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MAJOR REVIEW

Vitreous Substitutes: A Comprehensive Review

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Abstract. Vitreoretinal disorders constitute a significant portion of treatable ocular disease. Advances in vitreoretinal surgery have included the development and characterization of suitable substitutes for the vitreous. Air, balanced salt solutions, perfluorocarbons, expansile gases, and silicone oil serve integral roles in modern vitreoretinal surgery. Vitreous substitutes vary widely in their properties, serve different clinical functions, and present different shortcomings. Permanent vitreous replacement has been attempted with collagen, hyaluronic acid, hydroxypropylmethylcellulose, and natural hydrogel polymers. None, however, have proven to be clinically viable. A long-term vitreous substitute remains to be found, and recent research suggests promise in the area of synthetic polymers. Here we review the currently available vitreous substitutes, as well those in the experimental phase. We classify these compounds based on their functionality, composition, and properties. We also discuss the clinical use, advantages, and shortcomings of the various substitutes. In addition we define the ideal vitreous substitute and highlight the need for a permanent substitute with long-term viability and compatibility. Finally, we attempt to define the future role of biomaterials research and the various functions they may serve in the area of vitreous substitutes. (**Surv Ophthalmol 56**:300–323, 2011.

Key words. aging • retinal detachment • vitreoretinal surgery • vitreous body • vitreous detachment • vitreous substitute

I. Introduction

Recent advances in the treatment of vitreoretinal diseases and in intraocular drug delivery create new requirements for the substances used as vitreous substitutes. The ideal vitreous substitute should mimic all positive qualities of the vitreous body (transparency, elasticity, buffer capacity, and biocompatibility with neighboring tissues) and avoid some of the negative properties associated with the native substance such as liquefaction and biodegradation with age. The generation of this ideal substance remains a goal still to be achieved. Intensive research is underway to overcome at least some of the deficiencies of current substitutes and bring new, additional physiological replacements into clinical use.

The importance of the vitreous body as a biomechanical and optical presence, as well as its biochemical and physiological functions, was not recognized until recently.[182] The high water content of the vitreous led many clinicians to believe that the vitreous plays a relatively minor role; thus, most vitreous substitutes are currently used to maintain intraocular pressure and the biomechanical and optical properties of the vitreous space.

Considerable differences exist in the structure, composition, and biomechanical and physiological

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properties of the vitreous in different species. Thus we describe briefly species differences relevant to testing and development of vitreous substitutes. We then review pathological changes with an emphasis on complications related to vitrectomy and post-vitreal replacement events. We also classify and review current and experimental substitutes. Finally, we summarize selected prospective work and discuss aspects of an ideal substitute.

II. Structure and Function of the Vitreous Body

A. DEFINITION

The vitreous is a gelatinous structure that fills the space between the lens and the retina.[184] It is found in most animal species, from arthropods to mammals.

B. ANATOMY AND OPTICAL PROPERTIES

The normal vitreous body has excellent transparency, which makes it difficult to visualize its structural components. In vitro this problem was solved successfully using dark field microscopy, whereas in vivo the main advancement was the introduction of slit lamp biomicroscopy by Gullstrand in 1912.[55,182,190] Currently, several other techniques are used as well (see section IV.Evaluation and Testing).

1. Anatomical Properties

The formed vitreous is not homogeneous, but consists of several parts with different densities and biochemical composition. The part closest to the retina is the vitreous cortex, a denser part of the vitreous with variable thickness (~100–300 μm).[13,79] The vitreous overlying the ora serrata, called the vitreous base, is even denser than the cortex.[17,67]

The border between the vitreous and the retina consists of a membrane complex called the vitreoretinal interface, comprised of the internal limiting membrane of the retina (ILM) and a layer of dense collagen fibers adjacent to the ILM. The membrane of the vitreoretinal interface varies in thickness and is 5–6 times thicker around the macula than the equator.[57,74]

In some animals, such as the rabbit, the central structure of the adult vitreous body is defined by a well-demarcated central channel called Cloquet's canal, a remnant of the hyaloid artery. A typical, well-defined Cloquet's canal is not normally observed in humans, although a similar arrangement of vitreous fibers is present (Fig. 1).[67,116,118]

Although the central vitreous is a completely gelatinous structure at birth in primates, a progressive liquefaction develops with aging (see section III.A.Aging). The homogeneity of the central gelatinous vitreous has been investigated many times using relatively modern methods, and different structures have been described, such as cisterns[245] and fibers[191] (Fig. 2). Those structures undergo characteristic changes with normal aging and could contribute to vitreoretinal pathologies, such as posterior vitreous detachment or tractional retinal detachment. In addition, the inhomogeneities created by these structures have the potential to affect the rate of diffusion of intravitreally applied medications.

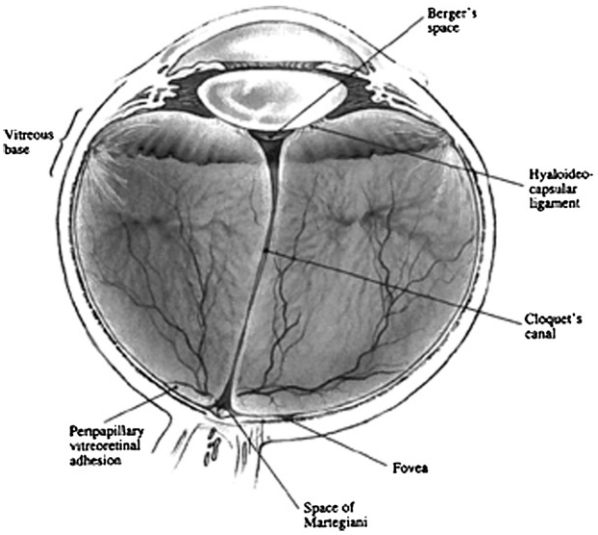

Fig. 1. Transverse section of the eye with an outline of the vitreous body landmarks. Reprinted with permission from Theime Medical Publishers.[98a]

C. CHEMICAL COMPOSITION

More than 95% of the content of the vitreous body by weight is water;[5,26,32] not all of the water is in the free form, however. Some is bound to proteins and glycosaminoglycans. The bound water is between 15% and 20% of all water content (the rest being free water), as measured in monkey and bovine vitreous, respectively.[5,32]

1. Proteins

The protein content of the vitreous, although small as a percentage of the overall content, is variable and rather complex in nature. Humans exhibit soluble protein concentrations from 200 to 1400 μg/mL,[212] a surprisingly wide range with a tendency for higher values with advancing age. In general, most of the soluble primate protein seems to be albumin (40%), and the other major components are iron-binding proteins (30%).[229] For example, presence of transferrin was confirmed in normal human vitreous,[247] and it is presumed that transferrin is synthesized in the vitreous itself, as

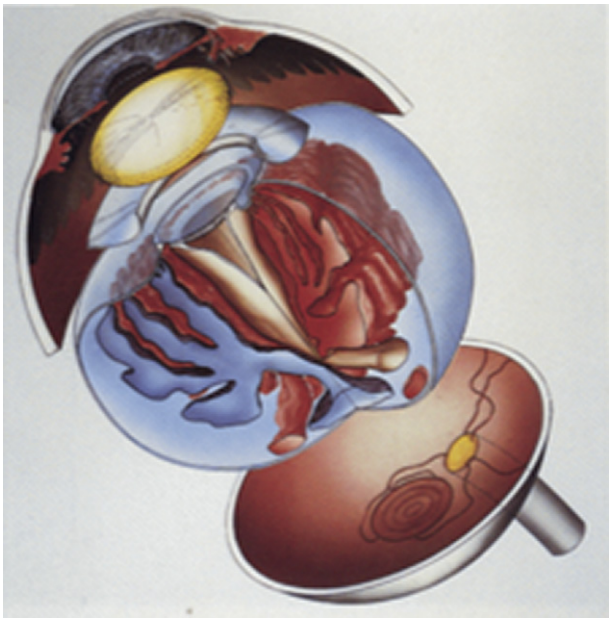

Fig. 2. Three-dimensional reconstruction of the vitreous body. Reprinted with permission from Springer Science/Business Media.[89a]

suggested by rabbit studies.[107] Transferrin and other iron-binding proteins could have a protective effect in cases of small hemorrhages in the vitreous by reducing iron toxicity.[244]

a. Collagens

Collagens, the most abundant insoluble proteins, are well represented with types II, V/XI, VI, and IX. Most vitreous collagen is type II (60–75%), followed by type IX (25%), type V/XI (10–25%) and type IV (<10%).[28,30] Collagen concentration is ~300 μg/mL in the human vitreous,[14] whereas the diameter of the collagen fibers is 10–25 nm.[80,210] The origin of the vitreous collagen is likely from retinal Müller cells, as it has been demonstrated that they can synthesize vitreous collagens in culture.[158]

