparent
Have refractive index and density similar to native vitreous
Be biologically and chemically inert
Be hydrophilic and insoluble in water
Be able to maintain the IOP within a physiologic range and support the intraocular tissues in proper position
Allow movement of ions and electrolytes and maintain the concentration of certain substances (oxygen, lactic acid, and ascorbic acid)
Be clear
Not induce toxic reactions
Be biocompatible
Be easily available, stable, and injectable through a small syringe
Be able to maintain its light transparency post-op without undergoing opacification

the needs of the surgeon but also the anatomy and physiology of the eye (Table 3).

We considered the fact that the vitreal substitutes could show some properties that correlated to a simple filling function (passive properties) and some properties that show interaction with intraocular structures or ocular physiology (active properties) [14, 15]. We considered as passive properties the filling action to maintain IOP, the viscoelastic characteristics to reduce shear stress on the retina, and the general inertness and biocompatibility without inflammatory ortoxic reactions [16, 17]; we considered as active properties the possibility of the new substance to interact with the biology and metabolism of the eye to permit the transportation of substances, ions, and oxygen and to maintain integrity and transparency over time [18].

An ideal testing protocol to evaluate the optimal vitreous substitute and the above properties could be summarized as follows: light transmittance, kinetics of hydration and water swelling, oscillatory and shear-stress analysis, shear-creep analysis, evaluation of solute diffusion, in vitro and in vivo biocompatibility, and degradation during injection.

These points represent the above-mentioned characteristics of the ideal long-term vitreous substitute. Numerous experimental phases must be applied to test these properties, and we are hopeful that a standardized effective model will be available in the future [15, 16].

3. Currently Available Vitreous Substitutes

Some of the listed substances have been known from more than 20 years, while others were developed only recently to ameliorate tolerability, tamponade effect, and stability. Here below we analyzed the advantages and disadvantages of available substances to show their current use and the short- and long-term ocular effects. Vitreal substitutes could be classified in different ways. A functional classification referred to as the surgical application is described in the literature: (i) vitreal substitutes as temporary fillers of vitreous cavity during the surgical procedure to maintain the ocular tone; (ii) vitreal substitutes used as surgical tools themselves during different phases of vitreoretinal surgery, requiring a short intraocular permanence; (iii) vitreal substitutes left inside the eye after vitreoretinal surgery with different permanence time [16, 17]. A different classification according to their molecular status, air- or gas-based and liquid, has been applied below in this paper.

3.1. Air. The gas used is filtered room air, composed of different gases (mainly N_2, O_2, CO_2, and others at lower concentrations). Colorless and inert, it diffuses easily in the blood circulation, reducing its tamponade effects in a few days [19]. It presents a variable refractive index (approximately 1,0003). The low refractive index causes a complete reflection of the light, reducing the possibility of fundus exploration.

Air was the first gas injected into the eye. It is used in vitreoretinal surgery for retinal detachment therapy: its tamponade effect depends on the dimension and the position of the intraocular bubble, consequent to the position of the patient's head [20]. It is naturally replaced by an aqueous humor produced by the metabolism of ciliary bodies [21].

3.2. Gases. Sulfur hexafluoride (SF_6), perfluoroethane (C_2F_6), and perfluorocarbon (C_3F_8) are colorless, odorless, inert, nontoxic, and expansive gas. They present a high surface tension and a specific gravity lower than water to maintain the tamponade effect [22]. When gas is injected in the vitreous cavity, it is possible to distinguish three different phases: expansion, equilibrium, and dissolution. The first phase is the result of the absorption into the bubble of nitrogen oxygen and carbon dioxide from the surrounding tissue fluid; the equilibrium phase is characterized by a balancing of the partial pressures of the media. During dissolution gases are ultimately absorbed into the bloodstream.

Sulfur hexafluoride (SF_6) and perfluorocarbon (C_3F_8) are the more commonly used gases. SF_6 expands to about the double of the volume injected within 24 to 48 hours and exerts an effect for 1 to 2 weeks; C_3F_8 expands to about four times its original volume within 72 to 96 hours and persists for 6 to 8 weeks. For these reasons, these gases are commercially available at a definite nonexpansive concentration (SF_6 20% and C_3F_8 12–14%) in order to avoid errors during presurgical dilution.

Nowadays they represent the standard gases used in pneumatic retinopexy and vitreoretinal surgery, as for their longer permanence compared to the air characteristics [21, 23]. As for the air, the intraocular gas bubble has buoyancy that keeps the retina against the pigment epithelium, and this effect is greatest at the upper of the bubble. The tamponade effect is conditioned by the dimension and position of the bubble and therefore by the position of the patient's head [24, 25]. The lower refractive index, compared to corneal

tissue or aqueous humor, causes almost complete reflection of light, creating fundus evaluation problematic until gas reabsorption.

Patients with intraocular gases should be advised against air travel or traveling to high altitude, since the reduction of atmospheric pressure will lead to expansion of intraocular gas bubble and cause considerable increase of intraocular pressure. At the same time they should avoid diving: the hyperbaric pressure occurring during scuba diving causes hypotony and partial globe collapse.

A great care must be applied if we expect to use these gases: if the surgery is performed in general anesthesia, dinitrogen monoxide (N_2O) is strictly forbidden as anesthetic and analgesic due to its strong diffusion tendency. In this case the rapid vascular/eye exchange of these gases causes a rapid expansion of the intraocular bubble with severe intraocular pressure increase [26].

3.3. Liquids

3.3.1. Saline Solution. The physical characteristics are very similar to those of the aqueous humor regarding transparency, refractive index, and density [4]. The Balanced Salt Solution (BSS, Alcon Laboratories, Randburg, USA) contains sodium chloride, potassium chloride, calcium chloride dihydrate, magnesium chloride hexahydrate, sodium acetate trihydrate, sodium citrate dihydrate, sodium hydroxide and/or hydrochloric acid (to adjust pH), and water for injection. The pH is approximately 7.5; the osmolality is approximately 300 mOsm/Kg. BSS PLUS (Alcon Laboratories, Randburg, USA) contains in addition dibasic sodium phosphate, sodium bicarbonate dextrose, and glutathione disulfide (oxidized glutathione). The reconstituted product has a pH of approximately 7.4; the osmolality is approximately 305 mOsm.

Saline solutions are used as temporary vitreous substitutes during exchange with air or liquids. They could change during intraocular permanence: proteins, cytokines, metabolites, and cells could transform this transparent fluid [27, 28] together with the aqueous fluid reaching the vitreous cavity. The solution represents a simple filling liquid, with no tamponade properties on the retina due to its low surface tension [5].

The use of different chemical compositions, like the BSS PLUS, represented a more expensive alternative. An in vivo study in rabbits has shown that BSS PLUS is more suitable than normal saline or Balanced Salt Solution for intravitreal irrigation because BSS PLUS contains the appropriate bicarbonate, pH, and ionic composition necessary for the maintenance of normal retinal electrical activity.

3.3.2. Perfluorocarbon Liquids (PFCls). They are completely fluorinated, synthetic, carbon-containing compounds that comprise exclusively fluorine-carbon bonds [29]. They are clear, colorless, and odorless; they present a density that is approximately twice that of water, low viscosity, and a refractive index similar to that of water. They are hydrophobic and lipophobic and so immiscible but they could form emulsions; they maintain the possibility of gases like CO_2 and O_2 to diffuse [4–30]. Three molecules are nowadays in use: perfluorodecalin (PFD), perfluoro-n-octane (PFO), and Perfluoro-tetradecahydrophenantrene that present different interface evidence when used with other fluids during surgery (PFD is at the moment the leading compound) [31].

They have been used as temporary tamponades to unfold and stabilize the retina during surgical manipulation. They have to be removed at the end of the surgical procedure [32, 33].

These substances present, if left into the eye after surgery, a retinal toxicity and intraocular inflammatory reactions, inducing the formation of epiretinal membranes and intraretinal layer disruption [34, 35].

Recently, a PFCl stained molecule has been tested to improve its surgical use with interesting results. Its usefulness will be evident during air or fluid exchange phases in which the stained tamponade will be well visible for a complete removal. Indeed, small little bubbles of PFCl adherent to the retina have been often observed a long time after the removal [36].

3.3.3. Semifluorinated Alkanes. Semifluorinated alkanes (SFAs) are also known as partially fluorinated alkanes or fluorinated alkanes. These materials consist of short alkyl chains joined at one or both ends to a perfluorocarbon chain [37]. SFAs are colorless, immiscible with water, and physically and chemically inert. They present a lower viscosity and density (1.35 g/mL) than PFCls. They present solubility in PFCl, hydrocarbons, and silicone oil [38–40].

They were the first intraocular tamponades used beyond surgical time [41]. In addition, it has been demonstrated that SFAs can be successfully used also as intraoperative tools to unfold and lay down the retina. Finally they have been marketed also as biocompatible solvents for silicone oil to facilitate its removal [40].

These tamponades currently are not used owing to their tendency towards emulsification and epiretinal membrane formation and for toxic and inflammatory reactions in case of long permanence [42].

Actually they are mixed to silicone oils to form the so-called third-generation silicone oils or "heavy oils" (see the following) [43, 44].

3.3.4. Silicone Oils

Silicone Oil. Silicone oil (SO) for ophthalmic use is a synthetic polymer belonging to the class of polydimetilsiloxanes. It presents a refractive index that is similar to the vitreous, a lower density than water, and a differing viscosity according to the type of molecule, generally 1000–5000 Centistokes (cinematic viscosity measured in Centistokes—Cs) [5].

Used in the past as an intraoperative tool to stabilize the retina and unroll the flaps of retinal tears, it is nowadays considered and recommended for long-term retinal support and tamponades, due to its chemical inertness and permanent optical transparency [45]. Its use is recommended in difficult cases as the presence of giant retinal tears, retinal detachment complicated by proliferative vitreoretinopathy [46, 47]. Due

to its surface tension and hydrophobic properties it could be considered a good tamponade that depends on the position of the bubble and the patient's head (the tamponade floats over residual vitreous or water). Its intraocular presence reduces the movements and compartmentalizes cytokines and cellular factors between the anterior and posterior segment of the eye [48].

Surgical experience shows several disadvantages of long-term persistence. The complications of silicone oil use as an intraocular tamponade are mainly cataract induction, corneal toxicity, glaucoma, and so-called "silicone retinopathy" [49, 50]. A frequent modification occurring to silicone oil is emulsification. Emulsification is defined as a dispersion of fine liquid particles in another liquid medium and results from shearing forces between the two media, causing droplets to be pinched off into the other media because of surface tension. There are multiple factors affecting the emulsification of silicone oil: viscosity and physiochemical properties present an important role. Clinical research observed that the less viscous oils (1000 and 5000 Cs) tend to emulsify earlier than more viscous heavy silicone oils (see below: Oxane HD, Densiron, and HWS 46-3000) and that silicone oils containing hydroxyl and phenyl side groups emulsify earlier than purified polydimethylsiloxane. Surface-active agents (surfactants) are agents that lower the surface tension of the medium increasing its emulsification: various biological substances like blood, fibrin, and gamma globulins could act as emulsifiers and destabilize intraocular applied silicone oils [51, 52].

Macular edema represents another severe complication of silicone oil; it is present just after the exchange or increases during intraocular SO presence. This fact could take origin from different reasons: the diffusion of intraocular molecules is slowed down, reducing transport in the vitreous cavity of molecules such as oxygen and other nutrients, growth factors, and cytokines; the vitreous tamponade provides a mechanical "flotation force" at its apex against the macular region, being responsible for macula inflammation and secondary ME, especially in dynamic patients [53].

During removal procedures, problems can arise, such as hypotony and/or persistence of diffused small emulsion particles on the retina causing chronic inflammation [49, 50].

A double-fill of silicone oil and SFAs has been studied for a complete tamponade of the superior and inferior retina. The critical phase is to maintain a regular filling and to avoid the "egg effect": in this case the separation of the two substances into two phases interrupts the correct tamponade effect [44].

Second-Generation Silicone Oils. Also called fluorinated silicones, they present similar characteristics to silicone oil, in particular the same viscosity and refractive index, but a higher density (greater than water) [54, 55].

They were used as vitreal substitute after surgery due to their efficacy on inferior retina tamponade. Surgical experience showed also the possibility to use them as temporary vitreal substitute to facilitate surgical procedures. Among them, the silicone fluorosilicone copolymer, a polysiloxane derivate, presents same characteristics to the fluorosilicones but due to its low viscosity facilitating injection and removal it has been used as temporary intrasurgical substitute.

All fluorosilicones present a higher emulsification rate and retinal toxicity, due probably to their high density and this fact limited their clinical use [56, 57].

Heavy Silicone Oils (HSO). They have been created by the combination of silicone oil and fluorinated alkanes in a homogenous solution. Like silicone oils, they have good transparency, higher density than water, and higher viscosity. They are chemically inert, presenting an emulsification tendency less than that of silicone oils [58]. We identified four molecules: Oxane HD, Densiron 68 and 68 LV, and HWS 46-3000, as the result of the mixture of silicone oil with various SFAs. Oxane HD is a mixture of ultrapurified silicone oil (Oxane 5700) and RMN3, a partially fluorinated and hydrocarbonated olefin with a density of 1.02 g/cm^3 and a viscosity of 3300 mPas (dynamic viscosity measured in milliPascal—mPas) [59]. 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 g/cm^3 (higher than water) and a viscosity of 1400 mPas (substantially higher than F6H8). 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 [60–62]. HWS 46-3000 is a new silicone oil composed of 100,000 Cs silicone oil (45%) and F_4H_5 (55%) with a density of 1.118 g/cm^3 and a viscosity of 2903 mPas [63].

They are used as long-term tamponades due to their high density and stability, in all cases where a tamponade effect on the inferior parts of the retina is necessary [64, 65].

Its removal requires strong active aspiration due to its high viscosity. The heavy SO may remain strictly adherent to the retina surface ("sticky oil phenomenon") causing inflammation and tissue reactivity [66].

