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Clinical findings on the use of long-term heavy tamponades (semifluorinated alkanes and their oligomers) in complicated retinal detachment surgery

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Abstract *Background:* Heavy tamponades for pathologies in the lower part of the retina are a new development, and different tamponades have recently come into clinical use: semifluorinated alkanes (F_6H_6, F_6H_8) and their oligomers (OL62HV).
Method: Nine patients had been operated on using F_6H_8 (n=5) and by OL62HV (n=4). In all cases the reasons for using the tamponades were complicated retinal detachments in the lower part. In three cases the use was primary and in six cases tamponades were used after reoperations. In all cases the endotamponade was removed within 6 weeks. Fluorescein angiography (FLA) was performed in the F_6H_8 group. *Results:* In the F_6H_8 group dispersion developed in two of the three aphacic patients. In two out of five cases soft epiretinal membranes and cellular material could be found between the substance and the lower periphery. In two membranes examined by light microscopy, cystic cells and amorphous material could be found. In one case (PDRP, aphacic) cyclophotocoagulation had to be performed because of persistent elevated IOP. FLA was unremarkable. In the OL62HV group, severe recurrent PVR reaction occurred in the lower periphery (2/4) and unusual precipitates were observed (4/4). In one case, after a normal postoperative period (VA 0.05 after 5 days) an extensive cellular reaction on the complete surface of the tamponade occurred. After 5 weeks VA was no light perception. During removal of the oligomer unusual adherent cellular components were found on the surface of the retina. The retina appeared necrotic, showed constricted retinal vessels and there was optic atrophy. Histologically, fluffy epiretinal material and a lens capsule obtained from one eye filled with OL62HV resembled the appearance with F_6H_8. *Conclusion:* Heavy endotamponades on the basis of semifluorinated alkanes can lead to an unusual biological reaction and need further investigation before clinical use.

Introduction

Silicone oil and long-acting gases are well-accepted and biologically well-tolerated tamponades in the clinical management of complicated detachment surgery. Proliferative vitreoretinopathy (PVR) is the most frequent cause of failure in detachment surgery, which occurs mostly in the lower part of the globe. Because the specific gravity of silicone and gas is lower than that of water (<1 g/ml), these tamponades are primarily used for the treatment of retinal pathologies in the upper quadrants. No comparable vitreous tamponades exist for the lower quadrants. If complicated pathologies in the lower quadrants (e.g. 4–8 o'clock) are present between the equator and the ora, additional measures such as extensive retinectomies, central buckling elements or intensive positioning of the patient are necessary. Therefore, long-term heavy tamponades with a specific gravity greater than

Table 1 Clinical findings after use of F_6H8

Patient	Age (years), diabetes	Indication	Lens situation	VA before F_6H_8 injection	VA after F_6H_8 removal	Retina attached	Remarks
B.B.	82	Three previous operations: silicone oil, PVR C2, rubeosis	Aphacic	0.02	0.028	With silicone oil	Patient refuses further surgery
W.M.	61, DM	Two previous operations: silicone oil, PVR C2	Pseudo-phacic	0.08	0.05	Yes	Soft material on the retina
R.T.	57, DM	Tractional detachment and PDRP, holes at the lower periphery	Pseudo-phacic	0.4	0.4	Yes	
B.J.	64, DM	Complete retinal detachment; C4, funnel shape	Aphacic	Hand motion	0.02	Yes	T=40 mmHg =>CPC; hazy cornea; soft material on retina and on surface of substance
K.J.	76	Trauma, 110° rupture of globe, 360° giant tear; complete loss of iris and lens, partial loss of ciliary body	Aphacic	Light perception	0.04	With silicone oil	Permanent silicone oil; decompensation of cornea after removal of F_6H_8; hypotonia; no further surgery

water would be helpful in the management of such pathologies.