2. Glycosaminoglycans

Other very important constituents of the vitreous structure are glycosaminoglycans (GAGs). Three major classes of GAGs are present, including hyaluronic acid (HA), chondroitin sulfate (CS), and heparan sulfate (HS).[177]

a. Hyaluronic Acid

HA, also called hyaluronan or hyaluronate, is a major component of the vitreous that was first isolated from bovine samples in the 1930s.[136] HA, which forms three-dimensional structures with collagen,[191] is one of the major factors determining vitreous body viscosity, and could serve as a template for the assembly of other extracellular macromolecules.[220] Variable results have been obtained regarding HA concentrations in human vitreous humor. Initial studies reported a large range of 65-400 μg/mL,[71] while later studies measured concentrations in the lower end of that range: ~96–115 μg/mL[86,147] and noted a marked linear decrease of HA levels with age ($r = -0.66$, $p < 0.001$).[86] More precise quantification and characterization of HA in human vitreous would enhance our understanding of the role of this important molecule in vitreous and pathology.

b. Chondroitin Sulfate

CS is a major component of the extracellular matrix and is also present in the vitreous in the form of two proteoglycans: versican and type IX collagen.[164,220] Mutations in the gene encoding for versican (CSPG2 gene) were found to cause sight-threatening, autosomal dominant Wagner vitreoretinal degeneration, typically manifesting with premature vitreous liquefaction with attachment to the equatorial retina, optically empty vitreous cavity, narrowed and ensheathed retinal vessels, retinal pigmentation, and choroidal atrophy.[102,138]

c. Heparan Sulfate

HS has been identified in small amounts in the vitreous body and is a renewable proteoglycan that is presumed to maintain adequate spacing between the collagen fibrils.[68] It has been identified in bovine,[6] rabbit,[91] chick,[227] and human vitreous.[62]

3. Metabolites

As an essential part of the cellular metabolism of neighboring tissues, it is not surprising to find both glucose and lactic acid in the vitreous body. The concentration of glucose was found to be half that in plasma for most species studied, such as rats, guinea pigs,[51] and rabbits.[76] Glucose may be needed to support the enzymatic activity in the vitreous (see section II.C.9.Enzymes and Metabolic Activity). Vitreous lactate concentration was found to be slightly higher compared to plasma levels in the rabbit (~12 mM vs. ~10 mM)[119] and is a major metabolite in human vitreous.[24]

4. Ascorbic Acid

Ascorbic acid is found in the vitreous body in higher concentrations than in plasma.[51] It is hypothesized that ascorbic acid is associated with the process of liquefaction during aging and after cataract extraction.[246] Ascorbic acid could act as

a neovascularization inhibitor[72] and could increase proliferation of hyalocytes.[200] Additionally, recent studies suggest that ascorbic acid may play an important role as a potent antioxidant, decreasing the amount of free oxygen present in the vitreous near the lens and thus preventing early cataract formation.[196]

5. Amino Acids

Various amino acids have been identified, and free amino acid concentrations in the vitreous are similar to those in plasma.[156]

6. Fatty Acids

Unsaturated fatty acids are ~50–55% of the total content of lipids in vitreous in humans, and this percentage remains stable with age.[165] Reddy et al found data indicating active lipid metabolism in dogs and humans.[165]

7. Prostaglandins

Prostaglandins (PG) are unsaturated carboxylic acids consisting of a 20-carbon skeleton that also contains a five-member ring. They are synthesized from arachidonic acid. The most studied PGs are prostaglandins PGE2, PGF2 alpha, prostacyclin, and thromboxane. The PG level in the human vitreous was estimated at ~100 pg/mL.[53,144,222] To the best of our knowledge, PG levels in other species have not been measured.

8. Cells

Three types of cells are identified in the vitreous body: hyalocytes (a term introduced by Balazs in the late 1950s),[216] fibrocytes/fibroblasts, and macrophages. The hyalocytes are sparsely distributed on the vitreous surface abutting the retinal inner limiting membrane (Fig. 3).[150] Rodent hyalocytes, which have been shown to express a tissue macrophage marker, are derived from basement membrane and are totally replaced within 7 months.[162] However, hyalocytes are not typical macrophages. Although hyalocytes express some typical macrophage proteins (e.g., S11), they do not express others (e.g., CD68).[109] About 10% of the cortical cells of the vitreous are fibroblasts.[20,65] Fibrocytes are presumed to be involved in the phagocytosis and/or secretion of collagen even in senile eyes.[64]

9. Enzymes and Metabolic Activity

For a long time, the vitreous body was considered a metabolically quiescent tissue. Rhodes et al demonstrated incorporation of intravitreally applied fructose, which indicates tissue metabolism,[168] as does the established turnover of HA.[88,108] The vitreous body contains very few cells; several enzymes, however, including a renin-angiotensin-converting enzyme, have been isolated from it.[49,206] In addition, recent studies suggest continuous oxygen metabolism (ascorbate being the substrate),[196] which supports the view for ongoing various metabolic activity.

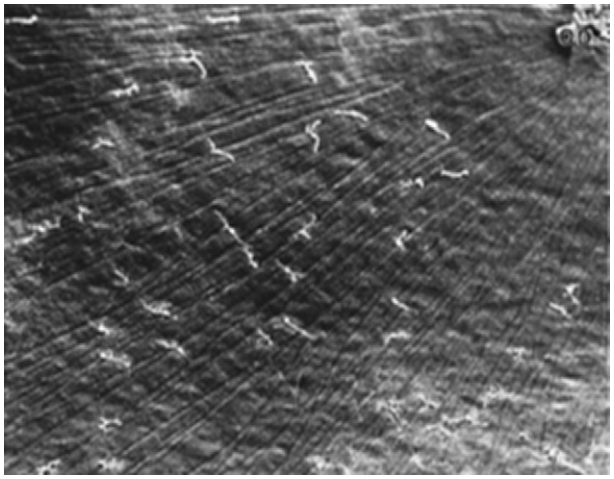

Fig. 3. Scanning electron microscopy of the retinal surface with hyalocytes. Reprinted with permission from the International Society of Histology and Cytology.[150]

D. PHYSICAL PROPERTIES

1. Organization

The gelatinous nature of the vitreous body is the result of long collagen fibrils suspended in a pattern of HA molecules, which surrounds and stabilizes water molecules.[191,252] The presence of both HA and collagen together in their natural molecular architecture determine the viscoelastic properties of the vitreous.[213]

2. Gradients

Although macroscopically the vitreous appears homogenous, microscopically there are inhomogeneities as described earlier (see Section II B. Anatomy and Optical Properties of the Vitreous). In addition, numerous compositional gradients have been identified. These include collagen, protein,[14] bound water,[32] HA,[14] glucose, lactate[31] and oxygen[21,140,195,224] gradients. In addition, a small pressure[195,208] gradient has been established. It is worth noting that various ions can easily penetrate the vitreous[83] gradients and that there is constant movement of ions through the vitreous, probably due to the standing potential of the eye. The anterior-posterior direction of most gradients is related to the presence of a denser and more viscous portion (the vitreous base) in the anterior part of the vitreous cavity. There are

corresponding differences in density, viscosity, and proximity to metabolically active tissues. Gradients are probably one of the major factors determining local differences in drug concentration in the vitreous after intravitreal administration of small molecules or delivery devices, which has been demonstrated several times.[47,60,96,129,208]

E. FUNCTIONS OF THE NATIVE VITREOUS

1. Eye Growth, Volume, and Elasticity

The vitreous is the largest part of the eye by volume and plays an important role in the growth of the eye and its structures. Studies have shown that the growth of the eye and the retinal pigment epithelium (RPE) (but not the retina) are dependent on the growth of the vitreous and that the production of HA may be an important part of this growth.[183] Hyaluronan may play a role in sustaining internal tension within the eye via the Donnan swelling mechanism.[145]

The eye is in constant motion during the awake period, even when the gaze is fixated on an object. Thus the vitreous endures a great deal of low-frequency mechanical stress, friction, and vibration. The high HA content of the vitreous makes it behave as a viscoelastic body rather than a viscous solution, and therefore the vitreous acts as an excellent shock-absorber.[235] This property of the vitreous undergoes a gradual decline with age as the gel-like portion of the vitreous liquefies and thus diminishes.