The inflammatory and toxic effects are evident on cataract induction, glaucoma, and keratopathy proving toxicity for the whole eye [67, 68].

Magnetic Silicones. They represent an interesting surgical experience to take advantage of the good chemical and physical properties of silicone oils. In particular, the dispersion of nanoparticles of metal (nickel, iron, cobalt, and rare metals) increases the superficial tension of the oil and therefore the tamponade effect [69].

This is carried out with the positioning of an encircling scleral magnetic band (scleral buckle). This interesting experimental project has been limited by the high toxicity of silicone oil metal dispersion on intraocular tissue [4, 69].

4. Experimental Substitutes

Clinical research for vitreous substitutes has essentially tried to reproduce two aspects of the original vitreous: on the one hand, a substance with the same vitreous molecular structure (simple filling function, to control elasticity and pressure of the eye), and on the other hand a structural

molecule presenting its chemical and physiological properties (to assure diffusion of metabolites and gases, to allow the perfusion of drugs, and to interact actively with intraocular structures). This approach has led research toward functional biomimicry: the use of synthetic molecules that not only mimic the rheological function of the vitreous but also might interact with the intraocular structure without time-dependent degeneration or optical transparency loss [13].

4.1. Natural Polymers. Natural polymers, such as hyaluronic acid (HA) and collagen, have been evaluated as the basis for vitreous substitutes. As the main components of the vitreous, they present great biocompatibility. Hyaluronic acid and its derivatives are present in various formulations for ocular use, but due to the short degradation time they cannot be used as intraocular tamponades. Collagen derivatives, such as gelatine, polygeline, and methylated collagen types I-II, as well as chitosan (a natural crustacean product), have been studied as structural polymer proteins for experimental vitreous substitutes with poor results [4, 5, 70, 71].

The intraocular gel hylan, created using cross-linked molecules of sodium hyaluronate formaldehyde, divinyl sulfone, and gellan molecule, could represent an interesting short-term vitreal substitute for its stability and composition. Its excessive water solubility made it at the moment not available for clinical experiments [66].

The above-described vitreous substitutes are not effective due to the tendency of the molecules towards degradation, their low viscosity, and poor tamponade effect [72, 73].

A promising approach, compromising the biocompatibility of HA and the duration of a complex polymer, is the application of dihydrazide photo-cross-linking reaction. This type of cross-linked HA presents good transparency, viscosity, and tamponade effect due to its hydrophilic properties. Degradation time is quite long (more than 4 weeks) [74]. The advantages of this substitute are the limited tissue inflammatory and toxic reaction [75]; the disadvantage is already the short time of degradation (from 60 to 150 days) due in part to the injection procedure that alters the gel molecular structure reducing the integrity and stability. The cross-linking processes by in situ gelification [76] and the intraocular injection of cellular components to actively produce polymer matrix represent a possible solution of this problem.

4.2. Hydrogels. Polymeric and Smart Hydrogels represent the new class of experimental vitreal substitute [77].

These substances are hydrophilic polymers that form a gel network when cross-linked and are capable of swelling by absorbing several times their own weight in water [78]. They present good and stable transparency, good biocompatibility, and viscoelastic properties like the vitreous body, mimicking its biofunctionality, yet they have different chemical and physical properties [4, 79]. Both types of molecule are synthetic polymers with different characteristics. In particular, Smart Hydrogels are able to respond to the environment and to external physical stimuli. Their characteristics determine long-term vitreous stability without toxic effects. The passive action of these molecules as tamponades is coupled with the active action as drug releasers or exchangers to ensure therapeutic and clinical effects [80].

Hydrogel molecules have been developed and carefully selected not only owing to their chemical-physical properties, but also due to their possible toxicity [77]. They represent the first biomaterials ever synthesized for human use and have various clinical applications.

Here we list the principal molecules, showing their advantages and disadvantages; several of these ones have been discarded due to toxicity or unable characteristics. We underline that in vivo research is as yet applied only to animal models [81].

(i) Poly(vinyl alcohol) (PVA): it is selected for its good optical properties making it a valid vitreous substitute; it is indistinguishable from the vitreous during the initial months following injection. PVA presents good biocompatibility and rheological properties. Adding different chemical reactants, in particular trisodium-triphosphate cross-linking agent, the molecule changes and improves its properties, particularly its rheological characteristics and diffusion behavior [82]. Further studies must be carried out on its ability to act as a retinal tamponade [83].

(ii) Poly(1-vinyl-2-pyrrolidone) (PVP): it is the first studied element for vitreous substitution. This molecule is the result of the polymerization of 1-vinyl-2-pyrrolidone with different cross-linking agents [84]. Experimental research has created several molecules of PVP, presenting a density and viscosity similar to the human vitreous, but with intraocular reactivity [85]. Transient or permanent vitreous opacification is the most frequent adverse event, as well as inflammation with vacuoles and granules, indicating early PVP degradation due to phagocytosis [86]. Further studies are underway to evaluate more tolerable and more stable PVP polymers [87, 88].

(iii) Polyacrylamide (PAA): it is created by the polymerization of toxic acrylamide by cross-linking agents (once injected into the vitreous cavity after the monomer) [89]. Experimental PAA polymers have been created with a disulfide cross-linking agent to produce highly purified molecules [90]. PAA presents similar density and viscosity to the vitreous, as well as good biocompatibility and long-term stability. Better results are expected in the future. Severe complications such as ocular inflammation and vitreous opacification were reported on the first experimental phases of these materials.

(iv) Copoly(acrylamide) (CPA): it is a variant of PAA presenting better gelification properties, acquiring polymerization after reduction of disulfide cross-linking bridges [90]. With the same refractive index and viscoelastic parameters of the vitreous, as well as good biocompatibility, it seemed to be a valid long-term substitution. The tested molecule showed clinical suitability and lack of significant ocular toxicity.

(v) Poly(glyceryl methacrylate) (PGMA): this polymer is nowadays excluded from research owing to its fragmentation upon injection [4]. The dehydrated molecule has been tested by direct intraocular positioning: in contact with intraocular fluids the molecule swells and became the vitreal substitute. The experimental evaluation found this process too slow and not effective for clinical use [91]. Although it has good biocompatibility and excellent physical properties, the molecule did not become clinically available [92].

(vi) Poly(2-hydroxyethyl methacrylate) (PHEMA): this polymer presents solid features. Experimental research has shown good inertness to degradation and inflammatory reactivity [89]. Because of its solid feature, it caused important surgical difficulties for its implantation, so it was considered unsuitable for clinical use [93, 94].

(vii) Poly(2-hydroxyethylacrylate) (PHEA): this hydrogel presents excellent physical properties similar to those of the human vitreous. Due to reported inflammatory reactions following injection, cataract, glaucoma, and the formation of fibrous membranes it was abandoned for human clinical research [4, 5].

(viii) Hydroxypropyl methylcellulose (HPMC): it presents good physical-chemical properties as well as good biocompatibility [95]. Different experimental polymers have been studied, varying the molecular weight [96]. Researchers have tried to reduce intraocular degradation time, but as of today it is not yet available as a long-term vitreal substitute [97].

(ix) Pluronic F127 (p-F127): it is a thermoreversible gelatin. It could form a gel at 21°C but it shows severe retinal toxicity making it unsuitable for clinical use [98, 99].

(x) Silicone gel: it is a hydrophobic polymer that maintains good intraocular transparency and cohesiveness. Its poor tamponade effect has deemed it unsuitable as an intraocular retinal surgical tool [100].

(xi) ADCON hydrogel: it is a polymer of proteoglycan esters in porcine gelatine and it is already used in neurosurgery. This hydrogel is highly biocompatible but presents potential retinal toxicity and postoperative inflammation. It is unsuitable for ocular use [101].

(xii) Poly(vinyl alcohol methacrylate) (PVA-MA): this polymer contains a photoinitiator that forms a gel network after irradiation at 365 nm. The degree of gelification can be regulated by polymer concentration and light intensity. PVA-MA properties must be tested in vitro and in vivo to evaluate vitreous biomimicry and biocompatibility [102].

Beyond all different experimental problems described above, a critical phase during physical tests for all these polymers was the injection through small caliper needles, a critical phase for clinical use. The shear stress of the needle during intraocular injection causes a loss on elasticity and a fluidification of the preformed molecules of hydrogel, due to the rupture of polymeric chains [77].

To resolve this criticality, hydrogel could be injected in an aqueous state and transformed into a gel in situ by light exposure or air oxidation, thanks to cross-linking processes. According to the different polymers, the liquid hydrogel could reach final gelification with defined elasticity and swelling in the presence of a photoinitiator or a disulfide cross-linker. In particular, PVA-MA is sensitive to a defined UVA wavelength, not yet applicable in eye surgery; differently, CPA is injected on a reduced form, sensitive to air oxidation for the gelification process [102].

Smart Hydrogels present similar characteristics compared to the polymeric hydrogels, but they have more interactive properties with the environment, such as glucose-, glutathione-, and pH-dependent activity and reactivity to light, pressure, and electric fields. These properties mean that these molecules could interact with retinal tissue, injected drugs, lasers light, or other chemicals and physical stimuli. These interactions induce an increased gelification, better drug diffusion, and increased gel expansion [103–106]. Little information regarding their toxicity or inflammatory action is available at present [107, 108]. Thermosetting gels are Smart Hydrogels that modify their status according to temperature (e.g., WTG-127 gel) [109]. This is important for the gelification status and viscosity, for their injection and handling. The disadvantage of this molecule is its reduced degradation time and its tendency to drift under the retina in the presence of tears before complete gelification [105].

All these molecules, as we described above, could actually cause adverse reactions of the ocular tissues at different stage, such as inflammation, phagocytosis, and vacuolization, due to molecular degradation and immune reaction. One of the major challenges is to make these molecules more and more compatible with the immune and biological systems [103].

Despite the above reasons, hydrogels seem to be the best candidates for vitreous substitution. They present all the characteristics needed to mimic the physical-chemical behavior of the vitreous, plus its biological function. We need to perform more experimental evaluations to tailor density and rigidity, as well as degradation times to match those of the natural vitreous [74, 75, 78].

4.3. Transplant and Implants. Many years ago, some authors described the first attempt to transplant vitreal tissue [110–112]. They observed that, if correctly stored, the vitreous body could maintain its structure and also its enzymatic properties, as described in the literature [8, 9, 11]. The implanted tissue showed a degradation time on the host, with a low inflammatory reaction and interesting surgical results on 40% of patients. Cataract, glaucoma, and more severe adverse events until ocular atrophy were described [110–112].

Regarding implants, bioengineering studies have shown interesting results in the use of artificial capsular bodies, made of silicone rubber elastomer and filled with a saline solution, silicone oil, controlled using a valve system. The system was described as being well tolerated on an experimental model. This foldable capsular vitreous body (FCVB)

presented good mechanical, optical, and biocompatible properties in vitro and in vivo and has been seen to be effective as a vitreous substitute in the treatment of severe retinal detachment. The presence of a filled capsule reduces the toxic effect, such as intraocular toxicity, emulsification, high IOP, and keratopathy [113]. A new polyvinyl alcohol (PVA) filling molecule has been evaluated in recent studies on a rabbit model. The 3% concentration showed the best results in rheological, physical, and cytotoxicity tests. This type of approach combines the efficacy of hydrogel as a vitreous substitute to the presence of an implant as an isolator that could reduce degradation time. In the PVA-FCVB rabbit implanted eyes, the structure of the retina was intact at 90 days postoperatively (a lensectomy was performed in all eyes due to frequent cataract induction of the implant); at 180 days retinal disorders were reported due to long-term capsule-induced mechanical pressure to the retina [114]. The advantages of this type of approach have also been reported on a therapeutic target: several nanometer wide apertures are available on the implanted capsule, so drugs could be added to the hydrogel and long-term release could be performed [115, 116].

4.4. Vitreous Regeneration. The challenge to create a new vitreous with the critical 3D structure might be very interesting and for this purpose different studies were performed. Controlled hyalocytes proliferation with specific growth factors (bFGF stimulates and TGF-B1 inhibits) and the production of HA with related components were evaluated [117, 118]. Reverse transcriptase polymerase chain reaction (RT-PCR) analyzed and compared the expression profiles for several genes in the human vitreous tissue-derived cells. The regulation of hyaluronan production in response to cytokine stimulation, the expression of hyaluronan synthase isoforms using RT-PCR, and hyaluronan production using enzyme-linked immunosorbent assay (ELISA) were also investigated[119].

5. Conclusions

The vitreous is a fundamental component of the eye. It has filling functions and extremely active properties on the stability and metabolism of the retina complex. Current long-term vitreous substitutes are clinically largely used but present some disadvantages. Many studies evaluated the possibility to realize the ideal vitreal substitute: long-term persistence and good biocompatibility to maintain transparency and integrity. Polymeric hydrogels have shown suitable characteristics with great variability of chemical composition: ideal substitution must be performed correctly, and experimental research is advancing.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Research Article

Heavy Silicone Oil as a Long-Term Endotamponade Agent for Complicated Retinal Detachments

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We retrospectively evaluated a heavy silicone oil (HSO) as a long-term intraocular endotamponade agent to treat complicated RD by inferior PVR in 25 eyes of 25 patients. Patients underwent PPV and injection of Oxane HD as an internal tamponade agent. A comparison of preoperative and postoperative BCVA at month 1, month 6, and last visit was made in the group in which HSO was removed and in the group in which HSO was not removed. Statistical calculations were performed using the Wilcoxon test. The HSO was removed from 11 patients after a mean of 26.55 ± 21.38 months. The HSO remained inside the vitreous cavity in 14 eyes due to a high chance of PVR recurrence (mean follow-up period, 11.07 ± 7.44 months). Anatomic success was achieved in 92%. The BCVA in the group, in which HSO was not removed, improved significantly during the first 6 months. Among the patients who had the oil removed, there was improvement in BCVA after 1 month. Oil emulsification was the most common adverse effect in 52% of eyes. HSO is an effective tamponade in complex rhegmatogenous and tractional RD complicated by PVR. HSO can remain in the eye for long periods with relative tolerability and safety.