The semifluorinated alkanes (F_6H_8, F_6H_6, O_{44}, O_{62}) and their oligomers are a new group of substances which offer the potential to act as long-term heavy tamponades [8, 9]. In Europe F_6H_8 and F_6H_6 are approved for clinical use and were recently introduced to the market [7, 9]. Other semifluorinated alkanes (O_{44}, O_{62}) are still under investigation. The semifluorinated alkanes have a specific gravity of 1.35 g/ml, a viscosity of about 2.5 mPas and a refractive index of 1.3. Hydrofluorocarbon oligomers had been developed with the idea that higher viscosity might improve the mechanical properties of intraocular tamponade and thus reduce dispersion and intraocular complications. Oligomers have a specific gravity of 1.6 g/ml and viscosity varying between 90 mPas (OL62LV low viscosity) and 1750 mPas (OL62HV high viscosity) (both from Bausch and Lomb, Munich, Germany). Their refractive index is 1.33. The oligomers have been so far been tested only in rabbits [8].

Patients and methods

We describe the clinical findings after use of the semifluorinated alkane F_6H_8 (Geuder, Heidelberg, Germany) and the high-viscosity oligomer OL62HV.

In five patients F_6H_8 was used. Since F_6H_8 is fully approved for clinical use in Europe, it was used during clinical routine surgery in selected patients, based on the underlying pathology. There was no standard protocol, nor were the patients included in a prospective study. The use of F_6H_8 was based on the surgeon's experience, rating the situation as very difficult to manage with conventional methods and rating the degree of success after use of F_6H_8 higher than after silicone oil. The mean age of the patients was 68 ±10.6 years. Two patients had already had several previous operations, one a complete funnel-shaped retinal detachment, one severe trauma with 110° rupture of the globe, 360° giant tear and complete loss of the iris and lens, and one had a tractional detachment due to PDRP and holes at the lower periphery. Details can be seen in Table 1.

High-viscosity OL62HV was tested in a prospective clinical trial with a standard protocol. Since this was the first use of this substance, the trial was approved by the local ethics committee and the patients gave their informed consent. Inclusion criteria for the use of the oligomer were holes in the lower periphery. The protocol required removal of the substance after 4–6 weeks. The mean age of all patients was 60.7 ±23.4 years. Two patients had had two previous operations, one had a schisis detachment at the lower periphery with a central hole, and one had vitreous bleeding due to proliferation after branch vein occlusion and several holes at the lower periphery. Details are given in Table 2. The study was stopped after four patients because of severe side effects, as described later.

Surgical procedure

A pars plana vitrectomy was performed in all patients. Epiretinal membranes were removed under Ringer solution. When necessary the lens was removed by phacoemulsification. If there was still residual traction on the retina, retinectomies larger than 90° were performed to relax the retina. The retina was attached using F_6H_8 or OL62HV. A direct exchange between Ringer solution and the heavy tamponades was performed in all cases. Laser photocoagulation by an diode endolaser (514 nm, 532 nm) for treating the edge of the retinectomies or retinal holes was performed under the heavy tamponades. At the end of surgery the eye appeared clinically completely filled by the substance. To avoid dispersion in aphacic eyes F_6H_8 was additionally injected over the limbus to ensure that the anterior chamber was completely filled.

The substances were removed after 4–6 weeks in all cases. F_6H_8 was removed by placing a standard-gauge needle over the optic nerve. No active suction was necessary. OL62HV was removed with a 0.5-mm-wide blunt needle applying active suction. When reoperation was necessary a procedure similar to the initial one was performed with the exception that gas or silicone oil was used as endotamponade. The follow-up period after removal was at least 6 months in all cases.