2. Transparency and Accommodation

The vitreous is a highly transparent ocular medium that transmits ~90% of visible and near-infrared light, with effectiveness very similar to that of the aqueous.[29] Little light scattering occurs in the vitreous, mostly due to the relatively large distance between collagen fibers as a result of the large HA molecules attached to them.[12] The vitreous also serves as a support for the lens capsule and could facilitate to some extent the natural process of accommodation.[44,183]

3. Barrier Function

The vitreous acts as a barrier to various biochemical substances (mostly macromolecules) and cells. In the normal state, as an important part of the blood–ocular barrier, the vitreous also acts as an inhibitor of proliferation, inflammation, and neovascularization.[46,183,197]

Although the vitreous might be effective in preventing bacterial infection and related inflammation, it may actually facilitate some viral infections. It was recently reported that the vitreous can be a suitable medium for spreading an adenoviral infectious process: addition of vitreous to cell culture significantly increased viral transduction.[38]

4. Nutritional/Metabolic Status

It has been recognized since the late 1960s that the vitreous can act as a metabolic repository for neighboring tissues.[166,234] Also, the transport of substances through the vitreous may influence the metabolism of surrounding tissues. Vitreous decreases lens exposure to oxygen, and thus the gelatinous state of the vitreous may protect the lens from oxidative damage and prevent or reduce cataract formation by consuming oxygen via an ascorbate-dependent mechanism.[196]

III. Vitreous in the Pathological State

A. AGING

Most lower mammals (rabbits, cats, dogs, sheep, cattle) show relatively small changes with age in the vitreous body.[16] By contrast, in rhesus monkeys and humans vitreous liquifies over time, with the portion of the liquefied tissue increasing with age[16,50,70,116] by a mechanism that is still not well understood. At birth, the human vitreous is entirely gelatinous. However, within the human lifespan, a linear increase in the volume of the liquid portion of the central vitreous is observed[15] in autopsy eyes as well as in vivo from 0 mL at birth to ~2 mL at age 80 (or ~45% of overall volume).[149] A large premacular liquefied vitreous pocket is a common finding in older adult eyes.[15,100,101,151] Additionally, there is an increase in collagen and protein concentration within the gelatinous vitreous with age, perhaps due to an increase in leakage of plasma proteins, and a collapse of the collagen fibrillar meshwork—a process known as *syneresis*.[15,178] Other substances such as plasmin also increase with age.[230] Liquefaction of the vitreous plays a role in vitreous detachment (see sections III.B.Retinal Tears, Retinal Detachments, and Vitreomacular Traction/Macular Holes and III.F.Posterior Vitreous Detachment).

It has been assumed that HA content does not change with normal aging;[15,25] a recent study, however, found a decrease in HA content with age ($r = -0.66$, $p < 0.001$) in vitrectomy samples from patients with macular holes or diabetic retinopathy.[86] A positive correlation also is observed between aging, liquefaction, and cataracts.[73] The gel state of the vitreous maintains relatively high ascorbic acid levels, thereby sustaining oxygen consumption. In contrast, the liquefied portion of the vitreous has lower ascorbate

levels, resulting in higher local oxygen concentration with more cataractogenic potential.[86,196]

Protein content increases with age,[25] and some ultrastructural evidence suggests that collagen breakdown into smaller fragments and decreased spacing between collagen fibers may play a role in the development of aging changes.[117,178,191] This increased protein concentration may also contribute to the observed thickening of the ILM[80] and the increase of the size and aggregation of collagen fibers of the vitreous base with age,[64,218] which can exert traction on the adjacent retina and thus could play a role in retinal detachment.

B. RETINAL TEARS, RETINAL DETACHMENTS, AND VITREOMACULAR TRACTION/MACULAR HOLES

Retinal tears and subsequent retinal detachment as a result of traction on the retina by the vitreous are well-established phenomena.[179] Especially important is the case of traction in the macular area or vitreomacular traction (VMT). Some recent studies have suggested that VMT is associated with severity of age-related macular degeneration ($p = 0.0082$),[139] possibly by a pulling on damaged RPE cells.[175] Alternatively, it can be hypothesized that due to the oxygen-regulating activity of the vitreous body, in cases of posterior vitreous detachment, the presence of more oxygen near the retina exerts an anti-VEGF effect, as summarized in a recent review by Holekamp.[82] VMT is also in part responsible for the formation of macular holes.[11]

C. DIABETIC RETINOPATHY AND VITREOPATHY

Glucose is elevated in the vitreous of diabetic patients,[120,181] possibly leading to an increase in non-enzymatic glycation products and advanced glycation end products (AGE),[192] which may affect vitreous collagen fibers. An additional mechanism could be the effect of AGE on HA, which was recently confirmed in vitro.[94] The biochemical changes from diabetes in the vitreous lead to morphological changes resembling senescence.[181]

D. CATARACT FORMATION

A positive correlation also is observed between aging, liquefaction, and cataracts.[73] Additionally, oxygen concentration near the lens is increased after vitrectomy,[21,81] which could lead to cataract formation[226] and may explain the high incidence of cataracts after vitrectomy.[154]

E. PROLIFERATIVE VITREORETINOPATHY

Although the connection between proliferative vitreoretinopathy (PVR) and vitreous abnormalities was suspected for some time, only recently has more evidence been presented to confirm the link. Intravitreal dispersion of RPE cells, breakdown of the blood–ocular barrier, and vitreous hemorrhages are currently considered risk factors for PVR.[142,228] Hyalocytes may be associated with PVR via hyaluronan synthase expression.[146]

F. POSTERIOR VITREOUS DETACHMENT

Posterior virtreous detachment (PVD) is the separation of the posterior vitreous cortex from the ILM. Currently it is well accepted that the prevalence of PVD is highly correlated with age; however, estimates of prevalence vary. Some researchers report relatively low prevalence (25–30%),[27] whereas others estimate higher prevalence (reaching ~63% at age 70);[58] still others report even higher numbers (up to 83% at age above 80).[4] There are no racial differences in the rate of PVD, whereas sex predisposition is controversial.[250]

PVD may induce glare due to differences in the light-scattering properties of the gel and liquefied portions of the vitreous and "floaters" due to condensation of collagen fibers into free-floating bundles.[188] Light flashes, which are a symptom of vitreoretinal traction, are a common complaint in the acute development of PVD.[240]

More serious complications of PVD could be retinal traction and vitreous hemorrhages.[115,205] Another complication of PVD is vitreoschisis, which refers to anterior displacement of the posterior cortex, leaving only part of the cortex still attached to the retina[43,90,180] (Fig. 4). Thus vitreoschisis can be viewed as a consequence of anomalous PVD.[187] Vitreoschisis is frequently associated with proliferative diabetic retinopathy (up to 80%)[43,176] and could be a factor in the development of this condition by activation of hyalocytes embedded in the outer layer of the vitreoschisis cavity, which can lead to stimulation of cell migration, proliferation, and membrane contraction.[189] Similarly, vitreoschisis is observed in Eales disease and could play a role in the pathogenesis of this condition.[10]

IV. Evaluation and Testing

A. IN VITRO TESTING

As with any biomaterial, vitreous substitutes need to be tested for a variety of properties, such as cytotoxicity, hemocompatibility, mutagenicity, and pyrogenicity.[128] Some of these procedures are performed in vitro. Most current vitreous substitutes are water-immiscible, making them extremely difficult to test in cell cultures. However, in vitro evaluation of fibroblast behavior at aqueous interfaces has shown that it is possible to test