1. Introduction

Silicone oil is an excellent endotamponade agent for superior breaks and detachments complicated by proliferative vitreoretinopathy (PVR). However, its density, which is lower than water, may result in fluid accumulation in the inferior quadrant, which is not covered by silicone oil, and ineffective tamponade at the retinal breaks [1–3]. Therefore, an aqueous environment with inflammatory and cellular proliferation may promote development of inferior PVR [4–7]. Despite improvement of vitreous microsurgical techniques, the surgical treatment of PVR is challenging in vitreoretinal surgery and can lead to blindness and ocular globe atrophy [3].

A high-density silicone oil was developed [3, 8–12] as an endotamponade agent for use in cases of complicated retinal detachments, especially those with inferior PVR.

Heavy silicone oil (HSO) has a high density and is heavier than water. Due to the properties of HSO, it has been proposed for use in treating complicated retinal detachments [3, 13, 14]. Oxane HD (Bausch & Lomb, Rochester, NY, USA) is a HSO comprised of a mixture of ultrapurified silicone oil (Oxane 5,700 centistokes) and RMN3 (partly fluorinated olefin). The mixture, with a density of 1.02 g/cm^3, a viscosity of 3,300 mPas, and a refractive index of 1.40, is homogeneous and stable in the presence of water and air and its surface tension is higher than 40 mN/m [2, 3]. Table 1 shows the HSO chemical and physical properties.

Some authors have reported that HSO is associated with ocular inflammatory reactions, increased intraocular pressure (IOP), cataract formation, and emulsification as well as difficulties to remove the HSO from the eye [15–17].

Several published studies have analyzed the complications and anatomic success rates after short-term intraocular tamponade with HSO. In most studies, the HSO was removed between 3 and 6 months postoperatively.

The aim of the current study was to evaluate the anatomic outcomes, functional results, and ocular adverse effects in patients with complicated retinal detachments in whom

Table 1: Physical properties of Oxane HD.

Viscosity 3,800 centistokes (3,300 mPas at 25°C) Density 1.03 g/cm^3 at 25°C
Refractive index 1.40 Volatility <0.1%
Surface tension >40 mN/m
RMN3 volume 11.9

Oxane HD was used as a long-term intraocular endotamponade agent.

2. Methods

We retrospectively studied 25 eyes of 25 patients with complicated retinal detachments by PVR. Patients underwent pars plana vitrectomy (PPV) and injection of Oxane HD as an internal tamponade agent. The surgeries were performed between 2006 and 2013 in the retina sector of the Federal University of São Paulo, São Paulo, and the Brazilian Institute of Fight Against Blindness, Assis, São Paulo, Brazil.

The inclusion criteria were primary or recurrent rhegmatogenous retinal detachments complicated by inferior PVR worse than CA3 [18] and/or complicated by hypotonia in eyes with combined rhegmatogenous and tractional retinal detachment associated with PVR that occurred in the context of diabetic retinopathy associated with retinal breaks due to severe fibrovascular proliferation. All retinal detachments in this study were considered to have a poor prognosis and the probable outcome should be the globe atrophy due to ciliary body traction related to advanced PVR. The follow-up period was at least 6 months.

The exclusion criterion was the presence of a severe systemic disease or inability to undergo regular follow-up examinations.

Patients were advised that the injection of HSO was based on published experience of 3-to-6-month use of this silicone oil as an endotamponade agent in inferior PVR. They were informed that, due to the complex clinical situations and the poor prognosis of the study eyes, HSO was used as a vitreous substitute for longer than the current reported time in the literature. All patients provided their informed consent and have authorized the use of their clinical data in the study.

The preoperative and postoperative data included the medical history, measurement of the BCVA using a Snellen chart, slit-lamp examination, intraocular pressure (IOP) measured by Goldmann tonometry, binocular fundoscopy, B-scan ultrasonography, and fundus photographs.

Follow-up examinations were scheduled for postoperative day 1, week 1, and months 1 and 3 after the initial surgery and every 3 months until the end of the follow-up period. Unscheduled appointments, complications, and additional interventions were documented.

The same vitreoretinal surgeon (Maurício Maia) performed all surgeries using local retrobulbar anesthesia. The surgery included a standard three-port, 23-gauge PPV, phacoemulsification. Retinotomy, retinectomy, and internal limiting peeling were performed if necessary. Endophotocoagulation was performed to treat retinal breaks. Scleral buckling was performed following retinotomies of 180 degrees or more or if there was residual vitreous at the vitreous base at the end of the surgical procedure.

Direct perfluorocarbon-silicone exchange was avoided to prevent "sticky oil" formation; in all patients, the perfluorocarbon liquid was aspirated completely due to a fluid air exchange followed by injection of Oxane HD (HSO) under air.

When the HSO was removed, it was aspirated using a 19-gauge needle BD (Becton Dickinson, USA) connected to an extrusion silicon tube; the needle was inserted by sclerotomy via pars plana and the extrusion silicon tube was changed 2-3 times due to obstruction of the system by the HSO. Many times, a bubble of residual silicon oil was deposited at the posterior pole and such technique of HSO removal is important information for vitreoretinal surgeons that will perform this surgical technique.

The preoperative and final postoperative BCVA levels were analyzed after they were converted to the logarithm of the minimum angle of resolution (logMAR).

The study adhered to the tenets of the Declaration of Helsinki and all federal laws. The ethics committee of our institution approved the study.

A comparison of preoperative and postoperative best-corrected visual acuities at month 1, month 6, and last visit was made in the group in which HSO was removed and in the group in which HSO was not removed. Statistical calculations were performed using the Wilcoxon test to compare the preoperative and postoperative VA levels. $P < 0.05$ was considered statistically significant. The SPSS (v15.0) statistical package was used for statistical analysis.

3. Results

Twenty-five eyes of 25 patients (19 men, 6 women; mean age, 49 ± 18.2 years; range, 17 to 80 years) were included in this study. The surgeries were performed between March 2006 and June 2013. The mean follow-up time was 21.44 ± 15.28 months.

Seventeen eyes had a rhegmatogenous retinal detachment complicated by inferior PVR; eight eyes had a tractional retinal detachment due to proliferative diabetic retinopathy complicated by retinal breaks and inferior PVR. All eyes included in this study had a macular detachment and also hypotony.

Among the eyes with a rhegmatogenous retinal detachment, one was secondary to toxoplasmosis uveitis, another had a complicated retinal detachment secondary to trauma, and the last one had multiple angiomas secondary to Von Hippel-Lindau disease.

The retinal detachments in all eyes were considered to have a poor prognosis due to the presence of advanced PVR. Table 2 shows the detailed patient data and the classifications of PVR [18].

Table 2: Pre- and postoperative records per patient.

Patient	Indication	Age/ gender	Lens status	Follow-up (months)	TA in the 1st surgery	PVR	TA in retreatment	Baseline VA (Snellen)	Final VA (Snellen)	Baseline IOP (mmHg)	Final IOP (mmHg)	Biomicroscopy findings	Time of HSO removal (months)	Redetachment	Comments
1	RRD	61/M	Pseudo	22	1000 cts SO	CP6	Oxane HD	20/200	20/40	16	14	Inflammatory cells in the AC, 1st month, KP in endothelium,6th month	6	No	Oil emulsification
2	RRD	53/F	Pseudo	18	C3F8 gas	CP3	Oxane HD	HM	HM	15	15	Normal	36	No	Ischemic optic nerve neuropathy; oil exchange due to IOP elevated; oil emulsification
3	RRD	57/M	Phakic	24	C3F8 gas	CA3	Oxane HD	HM	20/200	12	12	Inflammatory cells in the AC, 1st month	11	No	Ischemic optic nerve neuropathy; oil emulsification
4	RRD	63/F	Phakic	30	1000 cts SO	CP2	Oxane HD	LP	HM	10	13	Oil in the AC, 6th month	36	No	Oil emulsification
5	RRD	28/M	Phakic	36	C3F8 gas	CA6	Oxane HD	20/400	20/200	16	15	KP in endothelium and cells in the AC, 1st month	17	No	IOL fixation
6	RRD	22/F	Phakic	42	Oxane HD	CP1	NA	20/200	20/25	15	9	Normal	48	No	RD secondary to Toxoplasmosis
7	RRD	80/F	Phakic	24	5000 cts SO	CP8	Oxane HD	HM	CF 2m	17	16	KP in endothelium and cells in the AC, 1st month	NR	Yes	Giant tear; redetachment; oil emulsification
8	RRD	66/M	Phakic	24	Oxane HD	CA3	Oxane HD	HM	20/63	10	12	Normal	8	No	Epiretinal membrane; oil emulsification
9	RRD	62/M	Phakic	70	1000 cts SO	NA	Oxane HD	20/400	20/100	14	12	Normal	72	No	Oil exchange due to IOP elevated; oil emulsification
10	RRD	41/M	Phakic	6	Oxane HD	CP3	NA	CF 3m	20/80	13	13	Normal	NR	No	
11	RRD	66/M	Pseudo	12	5000 cts SO	CA10	Oxane HD	20/200	20/80	21	12	Normal	NR	No	
12	RRD	21/M	Phakic	12	Oxane HD	CA3	NA	HM	20/200	15	16	Inflammatory cells in the AC, 1st month	NR	No	RD secondary to open ocular trauma
13	RRD	62/M	Pseudo	12	Oxane HD	CP3	Oxane HD	20/200	20/80	14	17	Inflammatory cells in the AC, 1st month	NR	No	Oil emulsification

Table 2: Continued.

Patient	Indication	Age/ gender	Lens status	Follow-up (months)	TA in the 1st surgery	PVR	TA in retreatment	Baseline VA (Snellen)	Final VA (Snellen)	Baseline IOP (mmHg)	Final IOP (mmHg)	Biomicroscopy findings	Time of HSO removal (months)	Redetachment	Comments
14	RRD	68/M	Pseudo	6	1000 cts SO	CP2	Oxane HD	CF 1m	20/40	18	18	Inflammatory cells in the AC, 1st month	NR	No	
15	RRD	54/M	Phakic	6	1000 cts SO	CP1	Oxane HD	CF 3m	20/32	24	17	Inflammatory cells in the AC, 1st month	NR	No	
16	RRD	20/F	Phakic	8	1000 cts SO	CP3	Oxane HD	LP	CF 1m	22	14	Normal	NR	No	Von Hippel-Lindau
17	RRD	64/M	Phakic	7	1000 cts SO	CP8	Oxane HD	CF 1m	20/80	23	13	Inflammatory cells in the AC, 1st month	NR	No	Intraoperative bleeding in the first surgery
18	TRD	56/M	Phakic	20	C3F8 gas	CP4	Oxane HD	CF 1m	20/80	13	20	Normal	6	No	Oil emulsification
19	TRD	24/M	Pseudo	44	C3F8 gas	NA	Oxane HD	HM	CF 3m	14	14	Normal	46	No	Optical nerve atrophy; oil emulsification
20	TRD	49/M	Pseudo	34	Oxane HD	CA10	5000 cts SO	LP	HM	14	15	Normal	6	No	Oil exchange due to IOP elevated; oil emulsification
21	TRD	63/F	Phakic	13	1000 cts SO	CA10	Oxane HD	LP	HM	12	14	Normal	NR	Yes	Ischemic optic nerve neuropathy and persistent retinal detachment
22	TRD	29/M	Pseudo	36	Oxane HD	CA1	NA	HM	20/400	18	11	Normal	NR	No	Oil emulsification
23	TRD	17/M	Pseudo	12	1000 cts SO	CA3	Oxane HD	CF 1m	20/80	17	10	Oil emulsification, 6th month	NR	No	Oil emulsification
24	TRD	39/M	Phakic	12	Oxane HD	CA10	NA	LP	HM	11	20	Normal	NR	No	Ischemic optic nerve neuropathy
25	TRD	60/M	Phakic	6	1000 cts SO	CP3	Oxane HD	CF 1m	20/200	25	18	Inflammatory cells in the AC, 1st month	NR	No	

RRD = rhegmatogenous retinal detachment; TRD = tractional retinal detachment; F = female; M = male; TA = tamponade agent; PVR = proliferative vitreoretinopathy; VA = visual acuity; IOP = intraocular pressure; SO = silicone oil; HSO = heavy silicone oil; HM = hand motion; CF = count fingers; LP = light perception; AC = anterior chamber; KP = keratic precipitates; IOL = intraocular lens; RD = retinal detachment; NR = not removed, Pseudo = pseudophakic; NA = not available; cts = centistokes.

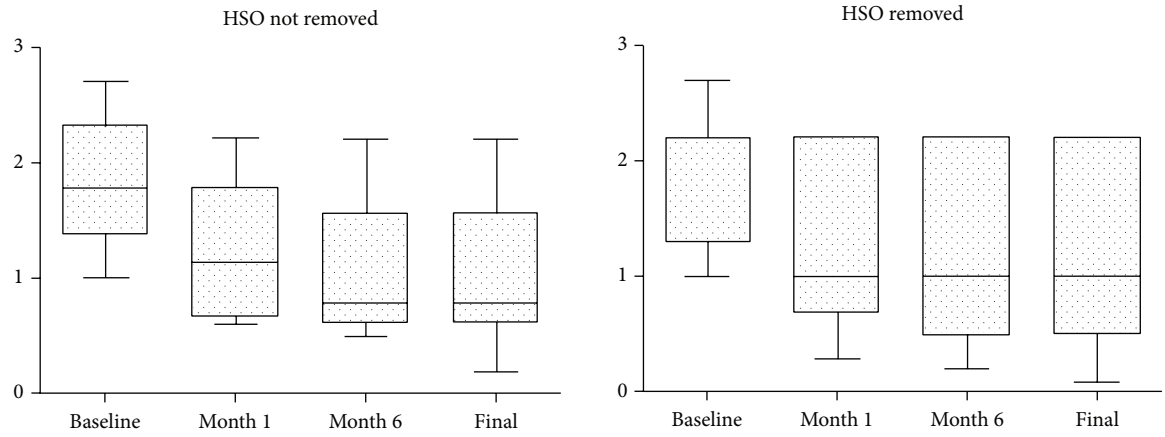

Figure 1: LogMAR BCVA Box plot at baseline, month 1, month 6, and final in patients in whom HSO was not removed and in patients in whom HSO was removed.