In two of the five cases where F_6H_8 was used, epiretinal membranes were intraoperatively removed for histological examination. The material was peeled off the retina with a blunt forceps, fixed with glutaraldehyde and stained with toluidine blue. In a

Table 2 Clinical findings after use of oligomer

	Age (years), diabetes	Indication	Lens situation	VA before oligomer injection	VA before oligomer removal	Retina attached/ final VA	Remarks
E.W	48	Two previous operations: PVR, detachment under silicone oil	Phacic	0.1	Light perception	Silicone oil/light perception	Atrophy of the optic nerve; extreme fluffy material; retinal necrosis?
I.P.	75	Schisis detachment at lower periphery with central hole	Phacic	0.2	0.2	Silicone oil/0.2	Severe PVR reaction; fluffy material; 3 reoperations;
E.T.	27	Two previous operations: PVR, redetachment	Pseudo-phacic	0.05	0.05	No/no light perception	Severe fibrin in anterior chamber; fluffy precipitates; retinal necrosis?; three reoperations
S.H.	63	Vitreous bleeding; detachment due to traction; branch vein occlusion; several holes at lower periphery	Phacic	0.3	0.03	Silicone oil/0.25	Fluffy material; one reoperation

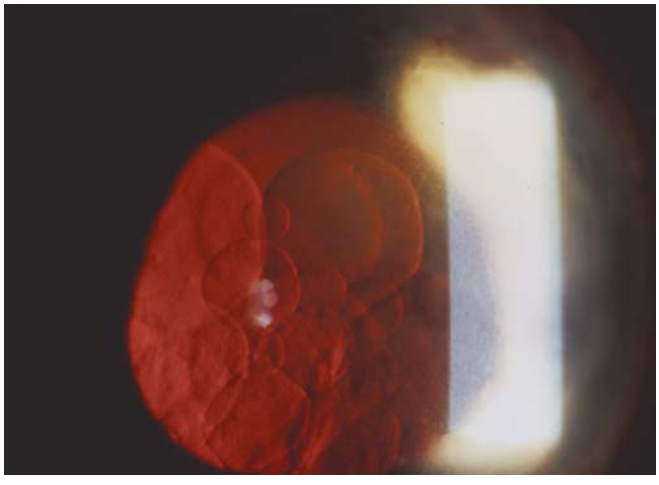

Fig. 1 Bubbles of F6H8 are filling the anterior chamber of an aphacic patient

Fig. 2 Clear fundoscopic view before removal of F6H8 of a patient 4 weeks after surgery because of 110° rupture of the globe (Patient K.J.)

similar way, in one of the four OL62HV patients soft material from the retina and the posterior capsule of the lens was removed and prepared for histological examination.

Results

Semifluorinated alkane (F_6H_8)

We describe the clinical findings after a long-term tamponade of 4–6 weeks using F_6H_8. Both injection and removal of the substance were unremarkable. In two out of three aphacic eyes severe dispersion occurred, as shown in Fig. 1. No dispersion was seen in the remaining two pseudophacic patients. One aphacic, diabetic patient, who initially had a complete detachment of the retina with a funnel shape and retinal folds in four quadrants, required cyclodestruction because of intraocular pressure of 40 mmHg. The stroma of the cornea of this patient became somewhat hazy after injection of F_6H_8. In another patient, who had a 110° rupture of the globe with loss of iris and lens, the cornea completely decompensated within 2 weeks after removal of F_6H_8 and replacement by silicone oil.

The retina remained attached in three of five patients without further surgery. Two patients required further silicone oil because of reproliferation. Visual acuity was unremarkable and showed no significant difference from what had been expected on the basis of the complicated preoperative situation. In four patients the fundoscopic view was clear (Fig. 2), in one patient turbid because of