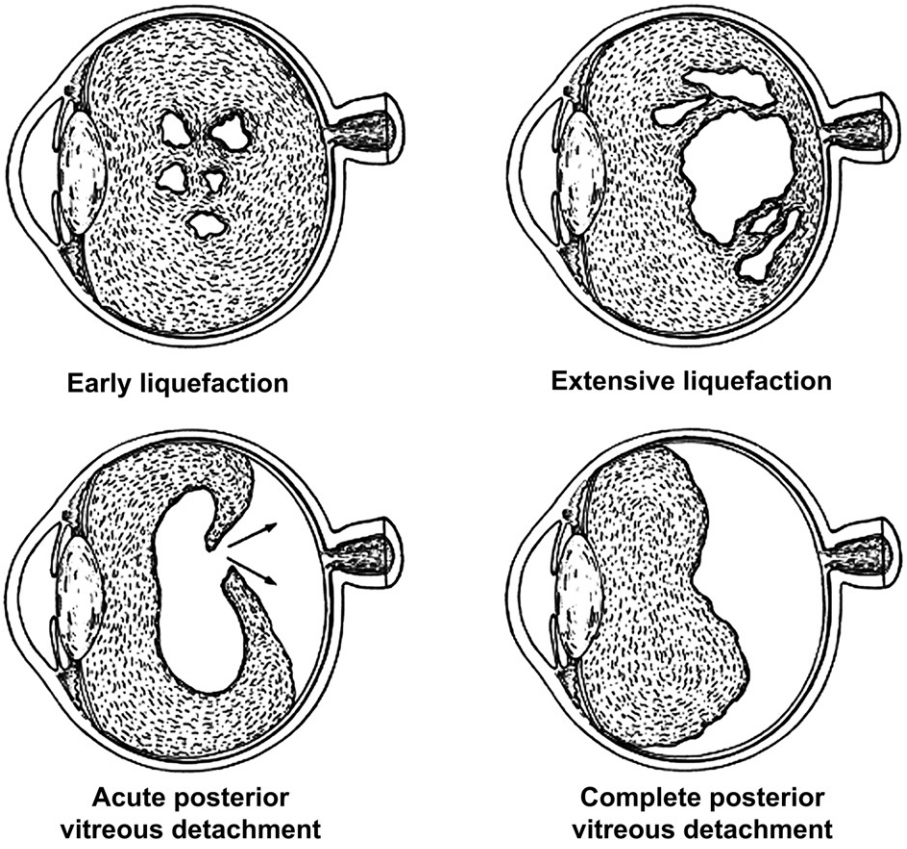

Fig. 4. Vitreous liquefaction and posterior vitreous detachment. Reprinted with permission from Elsevier.[27]

for surface active impurities in liquid vitreous substitutes by observing the behavior of attachment-dependent cells.[204] When cell culture testing is possible, the results may differ in subsequent in vitro testing,[128] suggesting that most in vitro results should be treated with caution.

B. IN VIVO TESTING

There are a variety of in vivo methods currently used to assess the structure and integrity of the living vitreous body. Non-invasive methods such as the ophthalmoscope and the slit-lamp commonly used in the clinic have provided insight into the role of the vitreous in retinal disease as early as the mid 1850s (i.e., Müller 1857, Iwanoff 1869, Koeppe 1918—see Smets[198]). More recent methods include various modalities of ultrasonography, optical coherence tomography, magnetic resonance imaging, scanning laser ophthalmoscopy, dynamic light scattering, and Raman spectroscopy.[186] In addition, for experimental purposes and evaluation of drug distribution in the vitreous, some invasive methods such as microdialysis can be used.[54]

During the course of pre-clinical testing of vitreous substitutes, in vivo testing plays an important role. However, the success of the in vivo evaluation depends largely on selection of the appropriate animal model.

V. Comparison of Vitreous from Different Species

Biochemical composition, biomechanical properties, and changes in both related to age vary substantially between species. Understanding species differences is important, particularly when testing in vivo vitreous substitutes for signs of toxicity and efficacy. Differences in vitreous properties among species include variations in protein, collagen, HA, ascorbic acid, and lipids.

A. PROTEIN

The rabbit has a high concentration of total protein (~2200 μg/mL).[125] Cattle, lamb, pig, and dog, however, contain much less protein in the vitreous, compared to primates.[39]

B. COLLAGEN

As outlined in section II.C.1.a, humans have a collagen concentration of ~300 μg/mL. Most

other species have less collagen, for example ~25 μg/mL in the owl monkey and 60 μg/mL[19] in the bovine vitreous. However, some species have higher concentrations (e.g., 700 μg/mL in the pig[147]). In addition, the diameter of the collagen fibers differ considerably among species: ~7 nm in the rabbit, 10–13 nm in the dog,[199] and 10-25 nm in humans.[80]

C. HYALURONIC ACID

Rhesus monkeys show similar concentrations of vitreal hyaluronic acid (HA) to humans at ~200 μg/mL,[153] whereas other species show a variety of concentrations ranging from 20–60 μg/mL for the dog, cat, rabbit and pig,[16,235] to ~470 μg/mL in cattle.[66] CS and HA are closely interrelated in the vitreous body; the profile of CS distribution in the human, pig, sheep, and goat follows that of HA.[147]

D. ASCORBIC ACID

Human vitreous levels of ascorbic acid[217] are similar to the levels in bovine and sheep models,[18] but higher than the levels in owl monkey,[18] rat,[173] and rabbit models.[18,173,254] Some new studies[A] provide more precise data in this regard.

E. LIPIDS

Human vitreous contains very little lipid (~2 μg/mL), similar to levels in adult bovine and canine vitreous. Most other species contain more lipid, including sheep (14 μg/mL) and rabbits (56 μg/mL).[191] The fatty acid composition of the human, bovine, rabbit, and canine vitreous is very similar.[22,97,165]

The species differences outlined herein indicate that a careful evaluation should be made before selecting a suitable animal model for evaluating normal structure and function, pathological conditions, or vitreous substitutes. For the past 40 years, the preferred choice for in vivo testing has been the rabbit.[52,137,143,221] In this context, it is useful to summarize some of the differences between the vitreous of a rabbit, pig, monkey, and human (Table 1). From the data presented in Table 1, it can be concluded that the pig and monkey could be better animal models than the rabbit.

VI. The Ideal Vitreous Substitute

The ideal vitreous substitute would mimic the native vitreous in both form and function while being easily manipulable during surgery. It should have similar viscoelastic properties and be able to maintain the intraocular pressure within a physiologic range and support the intraocular tissues (including the retina) in proper position.[127] At the same time, the substitute should allow movement of ions and electrolytes and maintain the concentration of certain substances (oxygen, lactic acid, ascorbic acid, etc.) comparable to that in the native vitreous. Like native vitreous, the ideal vitreous substitute should be clear. It should also be permanent, requiring only a one-time implantation. A self-renewing substitute is desirable, because interaction with products released by the surrounding retina can lead to degradation of the substitute. Also, it should not induce any toxic reactions and should remain biocompatible for long-term use. Once injected, it should not biodegrade or disperse into small particles that the body can resorb or respond to immunologically. For practical reasons, the ideal substitute should be easily available, stable during storage, injectable through a small syringe, and available at a reasonable cost.[161]

It has been a great challenge to develop one substitute that can match all of these ideal characteristics. Rather than match all the complexities of the vitreous body, the substitutes in clinical use have been created with the intention of acting as retinal tamponades.

VII. Classifying Vitreous Substitutes

Table 2 summarizes the properties of both the available and the experimental vitreous substitutes in terms of composition, physical properties, duration, and position.

TABLE 1

Comparative Anatomical, Biochemical, and Physiological Characteristics of the Vitreous in Adult Rabbits, Pigs, Monkeys, and Humans

	Rabbit	Pig	Monkey	Human
Volume (mL)	1–2[7,87,a]	3.2[7]	3–4[134]	4–5[80]
Collagen content (μg/mL)	75–900[16]	20[147]	N/A[b]	40–120[16]
HA content (μg/mL)	20–60[148]	70–80[148]	100–200[148]	100–400[148]
Protein content (μg/mL)	44–81[16]	1000–1200[147]	210–220[229]	450–1100[16]

[a]The lower end of the volume range is found in Dutch-Belted rabbits.
[b]Reliable data not available.