Oxane HD was the primary tamponade agent in eight (32%) eyes. Seventeen (68%) patients had undergone a previous unsuccessful surgery for retinal reattachment and underwent retreatment with Oxane HD due to development of severe PVR after the first surgery. During the first surgery, PPV with injection of octafluoropropane gas (C3F8) was performed in five of these eyes, 1,000-centistoke silicone oil was injected in 10 eyes, and 5,000-centistoke silicone oil was injected in two additional eyes. All the 12 eyes that received silicone oil during the first surgery had a redetachment despite use of an endotamponade agent.

Two eyes (eyes 11 and 16) had undergone a previous PPV associated with scleral buckling in another institution. In three other eyes (12, 13, and 23), scleral buckles were implanted during the retreatment.

Sixteen eyes were phakic and nine were pseudophakic. Among the phakic patients, 14 underwent cataract extraction associated with PPV and two underwent cataract extraction when the HSO was removed.

The HSO was removed from 11 eyes after a mean period of 26.55 ± 21.38 months. In these eyes, the IOP became elevated in four (16%) eyes during the follow-up period. The IOP was uncontrolled in three patients despite instillation of antiglaucomatous eye drops and the HSO was removed and replaced with a 5,000-centistoke silicone oil. The retina remained stable and reattached in all eyes after the HSO was removed. Additional procedures during HSO removal included phacoemulsification (2 eyes), epiretinal membrane (ERM) peeling (1 eye), scleral IOL implantation (1 eye), and secondary IOL implantation (1 eye).

The HSO was left in the eyes of 14 (56%) patients because of the high risk of recurrence of the retinal detachment and ocular globe atrophy. Among these eyes, one had an oil drop in the anterior chamber; however, we elected not to remove the HSO due to the poor prognosis. In another eye, the HSO was not removed due to superior persistent retinal detachment and PVR. Three of these patients needed topical antiglaucomatous eye drops to control the IOP. The mean follow-up period was 11.07 ± 7.44 months.

Table 3: Comparison between LogMAR BCVA at baseline, month 1, month 6, and final in patients in whom HSO was removed and patients in whom HSO was not removed.

	Baseline	Month 1	Month 6	Final
HSO not removed (n = 14)				
Mean	1.90	1.22	1.07	1.03
SD	0.58	0.58	0.63	0.66
Median	1.79	1.15	0.80	0.80
Min	1.00	0.60	0.49	0.20
Max	2.70	2.20	2.20	2.20
HSO removed (n = 11)				
Mean	1.87	1.33	1.24	1.11
SD	0.63	0.74	0.80	0.79
Median	2.20	1.00	1.00	1.00
Min	1.00	0.30	0.20	0.09
Max	2.70	2.20	2.20	2.20

Patients in whom HSO was not removed.
Baseline > month 1 (P = 0.001), month 6 (P = 0.001), and final (P = 0.001).
Month 1 > month 6 (P = 0.027), final (P = 0.027).
Month 6 = final (P = 0.180).
Patients in whom HSO was removed.
Baseline > month 1 (P = 0.008), month 6 (P = 0.008), and final (P = 0.005).
Month 1 = month 6 (P = 0.068); month 1> final (P = 0.028).
Month 6 = final (P = 0.068).

The mean preoperative logMAR BCVA in the group in which HSO was not removed was 1.90 ± 0.58, which increased significantly to 1.22 ± 0.58 at month 1 (P = 0.001) and to 1.07 ± 0.63 at month 6 (P = 0.027). Between 6 months and the last visit of follow-up, there was no statistically significant difference in the analysis of BCVA. In the group in which HSO was removed, the mean baseline logMAR BCVA was 1.87 ± 0.63 which increased significantly to 1.33 ± 0.74 at month 1 (P = 0.008). Between the first month and the last visit, there was no statistically significant difference in BCVA (Table 3 and Figure 1).

Ten (40%) eyes had cells in the anterior chamber without hypopyon or keratic precipitates during the first postoperative month. Inflammatory reactions resolved in all eyes with topical steroids within 15 days.

Oil emulsification occurred in 52% of the eyes. Complications such as development of an ERM during Oxane HD tamponade occurred in one (4%) eye. Lens opacity progressed in all phakic patients, and they underwent cataract surgery at the same time the HSO was removed. Table 2 lists the other complications.

Anatomic success was achieved in 92%. One eye had a recurrence of the rhegmatogenous retinal detachment and another eye had a persistent tractional retinal detachment. No additional surgeries were performed in these cases due to the poor prognosis and risk of ocular globe atrophy.

4. Discussion

In this retrospective study, we described the effects of HSO as an endotamponade agent for complicated retinal detachments with inferior PVR. Despite advances in PPV techniques, vitreoretinal surgeons are still challenged by complex retinal detachments complicated by PVR.

Standard silicone oil is an excellent tamponade agent for most retinal detachments [4, 19, 20]. However, the tamponade of the inferior retina may be unsatisfactory since the density of standard silicone oil is lower than water. This results in an aqueous inflammatory environment that may predispose and increase the possibility of inferior PVR development [10–12]. In such eyes, the use of HSO has been suggested to be effective and safe for the treatment of inferior retina [8–14].

Most studies about the use of HSO in complex retinal detachments report that the HSO remained in the eye for an average of 3 to 6 months [2, 9, 10, 21, 22]. We studied eyes with a poor prognosis due to complex retinal detachments and extensive inferior PVR. Because of the severity of the retinal detachments, we left the HSO in the eyes for longer than 3 to 6 months and observed the effects of HSO over time.

Among the 25 eyes studied, the silicone oil has not been removed from 14 eyes due to the complexity of the cases. These patients had the HSO in situ for a mean period of 11.07 ± 7.44 months. The HSO was removed from 11 eyes after a mean of 26.55 ± 21.38 months. To our knowledge, such study is unique because no published studies have reported the effects of HSO in situ for as many months as in the current study.

Another factor in the current study that has not been reported in other series is the use of HSO in cases of tractional retinal detachments due to proliferative diabetic retinopathy with associated retinal tears and development of inferior PVR. We included eight patients with combined tractional and rhegmatogenous retinal detachment secondary to diabetic retinopathy. These eyes did not have higher complication rates compared with patients with a rhegmatogenous retinal detachment.

We observed a high anatomic success rate (defined in this current series as success until 6 months of follow-up) in eyes with primary complex retinal detachment and recurrent retinal detachment. Eight eyes in which HSO was used as a primary endotamponade agent had an anatomic success rate of 100%. Seventeen (68%) eyes had undergone a previous unsuccessful surgery for retinal reattachment and underwent a second surgery with injection of HSO. One eye had a persistent retinal detachment resulting from severe tractional retinal detachment secondary to diabetes retinopathy and PVR. Another eye had a recurrent rhegmatogenous retinal detachment despite retreatment and HSO tamponade. Thus, we achieved an anatomic success rate of 92% when we analyzed the data from the 25 eyes from this series.

Despite the final low VA due to the severity of the cases, there was statistical improvement in BCVA in the group that did not remove the HSO and in the group in which HSO was removed. The BCVA in the group in which HSO was not removed improved significantly during the first 6 months and remained stable until the end of follow-up. Among the eyes that had the oil removed, there was improvement in BCVA after 1 month which remained stable until the last visit ($P < 0.05$).

Previous studies have reported an intraoperative common complication related to an interaction between the HSO and perfluorocarbon. When these substances come into contact intraoperatively, a hyperviscous solution that is described as "sticky oil" forms [23]. Thus, direct perfluorocarbon-silicone exchange should not be performed. In the current study, three patients had a giant tear. In these cases, such as in all eyes submitted to intravitreal HSO injection, fluid-air exchange followed by injection of HSO was performed successfully.

Some authors consider HSO to be poorly tolerated intraocularly, leading to early removal of oil (3–6 months). The well-known effects of this tamponade agent are cataract formation, oil emulsification, ocular hypertension, proinflammatory response, macular ERMs, and high levels of intraocular pressure (IOP) [16]. A previous study that evaluated the tolerance and efficacy of Oxane HD as an internal tamponade for retinal detachment surgery reported that Oxane HD was well tolerated and did not appear to have proinflammatory effects [3].

A recent study analyzed 61 eyes and compared Densiron (Densiron-68, Fluoron Company, Neu-Ulm, Germany) and a normal density 1,000-centistoke silicone oil. The study reported similar complication rates of cataract formation, elevated IOP, inflammatory reaction, macular ERMs, and silicone oil emulsification [24].

We observed inflammation in the anterior chamber in 40% of eyes, which is similar to other reported studies in which Oxane HD was used [25]. Emulsification occurs earlier with HSOs (Oxane HD and Densiron) than with standard silicone oils [3, 8, 16]. In the current study, HSO emulsification occurred in 13 (52%) patients at a long-term follow-up. However, despite the HSO emulsification, these eyes required silicon oil tamponade to avoid PVR progression, hypotony, and globe atrophy. New interventions and silicon oil change may be also alternatives for management of such complications [3, 8]; however, the surgeon must be aware of the possibility of globe atrophy and BCVA decrease due to

ischemic optic neuropathy [16]; so the risks versus benefits may be analysed before such decision for each specific case.

Similar to other studies, the IOP was elevated in 16% of patients in whom Oxane HD was injected [2, 11, 13]. Despite previous reports of high rates of IOP elevations in patients injected with HSO, the most recent data showed equivalent rates of IOP elevation when Oxane HD and Densiron were compared with standard silicone oil [24, 25].

5. Conclusion

In summary, this retrospective study found that HSO is an effective tamponade agent in both complex rhegmatogenous and tractional retinal detachments complicated by PVR.

Most patients had a good anatomic success rate with improved vision. Despite the high rates of HSO emulsification, it is possible to maintain the HSO in eyes for long periods with relative tolerability and safety resulting in useful vision for specific cases.

Conflict of Interests

The authors have no financial or conflicting interests to disclose.

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Clinical Study

Clinical Observations and Occurrence of Complications following Heavy Silicone Oil Surgery

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Purpose. To demonstrate development and complications in heavy silicone oil (HSO) surgery in 100 eyes following primary vitreoretinal surgery. *Methods.* 100 eyes were included in this retrospective study that underwent vitreoretinal surgery using HSO as endotamponade. Indication diagnoses were retinal detachments ($n = 76$), complicated macular holes (MH) ($n = 20$), and others ($n = 4$). HSO removal was performed after a mean period of 20.2 ± 19.0 weeks. In 18 eyes with poor functional prognosis the silicone oil remained permanently for stabilisation. Overall follow-up time was 35.9 ± 51.8 weeks. *Results.* The mean IOP before HSO surgery was 13.3 ± 5.6 mmHg and raised to an average maximum of 23.3 ± 8.5 mmHg postoperatively and decreased to 13.7 ± 7.2 mmHg after removal. Secondary IOP raise due to emulsification of the silicone oil endotamponade was seen in 29 eyes after 7.8 ± 4.5 weeks. Other complications being observed with HSO installed were persistent corneal erosion ($n = 3$) and prolonged anterior chamber inflammation ($n = 29$). In 13 eyes recurrent retinal detachments occurred during followup. *Conclusions.* According to our analysis HSO surgery might deliver satisfying results in complicated cases of ophthalmological surgery. However, potential complications should always be taken into account when making the decision if to use and when to remove HSO in complicated retinal surgery.

1. Introduction

In vitreoretinal surgery long-term endotamponades have become a helpful alternative to the already widely used short-term endotamponades such as air, sulfur hexafluoride (SF6), and octafluoropropane (C3F8) in complicated cases of retinal detachments, recurrent retinal detachments, trauma surgery, and proliferative vitreoretinopathy (PVR) [1–4].

HSO has been designed to overcome the disadvantages of silicone oil and gas endotamponades because they are heavier than water endotamponade agents. Because of their increased density, they provide a good endotamponade of both the inferior and the posterior pole in normal head positioning, making postoperative face-down positioning no longer necessary in certain conditions [5–7]. Hence, especially in the treatment of retinal detachments with large inferior breaks or PVR the characteristics of heavier than water endotamponades may appear beneficial compared to other endotamponades [5, 7, 8].

Nevertheless several complications have been reported due to HSO surgery, such as prolonged intraocular inflammation and secondary IOP raise with a possible relation to emulsification of HSO [9–15]. This retrospective clinical study was established to determine the functional and anatomical outcome of heavier than water silicone endotamponade surgery in complicated cases with special focus on the main complications that may occur in the short- and long-term course of time after the operation.

2. Methods

The records of 100 patients and 100 eyes, respectively, which have undergone vitrectomy combined with HSO endotamponade between 2008 and 2011, were reviewed. All patients were treated at the Department of Ophthalmology of the RWTH Aachen University. In most cases the indication diagnosis for vitrectomy with HSO was proliferativ

vitreoretinopathy (PVR) and/or patients with complicated retinal detachments ($n = 76$) including 5 patients with retinal detachment secondary to open globe injury. Some patients received HSO surgery due to complicated MH ($n = 20$). MHs are considered complicated by the authors when one of the following apply: (a) a history of MH for 6 months or more; (b) after primary or even secondary retinal surgery, for example, when short-term endotamponades, such as SF6 or C3F8, were unsuccessful; or (c) whenever a larger central substantial defect was appreciated when the indication for the operation was established. Other indications were endophthalmitis ($n = 2$) and macular hemorrhage (2). Two different types of HSO were used, Oxane HD (Bausch & Lomb; $n = 27$) and Densiron 68 (FLUORON; $n = 73$), respectively.