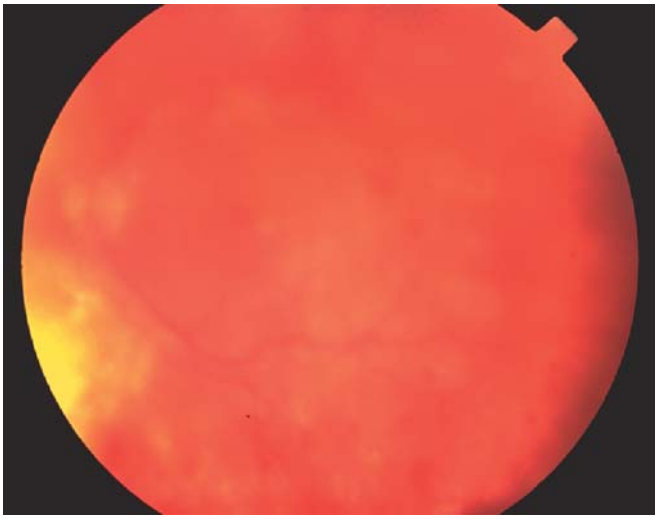

Fig. 3 Turbid fundus view before removal of F_6H_8 of a patient 4 weeks after surgery because of complete retinal detachment and funnel shape (Patient B.J.)

soft fluffy material on the anterior surface of the tamponade substance (Fig. 3). In two of five cases such material was found on the retina in the lower periphery during removal of F_6H_8. The F_6H_8 itself stayed clear. It was difficult to obtain the substance from the retina for histology. Histology of the soft material showed cystic cells and amorphous material (Fig. 4a). The clinical results are summarized in Table 1.

Oligomer (OL62HV)

During injection of the oligomer the interface between the oligomer and the Ringer solution was more difficult to visualize than was the case with F_6H_8. Complete removal of the substance could be obtained in all eyes but required active suction and a thick needle. Dispersion was not seen in any of the patients, who were all phacic or pseudophacic. However, in all patients extensive soft material was found between the posterior surface of the oligomer bubble and the retina as well as between the anterior surface and the lens (Fig. 5). In one eye soft material was even present in the anterior chamber despite the phacic situation. The amount of soft material was much greater in eyes filled with the oligomer than in those eyes filled with F_6H_8.The material was distributed all over the posterior pole. Severe fibrin reaction in the anterior chamber was seen in one case. After removal of the fluffy material the retina itself looked altered and fragile in two out of four cases, resembling the clinical appearance of retinal necrosis. All cases showed severe PVR reaction after oligomer removal, which required one to three further operations in three patients. One patient (E.W.) showed an unremarkable clinical situation 1