VIII. Currently Available Substitutes

Currently available vitreous substitutes can be classified into three major categories: gases (air, expansile gases), liquids (balanced salt solutions, perfluorocarbon liquids, semifluorinated alkanes, silicone oils, etc.) and polymers (mostly natural). Available substitutes currently satisfy only the biomechanical aspect of an ideal vitreous substitute, with their ability to serve as retinal tamponades, leaving much to be desired in terms of a long-term, nontoxic vitreal replacement.

A. GAS-BASED SUBSTITUTES

1. Air-based Substitutes

Air was first used by Ohm in 1911 to repair retinal detachments.[41,98] Air is inexpensive and readily available with no need for removal, as it is absorbed by the eye and replaced by aqueous humor. Unfortunately, intravitreal residence time is only a few days,[126] due to diffusion across the retina.[45] Additionally, the refractive index of the air (1.0008) is incompatible with the optically important tissues (~1.33).[185] As a result, air has a somewhat limited use as a vitreous substitute. It is used in pneumatic retinopexy,[193] at the end of vitrectomy surgery, and as an emergency option when other substitutes are unavailable.

2. Expansile Gas-based Substitutes

Expansile gases have been used since the early 1970s.[2] The most commonly used gases are sulfur hexafluoride (SF_6), which is five times heavier than air, and perfluoropropane (C_3F_8), which is six times heavier than air. Both gases are colorless, odorless, and nontoxic. They were approved for use by the U.S. Food and Drug Administration in 1993 for pneumatic retinopexy[238] and are used in non-expansile concentrations to fill the vitreous cavity.

a. Use

Gases are used for pneumatic retinopexy[34,35,123,124] and post-operative endotamponade.

b. Advantages

Gas has the highest surface tension of all vitreous fluid replacements at approximately 70 dynes/cm.[98] High surface tension and diffusion of other gases from the bloodstream into these gases allow them to be expansile and to maintain a tamponade effect.[45] They also have a good success rate, exceeding 90% for retinopexy.[126] Expansile gases last longer than air, but will resorb spontaneously in 6 to 80 days depending on perfluoropropane percentage[223] and will be replaced with aqueous humor, avoiding a second surgery to remove them.[9]

c. Disadvantages

Although the expansile nature of gas allows for maintenance of the endotamponade effect, a sudden increase in intraocular pressure could in severe cases cause central retinal artery occlusion.[98,157] Similarly, patients need to avoid higher altitudes in order to prevent dangerous gas expansion. With a density less than vitreous, perfluorocarbon gas does not effectively tamponade the inferior retina.[155] Although inferior retinal tamponade has been achieved clinically using expansile gas, awkward face-down positioning is required for several days until inferior breaks close and retinal fluid is reabsorbed, which can dramatically reduce patient compliance.[35,124,157] Adverse effects include gas-induced cataract formation and corneal endothelial changes.[110,238] Additionally, as with air, the refractive indices of the gases are lower (~1.17)[249] compared to that of the cornea, anterior chamber fluid, and the lens.

d. Conclusion

Both SF_6 and C_3F_8 gases are widely accepted for selected retinal detachments and have been the standard of care for retinal detachment repair since the early 1990s.[3] They are excellent short-term vitreous substitutes, but are not suitable as long-term vitreous substitutes.

B. PERFLUOROCARBON LIQUID

A liquid or gelatinous solid that can respond to head movement and maintain tamponade effect without being absorbed or degraded would be a more ideal substitute than gas. The first liquids used as vitreal substitutes were water and balanced salt solutions.[45] Modern liquid substitutes, the perfluorocarbon liquids (PFCLs), were investigated in the 1990s.[128]

PFCLs are fluorinated, synthetic, carbon-containing compounds that are clear, colorless, and odorless. PFCLs are approximately twice as dense as water and possess an extensive capacity for transporting and releasing both O_2 and CO_2.[157] They were originally designed as blood substitutes with good oxygen carrying capability.[98] Their use as an intraoperative tamponade has changed the surgical management of proliferative vitreoretinopathy because the retina can be flattened and stabilized intraoperatively, facilitating epiretinal removal and traction release.[36] The most commonly used PFCLs are perfluorodecalin (PFD), perfluorohexyloctane

TABLE 2

Summary of Vitreous Substitute Properties

	Composition																	
		Gas	Liquid	Viscoelastic	Hydrogel	Physical property	Water immiscible	SG > water	SG < water	Water miscible	Duration of need	Intra-operative	Temporary fill	Short-term (<3mos)	Long-term (>3mos)	Preferred tamponade location	Inferior	Superior
Currently available																		
Air		X					X		X			X	X	X				X
SF_6		X					X		X			X	X	X				X
BSS		X								X		X	X	X	X		X	X
PFCL			X				X	X				X					X	
SFA			X				X	X				X	X	X	X		X	
SiO			X				X		X					X	X			X
SiO/SFA			X				X	X						X	X		X	
Natural polymers				X			X		X			X	X	X				X
Experimental																		
PVA-MA					X			X		X				X			X	X
PVP					X			X		X				X			X	X
Smart hydrogels					X			X		X				X			X	X
WTG-127					X			X		X				X			X	X
Capsular artificial vitreous							X								X		X	X

BSS = balanced salt solution; PFCL = perfluorocarbon liquid; PVA-MA = polyvinyl alcohol methacrylate; PVP = polyvinylpyrrolidinone; SF_6 = sulfur hexafluoride; SFA = semifluorinated alkane; SG = specific gravity; SiO = silicone oxide; SiO/SFA = silicone oil/ partially fluorinated alkane combinations; WTC-127 = a thermo-setting gel from Wakamoto Pharmaceutical, Tokyo, Japan.

(F6H8), perfluoroperhydrophenanthrene, and octafluoropropane.

1. Use

PFCLs are used intraoperatively to temporarily flatten the retina in the repair of complex retinal detachments and are exchanged for silicone oil or another long-term substitute. By virtue of being heavier than water, PFCLs could potentially be used for long-term tamponade of inferior retinal detachments without face-down positioning, but are currently limited by long-term toxicity.

2. Advantages

The high specific gravity of PFCLs makes them effective for the intraoperative repair of complex retinal tears. Anterior and posterior segment complications are uncommon because PFCLs are usually removed intraoperatively.[98] With a refractive index near water, PFCLs allow for the use of a conventional contact lens for visualization during vitreous surgery.[157] Intraoperatively, the low viscosity of PFCLs allow for tissue manipulation, injection, and removal.[157] Animal studies have shown a potential neuroprotective effect on the ischemic retina, likely due to PFCLs' high oxygen solubility.[239]

3. Disadvantages

Currently, PFCLs are for the most part limited to intraoperative use as a result of their toxicity over longer periods. Their presence intravitreally in rabbit eyes over more than 2–4 days has been shown to lead to irreversible cell damage to the inferior retina, most likely as a result of mechanical damage to cells and near total emulsification by 6 days postsurgery.[152] In vitro experiments with PFD and perfluoroperhydrophenanthrene showed disorganization of retinal cell growth pattern, loss of neurites, and other toxic effects, suggesting that the high specific gravity of these perfluorocarbon liquids compresses and disorganizes retinal structure.[122,128] There are several studies, however, that demonstrate that PFCL toxicity may not be due primarily to mechanical compression.[121,135] Results from an in vitro study comparing the vitality and proliferation of cultured human RPE cells incubated in F6H8 or PFD showed significantly lower extinctions for vital cells and a non-significant decrease in proliferation of cells incubated in F6H8 compared to controls.[135] Therefore, decreased vital cells cannot be explained solely by mechanical effects or nutritional deficit due to direct contact since F6H8 has a lower specific gravity than PFD.[135] Some also believe that toxicity may be caused by impurities.[157] Emulsification and penetration in the retina with unknown long-term consequences could be a problem with PFCLs.[232] However, a recent study using F6H8, PFD, and a mixture of the two over 3 months in rabbits showed good tolerability with no gravity-related structural damage.[121]

4. Conclusion

PFCLs are routinely used intraoperatively for the repair of both routine and complicated retinal detachments. The direct toxicity of PFCLs and their tendency to induce inflammatory reactions limit PFCL use as a long-term tamponade.