In all patients 20 gauge standard system vitrectomy was performed. In cases of retinal detachment surgery HSO was installed in direct exchange with perfluorodecalin (PFD).

Complete ophthalmological examination was performed before and after treatment, and a database was created which included several parameters that were subsequently analysed.

Visual acuity was measured using decimal charts and converted into LogMAR units for statistical purposes. Non-numeric values, such as light perception (LP), hand motion (HM), and count fingers (CF), were decimally described: LP = 0.001 (LogMAR 3.0), HM = 0.01 (LogMAR 2.0), and CF = 0.02 (LogMAR 1.7).

The intraocular pressure (IOP) was measured by standard Goldmann applanation tonometry. Slit lamp examinations and direct or indirect funduscopy were performed at first visit, before and after surgery, and at each visit throughout the follow-up time. All patients were examined 6 weeks after surgery and thereafter every 6–8 or 10–12 weeks, respectively, depending on occurrence of complications, such as intraocular inflammation or IOP rise.

IOP raise is defined by the authors as a difference of 8 mmHg or more between the IOP measured before primary HSO surgery and the IOP at the time of HSO-removal indication or any IOP above 24 mmHg after the primary surgery. Values greater than 21 mmHg are assumed to be ocular hypertensive values that are to be monitored and if necessary even to be treated. Thus taking it from a mean IOP of 13.3 ± 5.6 mmHg at baseline examination before HSO surgery, an elevation of 8 mmHg would drop into the boundaries of the ocular hypertension range. Moreover any IOP higher than 24 mmHg is supposed to be treated due to regularities of our clinic as it exceeds the upper range of ocular hypertension.

The mean follow-up time was 35.9 ± 51.8 weeks after last surgery.

For statistical purposes in the matter of the IOP comparison and development, a student t-test was performed using *IBM SPSS Statistics Standard*.

3. Results

In 82 of 100 eyes, HSO was removed after a mean period of 20.2 ± 19.0 weeks. In 18 eyes with poor functional prognosis, the silicone oil remained permanently for stabilisation at final visit.

At the time of HSO surgery indication the mean best corrected visual acuity (BCVA) was LogMAR 1.0 ± 0.8. At last follow-up examination after HSO removal the mean BCVA was 0.7 ± 0.7 which demostrates a mean BCVA improvement of 3 lines logMAR.

In 76 eyes, HSO was used as endotamponade following vitrectomy for treatment of retinal detachments due to inferior breaks with or without PVR. Out of those 76 eyes in 42 cases PVR reaction was seen. Following the European Vitreoretinal Society (EVRS) staging for PVR in 3 eyes stage A, in 8 eyes stage B, in 12 eyes stage C1, in 10 eyes stage C2, in 7 eyes stage C3, and in 2 eyes stage C4 could be observed at the time of HSO surgery indication. The primary success rate for this procedure was 82.9% (63 of 76 patients). 3 eyes (4.0%) showed a persistent retinal detachment under HSO endotamponade and 10 eyes (13.2%) a retinal redetachment occurred after removal of the endotamponade.

49 of all patients (49%) were phakic prior to first surgery out of which in 11 patients (22.4%) primary vitrectomy was combined with phacoemulsification. In the 38 remaining phakic patients cataract progression was observed in 22 eyes (57.9%) requiring cataract surgery simultaneously to HSO removal.

At the time of HSO surgery indication the mean IOP was 13.3 ± 5.6 mmHg. With HSO installed the IOP rose to an average maximum of 23.3 ± 8.5 mmHg within the first few days postoperatively and could be lowered to a mean IOP of 15 ± 5.4 mmHg by using 1 to 4 different topical antiglaucomatous agents. In 15 patients (15%) the IOP rose above 30 mmHg within the first few days postoperatively. Within 7.7 ± 4.5 weeks after primary HSO surgery the IOP rose up to maximum values of 56 mmHg and a mean IOP of 23.4 ± 9.7 mmHg within 7.8 ± 4.5 weeks postoperatively. At 6 weeks postoperatively a mean IOP of 15.6 ± 8.1 mmHg was seen and still was significantly higher than preoperatively ($P = 0.007$). 15 patients needed 1 or 2 different topical antiglaucomatous agents to keep the IOP stable and 1 patient needed more than 2 different agents. At resurgery indication a mean IOP of 17.7 ± 8.5 mmHg was seen. Meanwhile 20 patients needed topical antiglaucomatous therapy out of which 9 patients needed 1 agent, 7 patients needed 2 agents, and 4 patients needed 3 or 4 different agents. In 8 patients extra systemic sulphonamides were needed to control the IOP until HSO-removal surgery. At the date of surgery the preoperative mean IOP was 15.8 ± 7.1 mmHg. After removal of HSO the IOP decreased to 13.7 ± 7.2 mmHg 6 weeks postoperatively ($P = 0.018$). Only 8 patients still needed topical antiglaucomatous therapy at that time out of which only 3 needed more than one agent. An overview of the IOP development throughout the whole treatment is given in Figure 1.

In 37 patients emulsification of the HSO was observed by slit lamp examination, gonioscopy, or indirect funduscopy as displayed in Figures 2(a) and 2(b), respectively.

In 22 eyes secondary IOP rise was seen after a mean period of 7.8 ± 4.5 weeks. In all of these 22 cases emulsification

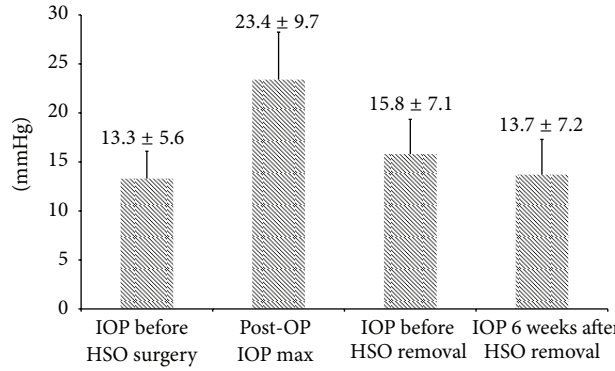


Figure 1: IOP development from pre-HSO surgery through 6 weeks after HSO removal.

of the silicone oil endotamponade was observed. In 15 more cases emulsification without IOP rise could be seen.

Other complications being observed with HSO installed were persistent corneal erosion ($n = 3$) (Figure 3) and prolonged anterior chamber inflammation ($n = 29$) out of which the majority ($n = 20$) was recurrent after HSO removal within the first 6 weeks postoperatively. In the residual 9 patients that still had anterior chamber inflammatory signs at the 6 week follow-up visit, the inflammation was recurrent within a few more weeks using topical steroids.

In 2 cases after HSO removal a cystoid macular edema occurred that was persistent throughout all follow-up visits and could neither be controlled with topical or intravitreal steroids nor with intravitreal bevacizumab.

4. Discussion

The most common indication for the use of heavier than water endotamponades is the use for the treatment of retinal detachments with inferior pathologies. In previous studies the primary success rate has been determined between 54% and 89% [5–7, 9, 16–18]. The high range in these rates may be explained by heterogenous preoperative retinal findings that seem to be relevant especially in smaller case series. However, in our study the primary success rate of approximately 83% was reached in a comparatively large cohort with, in our opinion, a representative case mixture. This may confirm the effectiveness of HSO in these indications.

In the literature the most frequently reported complication in the use of HSO is the progression of lens opacities with rates from 38% up to 100% [6, 7, 12]. These observations reveal certain limitations especially in retrospective studies, such as in this study, as there is little information about the preoperative cataract grade. On the other hand it is not clear whether cataract progression is primarily caused by the endotamponade or by the vitrectomy itself, which even if there is no documentation about intraoperative lens damage represents a risk factor for postoperative progression of lens opacities [19]. Finally, our results do not allow any statement about the progression in relation to endotamponade duration. However, while the combined surgery of cataract and HSO extraction is a common and feasible procedure, cataract formation represents an acceptable complication.

The two major issues in the use of heavier than water endotamponades seem to be secondary IOP rise after HSO surgery that in some cases even persists after HSO removal and a prolonged intraocular inflammation that seems to be induced by the HSO. In regard to the elevation of IOP we detected two peaks, one immediately after surgery, which could be controlled by conservative local or systemic antiglaucomatous therapy. There are several possible reasons for an early increase of IOP including inflammation, application of laser photocoagulation, the use of encircling bands, a pupillary block, or migration of silicone oil into the anterior chamber [20–22].

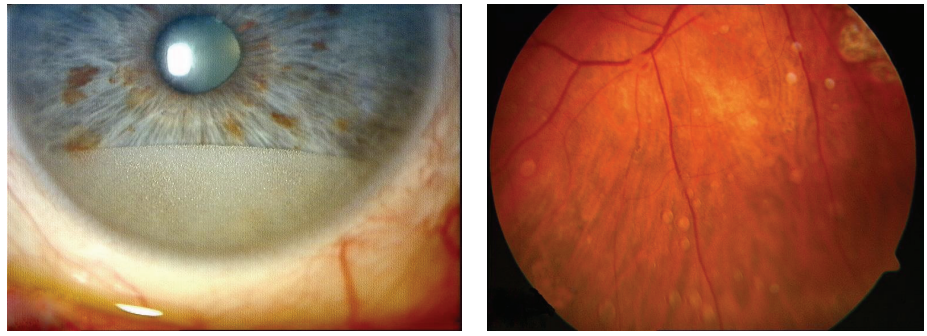
Wong et al. [23] described a postoperative early increase of IOP that was significant higher at the first postoperative day compared to another group of patients that underwent conventional silicone oil surgery. According to their results at day one postoperatively in 9 out of 71 patients (12.7%) the IOP rose above 30 mmHg after HSO surgery, while according to our results in 15 out of 100 patients (15%) the IOP rose above 30 mmHg within the first few days postoperatively. Wong et al. also state in their work that after 4 weeks the mean IOP deteriorated to 18.8 ± 9.4 mmHg. In our clinic the first planned visit after hospital discharge was after 6 weeks. After that period the mean IOP decreased to a value of 15.6 ± 8.1 mmHg. Our results are comparable to findings reported by Wong et al. in which IOP demonstrated an early rise postoperatively followed by a subsequent IOP decrease seen after 4 weeks.

In our patients we observed that inflammation and intraoperative laser might be the most common reasons for this early hypertension due to the absence of scleral buckling, pupillary block, or migrated silicone oil in the majority of the eyes.

In all cases where a second IOP elevation occurred after a followup of six weeks we found emulsification of HSO, which may have reduced the aqueous humour outflow. In the literature the rate of emulsification is indicated with rates between 5% and 18.5% [9, 18, 24]. These studies have in common that smaller amounts of cases have been investigated in each study and the mean endotamponade duration was shorter compared to our study. This may explain the higher rate of emulsification we found in our case series. However, removal of HSO including aspiration of emulsified bubbles out of the anterior chamber transferred IOP values to normal levels in most of the cases without requiring further antiglaucomatous therapy.

Romano et al. [25] described the development of a hyperviscous solution that could be described as "sticky oil" being generated by exchanging perfluorocarbon liquids (PFCL) such as PFD directly with HSO instead of air and HSO thereafter intraoperatively. In our opinion this could be a reasonable explanation for the relatively high complication rate, since our treatment regime regularly includes the direct exchange of PFCL and HSO.

The authors' decision to remove the HSO endotamponade strongly depended on the anatomical stability, functional outcome to be expected, and/or the occurrence of intraocular



(a) (b)

Figure 2: (a) Emulsification of HSO in the anterior chamber. (b) Emulsificated HSO adhesive to the retina.

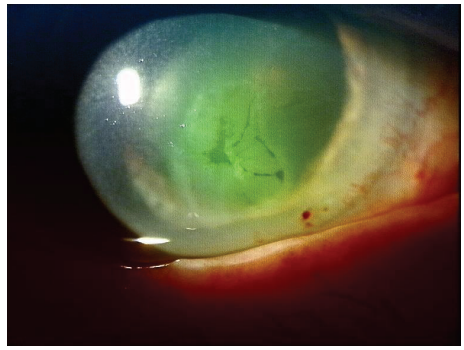


Figure 3: Example of a persistent corneal erosion after HSO endotamponade surgery.

inflammation of the individual patient's eye, which explains the relative wide standard deviation (SD) of the mean residence time of the HSO. The wide SD in the follow-up time as well as in the IOP measured at any time after the HSO operation is explained by the fact that this work was a retrospective clinical study and some patients had their last visit 6–8 weeks after HSO removal whereas other patients were monitored for several more months after the last operation due to a more complicated development and eventually in some patients the silicone oil remained permanently for stabilisation, due to poor functional prognosis or a probable development of hypotonia following trauma.

In two patients we observed the occurrence of a cystoid macular edema during followup after HSO removal. Neither a treatment with topical and systemic steroids nor intravitreal injections with triamcinolone-acetonide or bevacizumab showed any effect on these findings. To our knowledge this is the first report on chronic macular edema following HSO surgery and stands in contrast to all other cases of persistent intraocular inflammation in our study, which were treated successfully during followup after HSO removal.

We suppose that a pathogenetic factor could be a proinflammatory influence of the HSO that seems to be persistent even after HSO removal. This assumption, of course, cannot be proved with the data of this study, since this complication was observed in only two patients, so a larger cohort of patients needs to be observed in future investigations.

In most studies HSO was removed within three months and by now its feasibility as a long-term endotamponade could not definitely be proven [4–7, 9]. In fact, in our study inflammation or IOP elevation, if not sufficiently controllable, accelerated the decision to remove HSO. However, in more than two-third of all patients from the time of having HSO installed no major problems occurred, allowing the suggestion to remove HSO in regard to the anatomical situation of the retina alone. Moreover, in some cases, especially in eyes that needed antiproliferative HSO surgery after severe trauma, the HSO seems to stabilise the anatomical constitution and restrain the eye from IOP drop, persistent hypotonia, and phthisis by leaving HSO as permanent endotamponade installed.