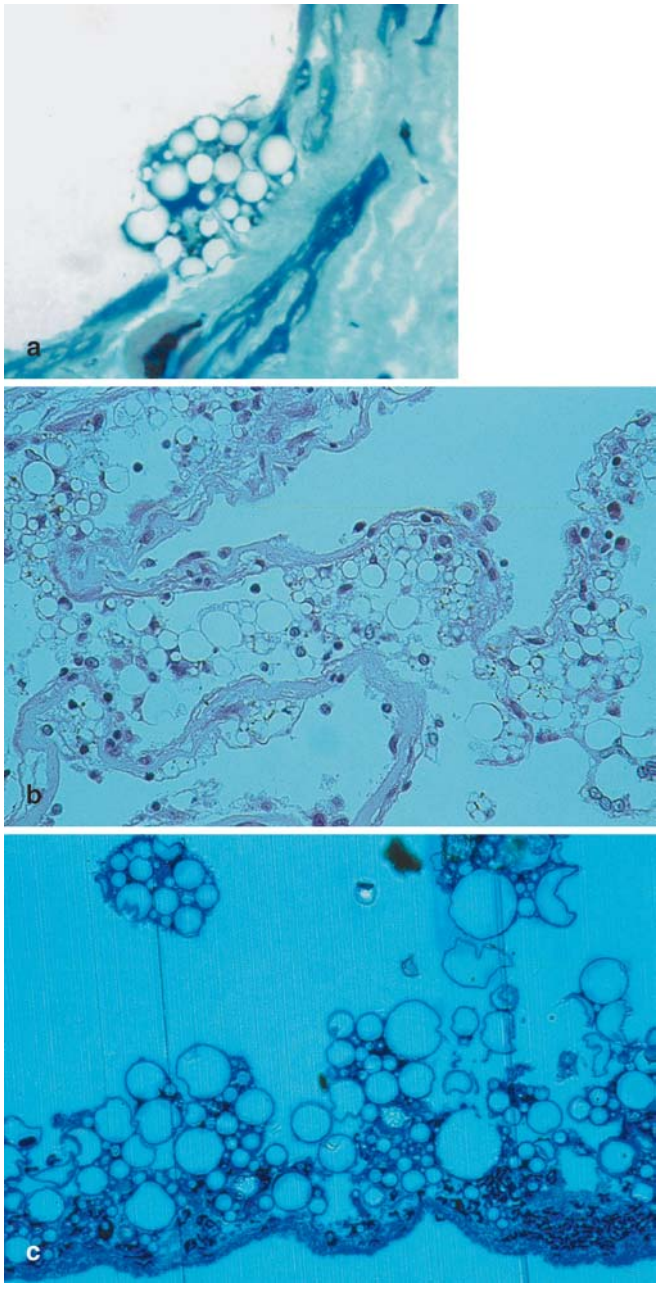

Fig. 4 **a** Histology of fluffy material removed from a patient's eye filled with F_6H_8. Cystic cells and amorphous material are visible. **b** Histology of fluffy material removed from a patient's eye filled with oligomer (OL62HV) and **c** histology of a lens capsule of the same patient with soft material behind the lens

week after surgery and visual acuity of 0.05 (Fig. 6a). He developed severe soft, fluffy material, PVR reaction and narrow retinal vessels under the oligomer tamponades within the next 4 weeks (Fig. 6b). Additionally he showed complete atrophy of the optic nerve with loss of light perception 4 weeks after oligomer injection. The clinical results are summarized in Table 2.

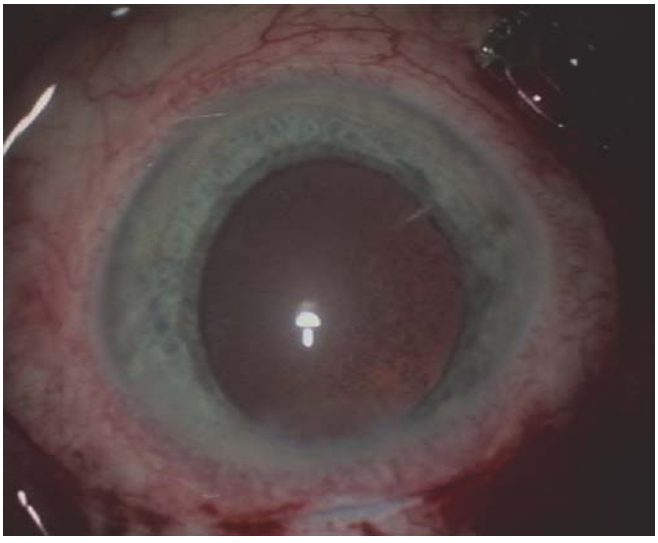

Fig. 5 Intraoperative view of soft material on the surface of the oligomer behind the lens (patient E.W.)

In one patient both soft fluffy epiretinal material and the posterior capsule of the lens, where soft material was present behind the capsule, were removed and examined by light microscopy. It was difficult to obtain the fluffy material from the retina for histological examination.

Discussion

There have been several attempts to find heavy endotamponades. In most cases concerns were raised because of poor biological tolerance or severe inflammation, as with fluorosilicone or in eyes filled with liquid perfluorocarbons for an extended period [1, 2, 3, 4, 10, 11, 12].

Hydrofluorocarbon oligomers were developed with the idea that higher viscosity leads to less dispersion than semifluorinated alkanes. In our clinical experience dispersion cannot be avoided using semifluorinated alkanes, despite complete filling of the eye including the anterior chamber. Similar results have been reported by others [7]. In two out of three aphacic eyes filled with F_6H_8, dispersion was observed. No dispersion was seen in eyes filled with hydrofluorocarbon oligomers; however, all four patients were pseudophacic or phacic.