C. SEMIFLUORINATED ALKANES

Semifluorinated alkanes (SFAs), also known as partially fluorinated alkanes (PFAs) or fluorinated alkanes, are the first internal tamponade agents that can be used beyond the intraoperative setting, even though they are heavier than water.[253] They were investigated in the early 2000s.[75,99,128,209] SFAs have a specific gravity of 1.35 g/mL and a refractive index of 1.3.[172] The low specific gravity of SFAs (compared to PFCLs) is thought to produce less retinal damage.[128]

1. Use

SFAs were initially used as a solvent for silicone oil[133,225] and then as a temporary endotamponade for special cases of retinal detachment when silicone oil failed to function properly.[209] Clinical trials have shown SFAs to be tolerated for extended periods of 2–3 months.[99]

2. Advantages

SFAs are soluble in PFCLs, hydrocarbons, and silicone oils and have a preferred refractive index.[133] SFAs' higher interface tension than silicone oil (49.1 vs 36 mN/l) may bridge larger retinal breaks.[99]

3. Disadvantages

Major problems with use of SFAs include cataract formation and emulsification accompanied by the presence of soft epiretinal membranes and cellular material.[99,103,172,225]

4. Conclusion

At present, the tendency is to combine SFAs with silicone oil because of the emulsification discussed in section VIII.E.

D. SILICONE OIL

Silicone oil (SO) has been in use as a vitreous substitute since the 1960s, but was not approved by

the FDA until 1994.[157] It is similar to silicon rubber, but shorter polymer chains and a lack of chemical cross-linking result in a liquid form.[98] It is a hydrophobic substance with a specific gravity slightly less than water (0.97 g/mL)[77] and a refractive index of 1.4 (slightly higher than the vitreal index of 1.33).

1. Use

SO is effective as a short- or long-term tamponade for complex retinal detachments, and is the only substance currently accepted for long-term vitreous replacement.[98] It is available in several viscosities, measured in centistokes, multiples of the viscosity of water. Currently 1000 and 5,000 centistoke oils are used clinically.[59] The ideal conditions for removal of SO are when the retina is attached, chorioretinal scars have formed, and retinal traction is absent.[155] Although SO is typically removed after 3–6 months, recommendations for removal have ranged from 6–8 weeks to 6–30 months.[98,155] Anatomic outcomes and visual acuity remain stable from 6 to 24 months, which suggests a potential for longer term use.[9] Outcomes of the largest published series of eyes (2573) support the growing body of evidence that silicone oil and C_3F_8 are preferable alternatives to long-acting gas tamponade using SF_6 for repair of complicated retinal detachments, and that silicone oil may have advantages over C_3F_8 in certain clinical situations such as hypotony.[9]

2. Advantages

SO is an attractive vitreous substitute due to its high surface tension, ease of removal, low toxicity, and transparency. Because it is immiscible with water, the high surface tension and low specific gravity create a tamponade effect on the superior retina, with a 70% success rate in preserving anatomical integrity.[9,98] It is preferable to use an SO tamponade if post-operative airplane or high elevation travel is planned, or with difficulties in post-operative positioning in children or adults with physical impairment, which makes it a more versatile replacement than air or gas.[98]

3. Disadvantages

With a surface tension less than that of gas or saline, SO can pass through retinal breaks under traction more easily than gas.[98] The oil is hydrophobic, and therefore does not have the desired retinal contact. Although SO is clear, its refractive index (1.4 compared to the vitreal refractive index of 1.3) requires optical adjustments.[238] Tamponade of the inferior retina is difficult given the low specific gravity of SO.[155] Emulsification has been shown to be a problem with SO,[61] although in several studies less than 5% of eyes showed oil emulsification after surgery.[9]

Corneal abnormalities have been reported with SO, although the Silicon Study showed a 27% incidence of corneal abnormalities at 24 months, which did not differ significantly from sulfur hexafluoride gas.[1] SO has also been reported to cause problems with both native and implanted lenses. Emulsified droplets can adhere to a silicone IOL.[98] Post-operative cataracts are common,[56,69,131,255] and if the oil is left in the eye after the surgery, cataracts often develop.[45] In a study of SO use in phakic eyes, cataract rates rose from 52% pre-surgery to 73% one year after surgery.[9] These data are confounded by the high incidence of post-surgery cataract found with vitrectomy surgery alone (see also section III.D).[132]

Another drawback to SO is that patients must be followed closely for possible complications and, in the majority of cases, the SO needs to be removed. The removal process can cause complications; therefore, careful clinical judgment is required when selecting patients for SO removal. Removal can induce or allow recurrent retinal redetachment in up to 67% of cases,[155] although reported rates have ranged from 5–67%.[9,155] SO removal has been accompanied by visual acuity loss, hypotony, and corneal abnormalities.[9] The phenomenon of "sticky

TABLE 3

Clinically Available SO/PFA Combinations

Combination	Densiron-68 30.5% F6H8, 69.5% SO 5000	Oxane HD 11.9% RMN3, 88.1% Oxane 5700	HWS 46-3000 55% F4H5 45% SO 100000
Manufacturer	FLUORON GmbH, Neu-Ulm, Germany	Bausch & Lomb, Rochester, NY	Not yet produced commercially
SG (g/cm^3, 25C)	1.06	1.02	1.12
Viscosity (mPa, 25C)	1387	3300	2903
Refractive index (20°)	1.39	1.4	1.37
Interface Tension vs. water (mN/m)	40.82	>40	41.3
Sources	75, 174, 207, 243	75, 241, 169	75, 170

SG = specific gravity.

silicone oil" adherent to the retina has been reported to complicate removal in approximately 12% of cases by Veckeneer et al.[231]

Other complications of SO include anterior chamber migration, corneal decompensation and band keratopathy,[1] glaucoma from papillary block or overfilling at rates of 2–40% (see multiple references in Kim[98]), and hypotony from underfilling.[98]

4. Conclusion

Although still used today, SO has several potential undesirable side effects on intraocular structures (e.g., cataract formation, band keratopathy) that may render it less suitable than other vitreous substitutes for long-term vitreous replacement. The toxicity issues associated with SO have stimulated the development of new, less toxic substitutes and reduced toxicity by using combinations of silicone oil and other liquids.

E. SILICONE OIL/SFA COMBINATIONS

Recently, mixtures of SFAs and silicone oil as tamponade agents have been investigated and approved for clinical use (Table 3).[236] By combining the two liquids, the solution takes advantage of the high specific gravity of the SFAs and the high viscosity of silicone oil in order to produce a vitreous substitute with a good tamponade effect and minimal emulsification.[236] Solubility experiments have shown that this mixture can produce homogenous clear solutions called "heavy silicone oils" or separated solutions called "double fills" depending on the ratio of the two liquids.[B,111]

1. Double Fill

Double fill (DF) is a combination of SO and SFAs, with the goal of having the light SO support the superior retina while the heavier SFA supports the inferior retina, resulting in fewer complications than each liquid alone. SO is required to form a single bubble, but the percentage of SO must be kept as low as possible to avoid toxicity and loss of lateral tamponade as the bubble pulls away from the walls.[77]

a. Use

DF may have the best results in complicated surgeries with large inferior retinal breaks,[111] although theoretically DF was intended for retinal tamponade of either superior or inferior breaks.

b. Advantages

DF produces a two-layered bubble appearing as a single bubble, which improves the utility of F6H8 as a tamponade agent and reduces dispersion.[77] An in vitro study showed the effectiveness of DF as a tamponade to be better than silicone oil alone on the inferior retina and that DF has reduced emulsification compared with using perfluorohexyloctane alone.[111]

c. Disadvantages

DF does not provide good simultaneous superior and inferior tamponade.[77] DF may not provide enough superior support: instead of producing a homogenous bubble, DF produces an "egg-shaped" bubble with a mass of pure F6H8 inferiorly and a lighter solution of F6H8 dissolved in silicone oil superiorly; the bubble as a whole behaves as a tamponade that is heavier than water.[75]

d. Conclusion

Although DF has not satisfied the requirements that its creators had intended, it is still used for large inferior retinal breaks.