In conclusion, in our study, as no alarming complications occurred in the majority of cases, safety of HSO endotamponade could be demonstrated. However, eyes carrying HSO need frequent follow-up examinations as the appearance of inflammations or IOP elevations could influence the decision of when to remove the endotamponade.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Review Article

Perfluorocarbon Liquid: Its Application in Vitreoretinal Surgery and Related Ocular Inflammation

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The application of perfluorocarbon liquids has been well acclaimed in vitreoretinal surgery. Its unique physical properties make it an ideal intraoperative tool to improve the efficiency and safety of surgical procedures in complicated cases. The main functions of perfluorocarbon liquids in vitreoretinal surgery include relocating and fixing the detached retina, displacing the subretinal and subchoroidal to fluid anteriorly, revealing proliferative vitreous retinopathy (PVR) for further maneuvers, protecting the macula from exposure to chemicals with potential toxicity, and assisting the removal of foreign body. The related clinical applications include retinal detachment with severe proliferative vitreoretinopathy, giant tear, diabetic retinopathy (DR), retinopathy of prematurity (ROP), and posterior dislocated crystalline and intraocular lenses. The application of perfluorocarbon liquids has been expended over the past fewer years. Several PFCLs related ocular inflammations have been observed in *in vitro* studies, animal studies, and clinical follow-up. The complete removal of PFCLs is recommended at the end of the surgery in most cases.

1. What Are Perfluorocarbon Liquids?

Perfluorocarbon liquids (PFCLs) are a serial of fluorochemicals in which all the hydrogen atoms are replaced by fluorine [1].

PFCLs are not found in nature. Those compounds are industrially produced by methods such as electrochemical fluorination, oligomerization, and telomerization [2].

Characteristically PFCLs have high specific gravity ranging from 1.76 to 2.03, low surface tension, and viscosity [3, 4]. These physical properties make perfluorocarbon liquids an ideal for intraoperative tool in vitreoretinal surgery.

2. Commonly Used Types of Perfluorocarbon Liquids and Their Characteristics

Several kinds of perfluorocarbon liquids have been applied in ophthalmology in different countries. They are perfluorooctane (PFO), perfluoroperhydrophenanthrene (Vitreon), perfluorodecalin (PFD), perfluorotributylamide (PFTB) and perfluorooctylbromide (PFOB), and so forth [5, 6].

The physical properties of PFCLs including high specific gravity, moderate surface tension, low viscosity, and optical clarity and transparency make them ideal intraoperative tools for vitreoretinal surgery [7].

The gravity of the above-mentioned PFCLs ranges from 1.76 to 2.30, which empowers the liquid to flat the detached retina and displace the underneath fluids anteriorly [8]. The transparency of PLFCs as a colourless and clear media also ensures that the intraoperative usage of the fluid does not affect the observation of the operators during the surgery and intraoperative photocoagulation. The surface tension of PFCLs ensures the liquid staying relatively cohesive after been injected into the vitreous cavity [9, 10]. The low viscosity makes PFCLs easier to handle while injection and removal [11].

3. The History of PFCLs in Ophthalmology

The potential application of PFCLs in medicine was discovered by Clark Jr. and Gollan in 1966. Mammals including mice and cats in the containers filled with fluorocarbon managed

to survive after weeks [12]. With further investigation, PFCLs' capacity to carry oxygen was confirmed and later developed as blood substitute [13]. In 1982, Haidt et al. used PFCLs as vitreous tamponade in experiments [14]. Zimmerman and Faris used PFCLs as intraoperative tool to relocate the detached retina in 1982 [15]. In 1987, after *in vivo* and *vitro* studies of the efficiency and safety of intraoperative application, Chang et al. use PFCLs in vitreous surgeries of retinal detachment patients with severe PVRs [16].

4. The Functions and Related Indications in Vitreoretinal Surgery

4.1. Relocating and Stabilizing the Detached Retina for Further Maneuvers. The gravity of PFCLs in use is about 2 times greater than perfusion solution. So while injected into the vitreous cavity during vitrectomy, the gravity of PFCLs generates a force against the interface downwards. While it is against the detached retina, the injected PFCLs relocate and immobilize the detached posterior retina. And, while PFCLs are gradually injected into the vitreous cavity, the subretinal fluid is pushed anteriorly and thus into the vitreous cavity through the retinal breaks, which often results in avoiding retinotomy for posterior drainage [17]. In some cases, this process can provide information about the location of the unidentified peripheral breaks if subretinal fluid drainage is observed through breaks other than the identified retinal breaks.

4.1.1. Retinal Detachment with Severe PVR. The very first application of PFCLs in vitreoretinal surgery was in patients of retinal detachment with severe PVR [18]. The application of PFCLs has changed surgical management of PVR. Before that, anterior PVR dissection was performed first and then followed by dissection of posterior PVR. The use of PFC eyes with retinal detachments complicated by PVR permits initial dissection of posterior PVR. The injection of PFCLs after initial dissection aids in opening the funnel to provide better visualization of proliferative membranes and a more thorough removal of the membranes [19].

Regarding the retinal reproliferation after surgery, Greve et al. reported that the intraoperative use of PFCLs in vitreoretinal surgery does not prevent postoperative surgery reproliferation, but it does reduce the severity since the application of PFCLs allows for a more complete removal of the epiretinal membranes. Several other studies have demonstrated the usefulness of PFCLs as an intraoperative tool, diagnostically and therapeutically as well in patients with retinal detachment and PVR [20].

4.1.2. Giant Tears. Retinal detachment with giant tears has been a challenging field in vitreoretinal surgery. The mobility of the detached retina is relatively higher and more difficult to be manipulated due to the size and location of the retinal tears. The application of perfluorocarbon liquids stabilizes the detached retina during vitrectomy and displaces the subretinal fluid [21]. Vitreon and perfluorooctane were well studied for clinical use [22, 23].

Zhioua et al. evaluated the usefulness of an intraoperative injection of PFCLs in 17 eyes with giant retinal tears (between 90 and 220 degrees) associated with grade 3 PVR. They found an improvement in both anatomical and functional prognoses [24].

In the perfluorooctane study group's work in 2002, Scott and colleagues included 212 eyes of 212 patients with giant tears and followed a median of 3.5 months. 59% percent of the postoperative visual acuity was improved, 24% remained stable, and 16% was worsened. At 6 months, the retina reattachment rate was 76% [25].

With the intraoperative use of PFCLs, giant tears with no severe PVR, the chance of preserving the lens during surgery has been increased. In some cases, no tamponade of silicon oil is needed [26, 27].

4.1.3. Diabetic Retinopathy. Application of PFCL during vitreous surgery for proliferative diabetic retinopathy (PDR) has been reported by several authors, mostly in quite severe cases. The functions of PFCLs during surgery are similar to cases of retinal detachment with severe PVR. PFCL is a useful adjunct during vitrectomy for severe PDR, especially to flatten shrunken retina. PFCL is also efficient to flatten retinal detachments that appeared when relieving tight vitreoretinal adhesion [28]. The application of PFCL also provides a better condition to perform panretinal photocoagulation if needed with lower energy.

In the study of Imamura and his colleagues, the surgical results were acceptable although the follow-up time was relatively short. PFCL was used in the most complicated cases among PDR patients. In those 18 cases, they all showed macular tractional detachment; two had combined rhegmatogenous retinal detachment and one had PVR due to a previous failed vitrectomy for PDR. The anatomical success rate was 89%, and a visual improvement was found in 10 eyes (55%) [29].

4.1.4. Retinopathy of Prematurity and Other Complex Pediatric Retinal Detachment. Perfluorooctane has been used in complex pediatric retinal detachment with severe PVR. While the posterior proliferative changes were in the inferior retina and gas or silicone was considered less effective or ineffective, perfluorooctane can be considered as a temporary postoperative tamponade [30, 31].

4.2. Floating the Foreign Bodies in the Vitreous Body. A confirmed vitreous foreign body often requires surgical removal. For nonmetal foreign bodies with gravity less than PFCLs (1.76–2.03), the injection of PFCLs into the vitreous body before removal can lift the foreign body away from the retina, thus simplifying the procedures of removal and, mostly, improving the safety of the process [32, 33].

4.2.1. Penetrating Trauma with Posterior Foreign Body. For patients with posterior foreign body after penetrating trauma, PFCLs can assist the removal of light foreign bodies. Trauma cases are often complicated by lens injury, retinal detachment, and vitreous and subretinal or choroidal hemorrhage. The application of PFCLs can also help with the management of retinal detachment, hemorrhage, and proliferation [34].

4.2.2. Posterior Dislocated Crystalline and Intraocular Lenses. In cases of posterior dislocated crystalline or intraocular lenses (IOLs), PFCLs can be applied for the same reason for low gravity vitreous foreign bodies. Even when the dropped lens coexists with a retinal detachment, PFCLs are valuable intraoperative tools because they can aid in the removal of fragments from the vitreous cavity without eliciting iatrogenic retinal damage. Similarly, removing a dislocated IOL by injecting PFCL reduces the risk of injuring the retina during the maneuvers required to retrieve an IOL from the posterior vitreous cavity [35, 36].

Jang reported a modified technique of phacoemulsification in dislocated crystalline lenses in a study of 11 eyes [37]. After the vitreous and posterior hyaloid membranes were removed, perfluorocarbon liquid (PFCL) was injected at the posterior pole to fill the vitreous cavity. The dislocated lens floated on the PFCL, and the injection was ceased once the lens had risen to the iris plane. The lens was then removed from the anterior chamber using standard phacoemulsification procedures. During the phacoemulsification, the PFCL provides a support underneath the nucleus, like a trampoline, and even small fragments can be completely removed. The best-corrected visual outcome was reported more than 20/40 in 11 eyes.

4.3. Protecting the Macula. During vitrectomy, for the purpose of treatment or assisting a procedure, biochemically active agents or drugs may be injected into the vitreous cavity to avoid related toxic effects to the macula. Before the injection of the potentially toxic agents, a small amount of PFCLs is injected into the vitreous cavity to form a bubble covering the macula area, thus separating the macula from the potentially toxic agents [38–40].

4.4. Suprachoroidal Hemorrhage. A suprachoroidal hemorrhage is defined as a hemorrhage in the suprachoroidal space. PFCLs may be useful for expressing suprachoroidal hemorrhage from sclerotomies after vitrectomy. When injected directly over the retina, PFCLs create a posterior tamponade effect, unlike air or gas, by pushing the subchoroidal hemorrhage anteriorly and making it exit through the anterior sclerotomies [41, 42].

PFD or PFO has also been successfully used as an endotamponade tool combined with a tissue plasminogen activator for the treatment of subfoveal hemorrhages in cases of exudative age-related macular degeneration ARMD by preventing or reducing the risk of massive subretinal hemorrhages as a possible complication of treating exudative ARMD [43, 44].

5. The Time-Related Ocular Inflammations Caused by PFCLs

5.1. In Vitro Studies and Animal Studies. Previous *in vitro* studies have evaluated the effects of direct toxicity and damage due to PFO gravity on human retinal pigment epithelium cells and retinal ganglion cells. They found that PFO was toxic to the ARPE-19, a spontaneously arising human RPE cell line after 7 days of exposure, and PFO generated damage through the mechanical force imparted to retinal ganglion cells [45, 46].

The short tamponade of PFCLs has been reported relatively safe by animal studies. Electron-microscopic studies of intravitreal perfluorotributylamine, perfluorodecalin, and perfluorooctane placed in pig eyes for up to 3 hours indicate a lack of retinal changes. Electrophysiological studies and morphological examination using both light and electron microscopy have revealed no evidence of retinal toxicity after perfluorophenanthrene intravitreal placement for periods up to 48 hours [47, 48].

Intraretinal macrophages and foam cells are observed after 1 to 2 weeks intravitreal placement of PFO, PFD, and PFOB [49]. The narrowing of the outer plexiform layer and degenerative thinning of the outer nuclear layer can be observed progressively as the perfluorocarbon liquids remain longer within the eye [50]. Only the inferior retina exhibits these changes, which are believed to result from the mechanical effects of the high specific gravity of PFCLs which exerting prolonged pressure against the retina. These changes may be only species specific, and similar observations have been made of the superior retina of rabbit eyes following silicone oil injection. Small droplets of perfluorooctane (0.1 mL) injected into the rabbit vitreous appear to be well tolerated, eliciting a macrophage response but no retinal alteration at 6 months [51, 52].

The purification and chemical stability of the perfluorocarbon liquids are highly related to PFCLs induced ocular inflammation. During the production of PFCLs, the impurities are often partly fluorinated substances H and double bonds which are biochemical active and result in ocular inflammation and cytotoxicity [53].

Velikay et al. reported the clinical and histological observations of PFD and PFOB both extremely purified and with 5–30% impurities as short time tamponade in a period of 8 weeks. PFD and PFOB which were not purified caused severe inflammation and retinal detachment. Distinct disarrangement of the outer nuclear layer, vacuolization in the inner nuclear layer, and both edema and vacuolization of the ganglion cell layer were observed [54].

5.2. Clinical Observation. PLFCs related ocular inflammation is also observed in clinical settings especially in cases of subretinal PFCLs [55]. Significant pigment epithelial atrophy throughout the area was vacated by subretinal PFCLs [56]. Subretinal PFCL also can cause local functional changes in the sensitivity of the retina, which has been demonstrated by SLO microperimetry.

Young patients are probably at higher risk for developing severe inflammation. Eyes that develop persistent inflammation, secondary membrane formation, or recurrent RD will need reoperation for removal of this material [57–59].

The use of PFO has been reported to be involved in the occurrence of sticky silicone oil. Interactions of PFCL with silicone oil or heavy silicone oil and variations in temperature are responsible for the increase in shear viscosity and opacity of the oil [60]. PFCL interacts with silicone, dissolving small amounts of the oil into solution over time. And the

surface tension of the surrounding aqueous material and/or contamination of silicone oil with PFCL reduced. While the presence of silicone oil remnants on the retina did not cause lasting side effect, forceful attempts at removal can lead to complications [53].