In the preclinical testing of semifluorinated alkanes vascular occlusion was described after long-term use in rabbit eyes [8]. In the postoperative fluorescein angiograms of two F_6H_8 patients we did not find very obvious signs of vascular occlusion; however, the quality of the images obtained by the angiograph (Heidelberg Engineering, Heidelberg, Germany) was not optimal due to turbid media caused by hazy cornea or dispersion. In the patients in whom the oligomer was used, no postoperative fluorescein angiography was performed because of severe turbid media or unwillingness on the part of the patient.

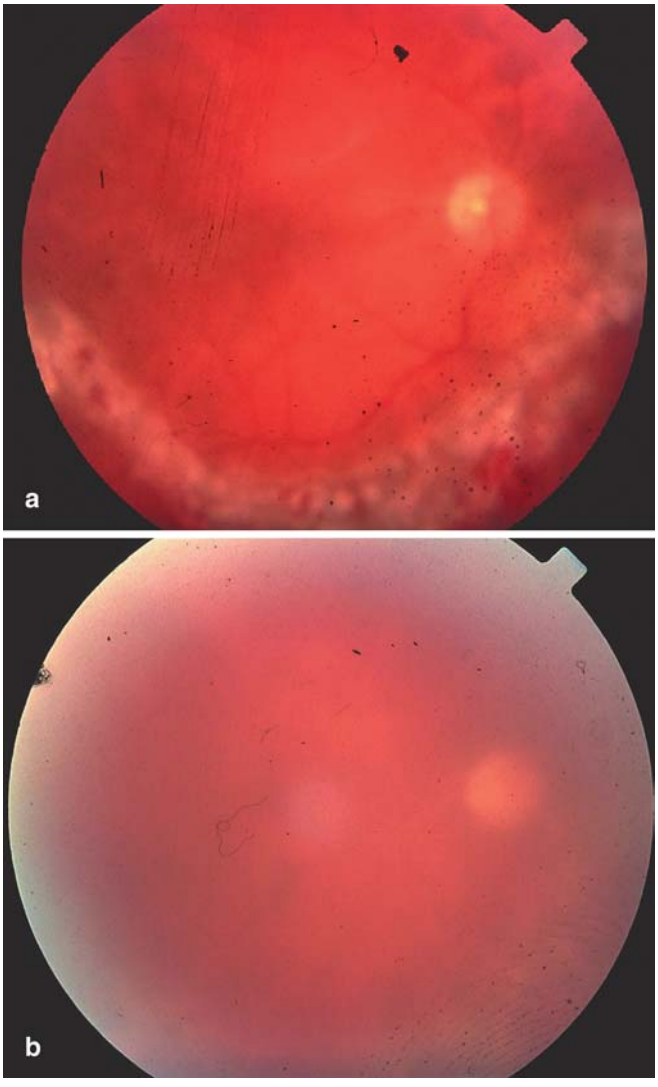

Fig. 6 **a** Fundus view 5 days after use of the oligomer (patient E.W.). Due to severe PVR a 180° retinectomy was performed. Visual acuity was 0.05. **b** Fundoscopic view 4 weeks later. No details of the fundus are visible because of fluffy soft material on the interface of the oligomer

The most striking and unexpected finding in the two substance groups was the fluffy soft material, which was much more pronounced in the oligomer group. In clinical appearance there was no difference between the soft material found after use of the semifluorinated alkane or the oligomer. This white material was located either between the surface of the heavy liquid and the retina or on top of the surface in the anterior part of the posterior segment; it was found in two eyes filled with F_6H_8 and in all four eyes where the oligomer was used. In one eye filled with F_6H_8 it was found only at the anterior part of the