2. Heavy Silicone Oil

Heavy silicone oil (HSO) is an internal tamponade agent that is heavier than water and is created by combining SO and a PFA in such a way as to create a homogenous solution. A multicentered, prospective, randomized controlled clinical trial (n = 700) comparing the standard SO tamponade to the HSO tamponade in the treatment and prognosis of eyes with PVR of the lower retina is currently underway (Heavy Silicone Oil study).[89]

a. Use

HSO has been promoted as a long-term endotamponade agent for complex retinal detachments involving inferior proliferative vitreoretinopathy.[112,114]

b. Advantages

The newest HSOs are more viscous, more stable, and consequently better tolerated than their predecessors, resulting in longer times until removal.[75] Removal with limited complications has occurred after 1–4 months for Oxane HD[169,219,241] and Densiron 68,[174,243] and up to 3 months with HWS 46-3000.[170] Densiron heavy silicone oil was piloted by Stappler et al[207] and shown to be an effective tamponade agent, with an 81% initial success rate in a two-center pilot study in Rotterdam and Liverpool.[243] The tamponade success rate of Densiron is from 85.2–87.6% in more recent studies.[78,112] Several recent studies of HSO have shown good anatomical success rates (54–81%) at 3 months or more and stable

visual outcomes with good intraocular tolerance and no significant emulsification.[23,169,241]

c. Disadvantages

HSO can be challenging to remove because it is heavier than water. 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.[207] A novel removal technique "from a distance" using a shorter (7.5 mm) and smaller (20-gauge) needle potentially reduces the risk of entry site tears, postoperative hypotony, or other iatrogenic damage.[207]

Complications of HSO include cataract, intraocular inflammation, emulsification, and elevated intraocular pressure.[112,219,242] Some oils (such as HWS 46-3000) have been associated with a very high frequency (~100%) of posterior subcapsular cataract formation.[170]

d. Conclusion

Use of HSO is still regarded as an experimental procedure, and although some very recent results are encouraging,[171] most clinicians are waiting for the results from the currently ongoing Heavy Silicone Oil trial.

F. NATURAL AND SEMI-SYNTHETIC POLYMERS

Natural polymers such as hyaluronic acid are an obvious choice for vitreous substitutes given their native presence in the vitreous humor, but have not gained popularity despite good biocompatibility because of their high degradation tendency. Hyaluronic acid has been investigated as a vitreous substitute since the early 1970s.[161,167] Collagen has been used clinically in patients with complicated retinal detachment.[159,160] Modified collagens such as methylated collagen have been investigated for use as vitreous replacements.[113] More recently, a natural crustacean product, chitosan, looks promising as a natural polymer substitute.[248]

In addition, attempts have been made to develop semi-synthetic polymer vitreous substitutes, such as solution or gel forms of "hylan," developed in the late 1980s, which uses covalent crosslinking of sodium hyaluronidate with formaldehyde or divinyl sulphone to decrease water solubility. The gel form showed promise as a vitreous substitute, but could migrate through retinal holes to subretinal space due to insufficient coherence.[42] The usefulness of semi-synthetic polymers as vitreous substitutes remains to be determined.

1. Use

Biopolymers are currently used for viscodissection of fibrous membranes or epiretinal membranes. They may be best used as a temporary and partial replacement.[85] Biopolymers of gellan, an exocellular heteropolysaccharide from the microbe *Sphingomonas paucimobilis*, and hyaluronic acid may be an alternative to silicone oil as a short-term vitreous substitute.[211]

2. Advantages

Because they are natural materials, biopolymers offer good biocompatibility[8] and have the potential to be used as drug delivery devices. A 6-year clinical study in 294 eyes demonstrated that hyaluronic acid was well tolerated with only mild and transient inflammatory reaction and no cataract formation.[161]

3. Disadvantages

Biopolymers are lighter than water, which limits their use as inferior retinal tamponades. Additionally, they have a tendency to degrade rapidly in vivo. The biodegradation rate of experimental hyaluronin implants is related to its chemical structure and ranges from 60 to 150 days.[8] Although hyaluronic acid has been used with limited inflammatory effect, the use of collagen has been limited by inflammation and moderate to severe ocular pain.[160] Collagen gels are fractured while passing through the syringe on injection, destroying their function as a structural gel.[160]

4. Conclusion

Natural polymers such as hyaluronic acid biodegrade too quickly to be considered as a long-term vitreous substitute. Until it is possible to culture hyalocytes and fibroblasts and to implant them into the eye in order to continuously produce HA and collagen (discussed in section X.B), other replacements will be sought.

IX. Experimental Substitutes

Current experimental vitreous substitutes are mostly synthetic polymers. We divide the experimental synthetic polymers into hydrogels and "smart hydrogels"; the latter respond to their environment. One promising type of smart hydrogel, the thermo-setting gel, is discussed in more detail. Transplants are historically interesting as an experimental substitute, although very little research has been published in this area for the past 25 years. Another interesting class of experimental substitutes is the implantable device.

A. HYDROGELS

Hydrogels, also known as "swell gels," are three-dimensional polymers that swell in aqueous solutions without dissolving.[106] They were the first biomaterials synthesized for human use.[105] Synthetic polymers that are being investigated include poly(vinyl alcohol), poly(1-vinyl-2-pyrrolidone),[45,84,85] poly(acryl amide), copoly(acrylamide),[215] polyvinyl alcohol methacrylate,[33] poly(glyceryl methacrylate), poly(2-hydroxythylacrylate), and poly(methyl-2-acrylamido-2-methoxyacetate).[41,127] Hydrogels in biomedical applications have been described in several recent reviews.[37,105] In vivo research on hydrogels as vitreous replacements is still in the animal model stage.

1. Possible Use

The intention is that hydrogels will be used in order to provide retinal tamponade, with the possibility of drug delivery by controlling network pore size.[127]

2. Advantages

Hydrogels offer significant advantages over previous substitutes because they can be injected in aqueous form and then transform into a gel in situ using a disulfide crosslinker that would retain structure and swell in the eye. In contrast, injecting a preformed hydrogel would cause the gel to shear and lose elasticity.[214] Polyvinyl alcohol-methacrylate (PVA-MA) is an injectable aqueous solution containing a photoinitiator that can form a hydrogel in situ when irradiated with the proper wavelength of UV radiation applied via an optical fiber.[33] However, the current radiation time required is not realistic for surgical application. PVA-MA seems to be well tolerated in crab-eating macaques, with no significant histopathological changes or abnormal rise in IOP after a 3 month period.[127]

A new type of modified poly(acrylamide) gel that appears to have solved the problem of shearing on injection has been developed and tested in rabbit eyes.[215] This copoly(acrylamide) gel is made soluble by reducing disulfide cross-linked bridges. The soluble gel can then be injected through a small-gauge needle, and consequently undergoes gelation in situ upon exposure to oxidation by air. Testing after one week indicated overall biocompatibility, clinical suitability, and lack of toxicity. Additionally, this gel has a refractive index and viscoelastic properties that closely match that of the native vitreous humor.

3. Disadvantages

The major challenge lies in making a hydrogel compatible with the immune system.[37] Some hydrogels incite intravitreal inflammation, fragmentation, and phagocytosis.[233] One rabbit study of polyvinylpyrrolidinone (PVP) showed 50% of polymer removal by the end of a 4-week period after vitreal injection.[85] Using light microscopy, researchers saw macrophages in the vitreous, neural retina, and subretinal space with large vacuoles likely to be polymer particles, which led them to suggest that the disappearance of the gel was phagocyte-mediated. They believed that syneresis had left the PVP gel particles prey for vitreal macrophages. Although the development of copoly(acrylamide) gel appears promising in terms of biocompatibility and optical potential,[215] longer term in vivo studies are required.

4. Conclusion

Hydrogels have distinct advantages in terms of ease of application and biomechanics, but need to be more biocompatible to gain widespread use.

B. SMART HYDROGELS

"Smart hydrogels" are a relatively new class of stimuli-sensitive hydrogels that can respond to a variety of signals including pH, temperature, light, pressure, electric fields, or chemicals.[37] They offer the possibility of self-assembly and targeted bioactivity within the eye in response to certain signals.[141,237]

1. Possible Use

Smart hydrogels are still only in the experimental stage, but if successful, may be the centerpiece of the next generation of vitreous substitutes.

2. Advantages

The potential of smart hydrogels lies in creating ionic hydrogels that can respond to environmental stimuli in an effort to create closed feedback loops for drug delivery and other applications.[37,203] So far there are glucose-,[92] glutathione-,[104] and pH-sensitive[40] hydrogels undergoing investigation as drug delivery devices. They could provide excellent biomechanical support and controlled, temporary expansion over retinal areas that need flattening.