6. Recent Developments in PFCLs

6.1. Perfluorocarbon-Perfused Vitrectomy. One of the recent developed applications of PFCLs in vitrectomy is perfluorocarbon-perfused vitrectomy. This system employs PFCL perfusion instead of balanced salt solutions (BSSs) during vitrectomy [61]. Oxygenated or nonoxygenated PFCL is used in a recycling or a nonrecycling system for this procedure. PFCL-perfused vitrectomy benefits from several properties of PFCLs [62–65].

In cases with severe diabetic retinopathy, oxygenated PFCLs can be an advantage for the circulation compromised retina. The high oxygenated PFCLs also allow the vitreous surgeons to raise the intraocular pressure to a relatively higher level during a hemostatic surgery. The immiscibility of PFCLs with blood and other intraocular fluids also allows for visible vitreous removal. And most of the functions of PFCLs as intraoperative tool are also applicable while being used as perfusate, such as relocating and stabilizing the detached retina for further maneuvers [66].

6.2. Hydrogenated Hydrofluorocarbon Liquids (HFCLs). To improve the intraocular tolerance of PFCLs as vitreous tamponade, modifications have been made to reduce the specific gravity of the liquids [67]. Hydrogenated hydrofluorocarbon liquids (HFCLs) were developed with reduced specific gravity values and increased lipophilic properties. HFCLs, such as F6H6, F6H8, O44, and O62, were developed to substitute for PFCLs as long-term tamponade in vitreoretinal surgery [68–71]. Due to their properties, these compounds have the potential to remove intraocular silicon oil remnants [72, 73].

7. Conclusion

Regarding the unique physical properties of PFCLs, they have been well accepted as intraoperative tools for vitreoretinal surgery. The application of PFCLs has simplified the surgical procedures and improved the safety of the process especially in severe and complicated cases. Continuous efforts will be made to further improve the compatibility and reduce the related toxicity and ocular inflammation.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Review Article

Inflammation Induced by Perfluorocarbon Liquid: Intra- and Postoperative Use

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Perfluorocarbon liquids (PFCLs) are useful and safe surgical tools in vitreoretinal surgery. The use of PFCL as a tamponade has been controversial due to the corneal toxicity, retinal infiltration, and inflammatory reaction in experimental studies. Several authors have studied in humans the anatomical and functional outcome and adverse effects of perfluorocarbon liquids used as short-, medium-, and long-term tamponade. PFCLs develop dispersion a few days after injection and droplets may move into the anterior chamber and cause corneal endothelial damage. When PFCLs are used as postoperative tamponades for more than one week, a foreign-body inflammatory reaction is observed in up to 30% of cases but such a reaction does not induce PVR, and it resolves after removal of PFCLs. Although most clinical studies have found no signs of retinal toxicity such as progressive visual acuity deterioration or macular anatomical changes, few performed ERG or retinal histological analysis.

1. Perfluorocarbon Liquids

Perfluorocarbon liquids (PFCLs) were introduced by Chang in 1987 as a tool to manipulate the retina in retinal detachment (RD) surgery. Since their first use in humans, PFCLs have improved retinal reattachment rates in RD surgery and increased their uses in vitreoretinal surgery [1].

PFCLs are synthetic fluorinated hydrocarbons fluids that are odorless and colorless, having low viscosity, and heavier than water. These features make PFCLs extremely useful tools in vitreoretinal surgery. Their optical clarity and refractive index allow surgical maneuvers under a visible PFCL-fluid interface. Their weight flattens the retina from posterior to anterior whilst draining the subretinal fluid. Their high interfacial tension keeps the PFCL bubble as a single bubble. Their low viscosity allows easy injection and aspiration and their high boiling point allows for endophotocoagulation under PFCL.

There are several PFCLs that have been studied for vitreoretinal surgery use; see Table 1 [2].

PFCLs are used mainly as intraoperative tools for the following purposes: to flatten the retina in RD, to peel membranes in proliferative vitreoretinopathy (PVR), to shave the vitreous base, to reattach giant retinal tears (GRT), to protect the macular area or lift dropped lenses, to drain suprachoroidal hemorrhage, to stop bleeding, to dissect membranes in proliferative diabetic retinopathy, or to peel the internal limiting membrane [2–5].

PFCLs have even been used as perfusion fluid for the complete vitrectomy procedure in complex retinal detachment cases due to proliferative diabetic retinopathy, rhegmatogenous RD, or vitreous biopsy procedures [6, 7].

The use of PFCL, as a vitreoretinal intraoperative tool, even with high volumes, does not appear to induce any inflammatory reaction or iatrogenic damage, as it has a good safety profile. However, toxicity from extended intraocular use has been reported in animals and humans when PFCLs are retained for more than 48 hours. This toxicity causes an inflammatory response, and it is generally agreed that PFCL should be removed at the end of surgery. This chapter will

Table 1: Perfluorocarbon liquids [2].

PFCL	Chemical formula	Molecular weight (g/mol)	Density	Surface tension (Dyn/cm AT 25°C)	Refractive index	Vapor pressure (mmHg AT 37°C)	Viscosity (CST AT 25°C)
Perfluoro-n-octane	C8F18	438	1.76	14	1.27	50	0.8
Perfluorodecalin	C10F18	462	1.94	16	1.31	13.5	2.7
Perfluorophenantrene	C14F24	624	2.03	16	1.33	<1	8.03
Perfluorohexyloctane	C6F13C8H18	433	1.35	20	1.34		2.5

summarize the current state of knowledge of the intraoperative and postoperative use of PFCLs [8, 9].

2. Experimental Studies of PFCL in Animals

PFCLs in the anterior chamber showed inflammatory reaction and corneal damage.

When half of the anterior chamber was filled with PFCLs (perfluorodecalin or perfluorophenantrene) the rabbit eye showed severe inflammation, mainly around the lower limbus in the first postoperative days. Within a week, the rabbit eyes developed corneal haziness due to stromal edema. This edema affected the whole corneal area, and not only the inferior half of the cornea, in two-thirds of the specimens. The corneal edema decreased after 2-3 weeks, and small clusters of exudates on the surface of the PFCL droplets could be seen. PFCL was removed after 2 or 4 weeks later, most of the specimens developed corneal scarring, particularly at the margin of the droplets. In addition, half of the specimens developed subepithelial vessel ingrowth [10].

Histological analysis found stromal edema, irregularly thickened endothelium, and vacuoles in the endothelial cells, iris, and inferior trabecular meshwork. In a few eyes a small number of macrophages were observed in the iris. The endothelial cell count persistently decreased by 50%, scars with fibroblast ingrowth formed, and subepithelial neovascular vessels developed inferiorly, whereas a monolayer of endothelial cells was observed superiorly. Chamber angle synechia was observed in the inferior angle [10–12].

If a minimal amount of PFCL was present in the anterior chamber, there was no corneal decompensation. Moreover, corneal thickness, endothelial cell density, and morphology remained unchanged. However, the histological analysis showed exudates in the inferior chamber angle and vacuoles in the inferior trabecular meshwork 8 weeks after injection [13].

Thus, the effects of PFCL in the anterior chamber depend on the amount of PFCL. When there is a high volume, endothelial cell damage occurs quickly as PFCL blocks endothelial cell nutrition. This leads to corneal decompensation and fibrotic tissue begins to replace the endothelium 2 weeks after anterior chamber injection [10]. Cell damage can be observed after injection of 0.05 mL of PFCL but amounts under 0.025 mL appear to induce no reaction in the corneal endothelium, although they cause changes in the trabecular meshwork [11, 12].

The amount of PFCL is reduced by half 2-3 months after injection likely due to absorption through the trabecular meshwork [14].

In one study, the intraocular pressure was not modified by the presence of PFCL, despite the fact that some PFCL dispersion was found [10].

When PFCLs were injected in the vitreous cavity of rabbits after creating space by gas expansion or vitrectomy, PFCL droplets developed a few days after injection but residues were rarely observed in the anterior segment tissues [15, 16].

PFCLs toxicity in the vitreous chamber has been assessed. No significant inflammation was clinically observed during a 4-week follow-up; however, there were histological alterations. PFCLs were observed infiltrating beyond the internal limiting membrane with enlargement of the intercellular spaces among the Müller cells 1 week after the injection in rabbit and pig eyes. The degree of alteration and the number of PFCL droplets increased with longer follow-up. Later, PFCL penetrated deeper through the retinal layers involving the photoreceptor nuclear layer and the outer segment layer and producing morphological changes. The plasma membrane of the retinal cells in contact with PFCLs appeared irreversibly disrupted, and infiltration of the liquid within the retinal discs with cytoplasm degeneration was observed. In the retinal pigment epithelium, PFCL induces alterations within the endogenous lipid-containing bubbles. There was no PFCL found beyond Bruch's membrane [11, 14, 17–22].

The degree of infiltration is related to the viscosity and the tendency of PFCL to emulsify. The histological changes have been observed with all PFCLs: C8F18 in less than 8 to 48 hours, C10F18 in less than 3 hours, C6F13C8H18 in less than 48 hours, and C12F27N in less than 2 days. However, C14F24 seemed to be well tolerated for 6 to 23 weeks [11, 14–22].

There were no ultrastructural changes in the outer plexiform layer and photoreceptors outer segments in rabbit eyes containing PFCL for up to 1 week. However, focal areas of narrowing of the outer plexiform layer and ultrastructural distortion of photoreceptor outer segments were noted in the inferior retina after 2 weeks. These changes could be due to PFCL high specific gravity. Similar changes have been reported in the superior retina of silicone oil-filled eyes [15, 16].

Electroretinogram (ERG) tracings in experimental animals showed alterations in the a and b wave amplitudes during vitreous replacement with PFCL for 48 hours [15].

An inflammatory reaction of monocyte-macrophage cells was observed on the inner surface of the inferior retina after 1 week of PFCL presence in the vitreous cavity. The cytoplasm of these cells appeared to be filled with phagocytosed material, engulfed in lysosomes. However, macrophages did not

Table 2: PFCLs used as short-term tamponade [24, 27–29].

PFCL	Pathology	Tamponade time	Follow-up	Study	Results	Inflammation
C8F18	Inferior RD with PVR	7 days to air, C3F8, or silicone oil	14 months	Case series $N = 17$ (Drury and Bourke 2011) [24]	Primary reattachment after PFCL and tamponade removal 76% VA improvement 65% VA stable 18% Cataract 60% Macular changes 12% Inflammation 6% IOP > 21 29% Retained PFCL 24%	Iris 6 months after PFCL removal
C8F18	RD with giant retinal tear	7–5 days to SF6, C3F8, or silicone oil	24.5 months	Cases series $N = 62$ (Sirimaharaj et al. 2005) [27]	Primary reattachment after PFCL and tamponade removal 80.6% VA improvement 54.8% VA stable 32.3% Cataract 80.5% Macular changes 0% Inflammation 0% Glaucoma 4.8% Retained PFCL 0%	
C8F18	RD with giant retinal tear and PVR	5 days to C3F8 or silicone oil	16 months	Cases series $N = 10$ (Ventura et al. 2007) [28]	Primary reattachment after PFCL and tamponade removal 80% VA improvement 50% VA stable 20% Inflammation 30%	30% hypotony with anterior chamber and vitreous cell reaction
C10F18	RD with GRT and PVR	5 days to fluid	18 months	Cases series $N = 11$ (Bottoni et al. 1994) [29]	Primary reattachment after PFCL removal 82% VA 64% > 20/40 High IOP 30% Inflammation in AC 28% MER 9% ERG normal	28% AC flare or fibrin reaction

seem to be organized in epiretinal pseudomembranes. At 4-week follow-up, fibroblast-type cells formed highly organized thick pseudomembranes with a large number of newly formed extracellular matrix components. The inflammatory reaction may be related to the presence of impurities. Further, at one week, IgG, IgM, and complement factor 3 were found in the retina and the choroid, especially around the PFCL droplets. No massive infiltration of cells from the peripheral blood was observed, suggesting that the inflammatory reaction is local [13, 17].

Other authors have also reported deposition of white precipitates at the PFCL-vitreous interface when PFCLs were left in the vitreous cavity for more than 4 weeks. Histopathologic studies identified it as an amorphous proteinaceous material that was acellular, except for macrophages. When animal vitreous and PFCLs are shaken, this white precipitate appears, and it was identified as noncellular denatured proteins consistent with precipitated or compressed vitreous [14, 16, 23].

3. Studies of PFCL in Humans

PFCL tamponade in human studies has been arbitrarily classified as short-term (less than 1 week), medium-term (between 1 and 3 weeks), and long-term (more than 3 weeks) tamponade.

3.1. PFCL as a Short-Term Intraocular Tamponade. Despite the fact that PFCL is commonly used as an intraoperative tool in vitreoretinal surgery, there is concern about its use as an intraocular vitreous replacement because of the potential histological and electrophysiological changes observed in experimental studies, in addition to reports of potential mechanical compression, submacular migration, and inflammation [9, 24–26]. The origin of PFCL intolerance is not precisely known. It may be a combination of impurities, chemical effects, and mechanical compression. Nevertheless, several studies have used PFCL as short-, medium-, and long-term tamponade. The physical features of PFCLs make them excellent vitreous substitutes for dealing with inferior retinal pathology, where common tamponades with a density lower than water, like silicone oils or gases, are not so effective.

The studies on the use of PFCLs as short-term tamponade are shown in Table 2 [24, 27–29].

When PFCL is used as an intraocular tamponade the reattachment rate reported is high, averaging between 76% and 82% [24, 27–29], which is comparable to the rate obtained with the use of heavy silicone oil [30–32]. The low rate of redetachment when PFCLs are used as a postoperative tamponade may be due to the extended apposition of the retinal tear to the underlying retinal pigment epithelium (RPE), resulting in more effective chorioretinal adhesion.