circumferential buckle at the 6 o'clock position. In another F_6H_8 patient the material covered the entire anterior surface of the F_6H_8 bubble, impairing the view into the eye (see Fig. 3). As mentioned above, the soft material was found in all patients of the oligomer group and it was much more pronounced than in the F_6H_8 group. It was located on the surface of the retina and on the surface of the oligomer tamponades. Endophthalmitis as an explanation for the presence of the material can be ruled out for several reasons. Soft material occurred with two different substances manufactured by different companies. Surgery was performed at two different locations by different surgeons. No hypopyon was found in any of the patients, and no granulocytes or bacteria were seen on histological examination. Histology of soft material obtained from two F_6H_8 patients and one oligomer patient showed cystic cells and amorphous material, and there was no difference as seen by light microscopy. We were not able to explain the origin of the material. Others have demonstrated that cells tend to clump into isolated aggregates or form nearly confluent monolayers containing "lake-like" openings [5]. Similar fluffy material is occasionally found after the use of silicone oil, but the amount found after silicone oil cannot be compared with that after heavy tamponades.

The other important and completely unexpected finding in the oligomer group was the necrotic appearance of the retina, resembling retinal necrosis,. The retina appeared grey and fragile. The retinal vessels appeared narrowed, especially in the lower part of the globe. This may suggest a phagocytic reaction originating in the retina.

Neither of these reactions – soft material and necrotic appearance – has not been found in any animal experiments, all of which have been performed in rabbits [8]. The findings in those animals are in complete contrast to the findings in humans, raising the question of whether the rabbit is a suitable model for testing biological tolerance of new substances. It could be speculated that this discrepancy can be explained by the way of vitrectomy itself. Rabbits were "vitrectomized" just by gas injection leading to liquefaction of the vitreous. In all patients the vitreous was been completely removed by a mechanical cutter. The retinas of the animal were healthy, while all patients showed severe retinal pathologies.

In one patient optic neuropathy developed within 4 weeks after use of the oligomer. This could be explained, for example, by an occlusion of small capillaries within the optic nerve. The clinical findings of the contracted vessels as described before would be consistent with this theory. These findings again are completely contradictory to the experimental findings in rabbits, where a major advantage of the oligomer was the absence of any occlusion of retinal capillaries, in contrast to the semifluorinated alkanes 8.

It can be speculated whether cleaving of highly toxic C-F components from the partially fluorinated alkanes occurred, perhaps initiated by enzymes which are present in human but not in rabbit eyes. C-F formation could be excluded by magnetic resonance imaging of the substance removed. This does not completely rule out such a mechanism, because theoretically rebinding between the components could occur in the substances removed. For example, this phenomenon is the reason why chemical analysis of even extremely emulsified silicone oil is impossible. Silicone oil converges again as soon as the emulsified oil is in a syringe and being transported for chemical analysis.

Based on the clinical findings we cannot tell whether either of the substances, F6H8 or OL62HV, has any other toxic side effects on the anterior part of the eye, e.g. damaging the endothelium or the angle of the anterior chamber. Effects such as hazy stroma or glaucoma, as seen in two F_6H_8 patients, could also be explained by the surgical trauma or the underlying disease.

However, our preliminary data suggest no biological tolerance of the oligomer in human eyes. It is not suitable as a vitreous tamponade. Its theoretical advantages such as high viscosity or low oxygen capacity may be seen as of minor importance compared with the severe side effects found in patients. For this reason we stopped the clinical trial. However, the chemical similarity of semifluorinated alkanes and their oligomers and the common findings of soft material after use of each of the two substances in our study suggest a common pathway which is unknown and obviously cannot be predicted by experiments in rabbits. Therefore, further testing of new substances should be carried out in animals other than rabbits. Experiments in pigs are currently under way in the attempt to clarify the cause of these findings.

Based on our clinical findings silicone oil is still the best-tolerated substance and should be the substance of choice even in complicated situations with pathologies in the inferior quadrants. Whether other new heavy substances, e.g. the recently described mixture of silicone oil and semifluorinated alkanes (Oxane HD; Chauvin-Opsia, France), have much better biological tolerance remains to be clarified in future studies, but they show signs of promise [13].

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