3. Disadvantages

Because of the early, experimental nature of the materials, complications associated with smart hydrogels are not well known. One problem could be biocompatibility.

4. Conclusion

Smart hydrogels are an important avenue of research.

C. THERMO-SETTING GELS

Thermo-setting gels are a type of "smart" hydrogel that react to tissue temperature originally developed as a vehicle for improving bioavailability of ophthalmic solutions for application to the surface of the eye.[93,130] The experimental substance WTG-127 (Wakamoto Pharmaceutical, Tokyo, Japan) is a type of thermo-setting gel that has been investigated recently as a vitreal substitute. It can gelate at 36C and retains transparency upon gelation.[93]

1. Possible Use

Thermo-setting gels can be expected to have an intraocular tamponade effect, given their gelation at body temperature.

2. Advantages

Thermo-setting gels currently being investigated have low viscosity for easy handling and injection prior to gelation, are transparent post-gelation, maintain normal intraocular pressure, and cause no noticeable damage to the anterior segment, lens, or retina.[93]

3. Disadvantages

In a study of WTG-127, investigators noticed that the gel drifted under a retinal tear.[93] The gel could potentially drift and gelate under the retina in the presence of a tear. The investigators could not confirm the presence of the gel in the vitreous cavity after 7 days. Although intraocular pressure was maintained in an experimental setting, there have been no studies to determine the biodegradation time of this type of gel.

4. Conclusion

Thermo-setting hydrogels are still at an early experimental stage, but look promising.

D. TRANSPLANTS AND IMPLANTS

1. Transplants

Experimental attempts were made as early as 1946 to transplant human vitreous.[48] In all transplants, the donor vitreous was drawn out through a needle and injected into the recipient posterior chamber, rather than being removed and transplanted as a whole. The first documented animal experiment using a rabbit model with control groups was performed in 1947 by Katzin and Blum.[95] Twenty-four rabbit eyes had native vitreous removed and rabbit donor vitreous injected with a follow-up period of six months. The most common complication was vitreous haze (20 of 24 animals) that persisted at six months in two animals.

The most recent human vitreous transplant study was published in 1976 by Shafer as a case series of 200 human vitreous transplants performed for retinal detachment.[194] Vitreous was obtained via stored eye-bank aspirate stored at 4C for 2 to 14 months, plated on blood agar and incubated for 48 h at 37C prior to use. The vitreous was planted using an 18-gauge needle through a pars plana incision with the needle tip just posterior to the recipient lens. Patients received daily antibiotic therapy with tetracycline for 4 days postoperatively. The retinal reattachment rate was 40% overall. The most frequent post-operative complication was mild vitreous haze that disappeared without treatment after 2–5 days. Uveitis occurred in 3.5% of cases, clearing after 2–9 months of corticosteroid therapy. In the transplants that failed to reattach the retina, regressive phenomena of cataracts, glaucoma, and phthisis occurred with the same frequency that would have been expected using other techniques. Shafer noted that the vitreous transplants lasted longer than air, but not saline. Despite losing structural integrity as the result of the shear forces of passing through a syringe, Shafer observed that the donor vitreous was able to dissolve light and moderate vitreous bands, perhaps retaining some proteolytic enzymatic function. Unfortunately, there has been no more recent study of human vitreous transplantation.

2. Implants

Implantable devices may be able to support the retina and control intraocular pressure without the need of a potentially reactive and biodegradable intravitreally injected solution. This concept has been compared to the breast implant, a thin silicone sac filled with a saline solution.[63] One device that has been tested in a rabbit model is the capsular artificial vitreous body with a pressure-control valve.[63] It is a thin, vitreous-shaped capsule made of a silicone rubber elastomer with a silicone tube valve system filled with a physiologically balanced solution. The elastomer is formed by crosslinking polymers of polyvinylsiloxone and polyhydrosiloxone. The capsule itself is 0.01 mm thick with a 1-mm diameter silicone tube leading to the pressure-control valve. The silicone rubber capsule has shown good biocompatibility and is easily implanted and removed experimentally in rabbit eyes via a 1.5 mm scleral incision. Over an 8-week treatment period, there was no corneal opacity, intraocular inflammation, cataract formation, or vitreal opacity.[63] However, the feasibility of a synthetic implant in the human eye is untested, and longer term

animal data are first needed to assess the potential use of this approach.

X. The Future of Vitreous Substitutes

A. VITREOUS SUBSTITUTES AS A DRUG DELIVERY MEDIUM

Many researchers have assumed that as the vitreous liquefies with aging, convection is the predominant way of drug distribution, and therefore drugs applied intravitreally would spread quickly in a uniform fashion. However, as stated in section III, vitreous liquefaction is non-uniform, so convection is the dominant way of distribution only in certain regions.

Vitreous is isolated by blood–retinal and blood–aqueous barriers, making it difficult to deliver drugs via topical or systemic application.[46] The most direct method of delivery is an intravitreal injection, but there are several disadvantages, including rapid clearance within a few days.

A proper vitreous substitute used as a long-term (>3 months) drug delivery system could either reduce or eliminate the need for multiple intravitreal injections and improve patient compliance and comfort.[45,251] Hydrogels may be a promising biomaterial for fragile protein drug delivery because no organic solvent, elevated temperature, or harsh pH is needed in formulation or patient administration.[163]

B. CELL CULTURE/GENE THERAPY: CAN WE GROW VITREOUS?

A fascinating possibility could be the artificial generation of vitreous in vitro, which could solve many problems plaguing artificial substitutes, including biomechanical properties, biocompatibility, and lack of a role as a transport and repository medium. The complexity of the vitreal 3-dimensional structure (as summarized in section II) presents a formidable challenge to this effort; however, some early data from Sommer and others seem promising.[146,202]

One way to stimulate vitreous synthesis is to enhance hyalocyte proliferation. It has been demonstrated that ascorbic acid enhances hyalocyte proliferation in a dose-dependent manner at concentrations between 0.1–3 μg/mL by increasing collagen production and mRNA expression of cells in vitro.[201]

However, indefinite hyalocyte proliferation is also undesirable. Control of hyalocyte growth can be regulated by specific growth factors in vitro. It has been shown experimentally that hyalocyte proliferation could be increased with bFGF and reduced by TGF-ß1.[202]

Recently, a hyalocyte culture has been developed through immortalization of porcine cells, which demonstrated production of HA and other vitreous components.[146] Together with other recent studies demonstrating successful regulation of hyalocytes in vitro,[201,202] such research brings the possibility of generating natural vitreous gel in a dish one step closer.

XI. Conclusion

The vitreous body has distinct biomechanical, biophysical, and biochemical properties that change during development and aging and differ between species. With the aging of Western populations, age-related pathologies of the vitreous and surrounding tissues require increasingly frequent partial or complete removal and replacement of this tissue. Currently used substitutes have various shortcomings, mostly related to the lack of local biocompatibility and an inadequate physiological role. With our increased understanding of the structure, properties, and importance of healthy natural vitreous, strides toward development of an "ideal" substitute continue. A new generation of vitreous substitutes under development, including smart hydrogels and implantable devices, hold considerable promise to better address the need for a substitute that is both more physiological and longer lasting. Future developments based on stem cell approaches and gene therapy, together with efforts to develop vitreous substitutes as long-term drug delivery media, hold even more promise to fully satisfy patient needs and ophthalmic surgeons' requirements.

XII. Method of Literature Search

The literature search was conducted through Medline, BioMed Central, and EMBASE. For vitreous body structure and function, all years from 1950 to the present were included in the search. For vitreous substitutes, all years from 1970 to the present were included, although historical articles prior to this year were included in the vitreous transplants section. The following search terms were used: *vitreous substitutes, vitreous humor, vitreous body, vitreous replacements, artificial vitreous, ideal vitreous substitute, viscoelastic, hyaluronic acid, gellan, hydrogel, stem cell, cell culture, silicone oil, heavy silicone oil, double fill, gas tamponade, biopolymer, synthetic polymer, carboxymethylcellulose, pneumatic retinopexy* or a combination of these. References in relevant articles were also used. All peer-reviewed articles in English were considered.

XIII. Disclosure

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