Moreover, the incidence of inferior PVR is reduced because of the lack of pooling of RPE cells, chemoattractants, and serum components on the inferior retina. Redetachment tends to occur in the superior retina because of the lack of tamponade, new superior breaks, or PVR progression [24, 27–29].

VA improvement was observed in 50%–86% of cases [24, 27–29], with no clinical evidence of toxicity, such as a decline in visual acuity during the follow-up, or visible macular changes.

In one case series, an inflammatory reaction was described in 30% of cases. It was associated with hypotony, and it disappeared after PFCL removal [28].

Therefore, the use of PFCL as a short-term tamponade, removing PFCL with or without gas or silicone exchange, did not appear to induce either severe inflammatory reaction or toxic retinal effects (shown by absence of visible macular alterations and recovery of visual acuity) in several clinical reports. However, experimental studies have shown histological infiltration of PFCL droplets through all retinal layers, from the ILM to the RPE, although it is known whether this finding impairs retinal function.

3.2. PFCL as a Medium-Term Intraocular Tamponade. When PFCLs were used as a medium-term postoperative tamponade, the primary reattachment rates ranged between 86% and 92% [33–38]. Visual improvement was reported in up to 69% of patients, and the visual acuity results were mainly related to macula status.

The most common causes of retinal redetachment were development of PVR, superior tears, or tears anywhere.

The studies about PFCLs as medium-term tamponade are shown in Table 3 [33–38].

When PFCLs were used for 2 to 3 weeks, a typical granulomatous inflammatory reaction with precipitates was observed on the posterior lens capsule, retina, optic nerve head, or retinal blood vessels in 28% of patients. This reaction was different from the characteristic inflammation observed after vitrectomy, and it appears as white, round, spiculated deposits on the posterior lens surface, within indwelling PFCL and over the retinal surface. The posterior capsule deposits may obscure visualization of the posterior segment [35]. In most instances, vitreous cavity deposits seem to have a perivascular predominance and are more prominent, in the inferior vitreous cavity and retinal surface.

The inflammatory reaction started between 7 and 10 days after surgery, and it progressed in 64% of patients, impairing posterior segment visualization by the time PFCL was removed. Such patients with no foreign-body response within the first 10 days did not develop inflammation later. The inflammation cleared with topical or periocular corticosteroids in all eyes 1 to 3 weeks after PFCL removal. The inflammatory reaction did not correlate with final visual acuity, retinal attachment, PVR development, or persistently high intraocular pressure [33–37].

Histopathologic analysis demonstrated the absence of neutrophils, lymphocytes, or additional inflammatory cells, but rather the presence of numerous macrophages with clear cytoplasmic inclusions consistent with an acute foreign-body-induced phagocytic response. Occasional clumps of extracellular pigment granules were present. The absence of additional inflammatory cells seems to exclude a macrophage response induced by classically activated TH1 (mediated by INF-gamma or TNF-alpha) or traditional alternate TH2 responses. Both responses are associated with inflammatory cell recruitment and the elaboration of extracellular matrix and local tissue destruction; however, PFCL-induced macrophage response was not associated with synechiae, iris atrophy, PVR, retinal toxicity, or any other types of tissue damage [35]. Nevertheless, retinal toxicity was ruled out due to the lack of visual acuity deterioration or visible macular alterations, but it was not evaluated with electrophysiological tests or retinal histology.

One potential source of macrophages is systemic circulation, having migrated from the retina, the ciliary body, or iris vasculature, but the absence of deposits within the anterior chamber indicates that the response may be limited to the vitreous cavity. Another potential source of cells inducing the foreign-body response is residual vitreous macrophages. However, the observed cellular density seems greater than can be accounted for only by this source, especially in the context of recent complete vitrectomy. Central nervous system microglia have shown the ability to locally proliferate through the activity of resident colony-forming cells, which may be the primary source of the macrophage response [35, 39, 40].

Some reports have suggested that the phagocytic response observed within indwelling PFCL is caused by regulatory macrophages. These are distinct macrophage populations that have an inflammation-limiting housekeeping role. Their activity may be enhanced by glucocorticoids, and they produce an anti-inflammatory cytokine, interleukin-10 (IL10). Further cytochemical analysis (IL10 and IL12) may be useful in differentiating the nature of the macrophage population. PFCLs have shown cytoprotective properties, such as the ability to downregulate the toll-like receptor inflammatory pathway (which is essential for lipopolysaccharide-induced cytotoxicity). Therefore, PFCLs may inhibit the macrophage proinflammatory cascade, making glial recurrence of PVR less likely and reducing postoperative inflammation in the early postoperative period [35, 41, 42].

A similar reaction has been described when small amounts of PFCL are left in the eye after PFCL removal. When PFCL accumulated in the retrolental space, between the posterior capsule and the anterior hyaloid, a typical inflammatory reaction appeared. Adjacent to the PFCL debris, there was one layer of flattened epithelial cells (cytokeratin positive, GFAP negative, and melanin positive), which was likely of retinal pigment epithelial origin. Beneath that layer, there was another layer of highly vacuolated cells with brown pigment (CD68 positive) which contained engulfed PFCL. There were no other inflammatory cells. This seems to be a foreign-body reaction induced by altered PFCL. The nature of PFCL can be altered by emulsification, absorption of biological substances, and close tissue contact, and such altered PFCL enhances macrophage phagocytosis. Pigment epithelial cells eventually try to engulf the altered substances, thus causing this typical inflammatory reaction [38].

Table 3: PFCLs used as medium-term tamponade [33–38].

PFCL	Pathology	Tamponade time	Follow-up	Study	Results	Inflammation
C8F18	Inferior RD with or without PVR	17.4 days to SF6	32 months	Case series $N = 157$ (Sigler 2013)	Primary reattachment rate after PFCL and tamponade removal 87.5% Mean VA change in logMAR 0.15 ± 0.87 PFCL in anterior chamber 22% IOP high 34% PFCL in anterior chamber 21% Inflammation 27% Cataract surgery16% Glaucoma surgery 6%	Granulomatous inflammatory precipitates 27%
C8F18	Recurrent inferior RD with PVR	18.3 days to fluid	30.71 months	Case series $N = 44$ (Sigler 2013)	Primary reattachment rate after PFCL removal 86% Mean VA change in logMAR 0.08 ± 0.13 PFCL in anterior chamber 22% IOP high 36% PFCL in anterior chamber 32% Inflammation 32% Cataract surgery 42% Glaucoma surgery 5%	Granulomatous inflammatory precipitates 32%
C8F18	RD with GRT without PVR	16.4 days to C3F8	53.9 weeks	Case series $N = 16$ (Rofail and lee 2005) [36]	Primary reattachment rate after PFCL and tamponade removal 100% Redetachment 6,3% VA improvement 68.8% VA stable 12.5% Cataract 54.5% ERM 25% Hypotony 18.6% Inflammation 6%	Inflammatory reaction in AC after PFCL removal with fibrin over the pupil
C8F18	Inferior RD	19 days to air	29.7 months	Case series $N = 181$ (Sigler 2013)	Primary reattachment rate after PFCL removal 88% Final VA 0.81 ± 0.67 Inflammation 28%	Foreign-body response 28%
C8F18	Inferior RD with or without GRT	11 days		Case series $N = 39$ (Rush et al. 2012) [37]	Primary reattachment rate 92.4% Severe inflammation 20.6% IOP > 21 35.9% Cataract surgery 84%	Mild inflammation 79% Severe inflammation 21% Pupillary membrane 9%
C10F18	RD with GRT	2 weeks to SF6		Single case (Singh et al 2001) [38]	Typical inflammatory reaction 7 days after PFCL removal	Macrophages and epithelial cells

PFCLs migrate to the anterior chamber in 22% of cases in both phakic and pseudophakic eyes, in the absence of obvious zonular dehiscence [33]. The low viscosity of PFCLs and their high rate of dispersion allow them to course through intact zonules, reach the retroiridal space, and enter the anterior chamber through the pupil.

PFCL in the anterior chamber may block trabecular meshwork outflow, damage the corneal endothelial cells, or induce an inflammatory reaction. When there is a gross presence of PFCL in the anterior chamber, it may induce persistent IOP elevation. The anterior chamber inflammatory reaction was highly correlated with the presence of foreign-body response, indicating that anterior chamber reaction may largely consist of macrophages or that eyes with a severe anterior chamber inflammatory response are more likely to develop foreign-body reaction. However, this inflammatory reaction consists of mild deposits in the angular recesses with no evidence of synechiae [35].

The granulomatous inflammatory reaction is hypothesized to be due to a PFCL induction of local, foreign-body-type, macrophage-stimulating molecular pathway that does not appear to generate structural retinal damage within

Table 4: PFCL as long-term tamponade [9, 43–45].

PFCL	Pathology	Tamponade time	Follow-up	Study	Results	Inflammation
C14H17F13	Inferior RD with or without PVR	76 days to fluid	97 days	Case series $N = 23$ (Kirchhof et al. 2002) [43]	Primary reattachment rate after PFCL removal 78,3% PFCL in anterior chamber 48% IOP high 8,7% by pupil block Inflammation 17% Cataract 90% Dispersion 50% MER 22%	AC flare and pigment cells with pigmented clumps behind lens 17%
C8F18	RD with retained PFCL			Case series $N = 5$ (Elsing et al. 2001) [9]	Inflammatory reaction 100%	White flake-like material of macrophages and multinucleated giant cells
C14F24	RD with GRT	87.2 days to fluid	13.7 months	Case series $N = 15$ (Kertes et al. 1997) [45]	Primary reattachment 63% Cataract 44% PFCL migration 19% High IOP 19% PFCL in anterior chamber 19%	
C14F24	RD	From 5 days to 4 weeks to fluid, SF6, C3F8, or silicone oil	20.32 weeks	Case series $N = 60$ (Verma et al. 1995) [44]	Primary reattachment 90% ERM 7% Residual PFCL 3% Vitreous hemorrhage 2% Choroidal detachment 2% Vitreous fibrinous reaction 4%	Fibrinous reaction in vitreous 4%

a 3-year postoperative time period. After PFCL removal, no deposits were observed and no iris synechiae were found. Residual foreign-body deposits appeared as contracted pigmented flecks over the posterior lens capsule and resolved within 1 month after PFCL removal in all cases, rarely leaving residual pigmentation on the posterior lens capsule. Thus, the inflammatory reaction improved after PFCL removal without producing delayed-type hypersensitivity, such as uveitis or sympathetic ophthalmitis or leaving obvious anatomic or visual sequelae.

3.3. PFCL as a Long-Term Intraocular Tamponade. The use of long-term PFCL tamponade is a controversial topic due to the experimental observations of outer retinal layer damage in several studies [11, 14, 17–22]. However, PFCLs have been used without clinical evidence of damage to the optic disk or to the retina assessed by the lack of progressive visual deterioration or RPE changes. Retinal reattachment rates ranged between 63% and 90%.

The studies on the use of PFCL as long-term tamponade are shown in Table 4 [9, 43–45].

Although an inflammatory reaction was found in 17% of patients at 2 to 6 weeks after surgery with flare in the anterior chamber and pigment clumps at the back of the lens, the intraocular lens, or the anterior chamber, there was no postoperative PVR.

When a significant quantity of PFCL (more than 0.25 mL) is left in the eye for an extended period of time, an inflammatory reaction develops as early as the third postoperative week in all cases. A white flocculent, flake-like material on various intraocular structures is found on various intraocular structures, such as the posterior lens capsule, the pars plana, the vitreous base, the optic nerve head, and the posterior retina [9, 43]. Histopathologic examination disclosed compression of the residual vitreous, macrophages, and, in some cases, multinucleated giant cells. Macrophages contained intracellular vacuoles filled with electron-lucent material, identified by energy-dispersive spectroscopy as PFCL.

PFCL disperses and migrates in the anterior chamber, inducing corneal edema and endothelial cell loss after 4 weeks of PFCL contact. They may also cause keratic precipitates, deep corneal stromal vessels, and nuclear cataract. Histopathologic examination showed epithelial edema, an extensively deficient Bowman membrane, corneal stroma vascularization with inflammatory cells, and PFCL engulfed in keratocytes and macrophages around the vessels. The endothelium was largely deficient, and a thin collagenous membrane containing melanin pigment was present on the posterior surface of the cornea [46, 47].

4. Conclusion

PFCLs are useful and safe intraoperative tools in vitreoretinal surgery that do not induce inflammation. When used as a tamponade, PFCLs achieve excellent anatomical reattachment results, with a primary average success rate of 97–100% under PFCLs and 63–100% after PFCL removal. This outcome may encourage us to accept PFCL as a useful tamponade. However, when PFCLs are used as a postoperative tamponade for more than 1 week, an inflammatory reaction develops

in up to 30% of cases in clinical studies, and experimental studies have also shown retinal infiltration by PFCL.

Most clinical studies have not found signs of retinal toxicity such as progressive visual acuity deterioration or macular anatomical changes, but ERG or retinal histological analysis has not been performed.

When PFCLs are left in the vitreous cavity, dispersion develops a few days after injection and PFCL droplets may move into the anterior chamber, although there is no evidence about how much PFCL and how long it should stay in the vitreous cavity to cause this complication. PFCLs in the anterior chamber induce endothelial damage in the long term. Further, PFCLs induce a foreign-body reaction in the vitreous cavity, with macrophages engulfing PFCL droplets. However, this inflammatory reaction does not induce PVR and resolves after PFCLs removal.

Given their adequate physical properties and anatomical results, PFCLs might be a useful vitreoretinal surgery tool to deal with inferior retinal pathology. Nevertheless, retinal toxicity has not been ruled out in humans by means of ERG or histological examination. On the other hand, heavy silicone oil is an approved and safe tool to treat inferior retinal pathology. If PFCL is used as a tamponade, it must be removed completely as soon as possible once the retinopexy is complete, in order to avoid inflammation, dispersion, endothelial damage, or retinal damage. Special care must be taken to avoid using PFCL together with silicone oil or heavy silicone oil, because they can mix generating a new fluid with different physical properties known as sticky silicone oil [48, 49].

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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