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New substances for intraocular tamponades: perfluorocarbon liquids, hydrofluorocarbon liquids and hydrofluorocarbon-oligomers in vitreoretinal surgery

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Abstract Perfluorocarbon liquids (PFCLs) and heavy fluorocarbon liquids (HFCLs) are being increasingly used as soft tools during vitreoretinal surgery. However, since long-term intraocular tolerance is still unsatisfactory, at present complete removal at the end of surgery is recommended. With the aim to improve long-term intraocular compatibility and to enlarge the spectrum of clinical applications, modified HFCLs have been developed. HFCL-oligomers with a higher viscosity represent the latest perspective. All three groups of fluorocarbon liquids will be compared with respect to their physical and chemical properties, experimental and clinical results, and prospects for clinical applications. Common features of PFCLs, HFCLs and HFCL-oligomers are biological inertness, specific gravity higher than water, immiscibility with water or blood, and a high gas binding capacity. In PFCLs such as decalin, octane, or phenanthrene, all carbon atoms of the carbon backbone are completely fluorinated. In experimental and clinical use, emulsification, vascular changes and structural alterations of the retina have been described. By only partial replacement of hydrogen atoms by fluorine, the specific gravity of HFCLs is reduced, whereas lipophilic properties increase. Thus HFCLs are potential solvents for intraocular silicone oil remnants. However, after long-term application, side-effects are similar to those observed with PFCLs. Substances of this group, such as F6H6, F6H8, O44, and O62 are used intraoperatively and are currently being investigated for clinical long-term application. With the aim to avoid emulsification and to improve intraocular tolerance, we have developed HFCL-oligomers consisting of 2–4 HFCL molecules with increased viscosity. The oligomers were tolerated well in rabbit eyes for up to 4 months. In contrast to PFCLs or monomers, they did not emulsify nor show vascular alterations. ERGs returned to normal after removal of the oligomer from the eye. Histology of the retina showed mild alterations. *Conclusion:* according to physical properties, experimental intraocular compatibility and stability against emulsification, HFCL-oligomers are promising candidates for improved long-term tamponade of the lower retina. At present, indications for an application in human eyes have to be determined in clinical trials.

Background

Since perfluorocarbon liquids (PFCLs) were first introduced into vitreoretinal surgery by Haidt and Clark [21] and Chang et al. [8, 9, 10], they have been used increasingly and successfully as intraoperative soft tools for manipulation and reapposition of the retina [4, 7, 11, 37]. However long-term intraocular tolerance of PFCLs is still unsatisfactory, so that at present complete removal at the end of surgery is recommended [2, 3, 6, 7, 14, 46, 47]. Attempts have been made to modify the physical and chemical properties of PFCLs in order to improve the intraocular tolerance [26, 30, 45] and the spectrum for applications of this very suitable and variable group of substances. Thus the first generation of heavy, fully fluorinated carbon liquids, such as perfluorodecalin, perfluorooctane and perfluorophenathrene, has recently been supplemented by new partially hydrogenated hydrofluorocarbon liquids (HFCLs), which feature reduced specific gravity and increased lipophilic properties. This new group of partially hydrogenated fluorocarbon liquids, such as F6H6, F6H8, O44, and O62 are advantageous for intraoperative manipulation of the retina during macular rotation. Due to their lipophilic, silicone oil solvent properties, they have the potential to remove intraocular silicone oil remnants. Long-term intraocular clinical tolerance of HFCLs is currently under investigation [51].

The latest perspective represent hydrofluorocarbon oligomer liquids (HFCL-oligomers) (OL62 LV/HV), a new group of substances with increased viscosity, which we have developed recently with the aim to improve long-term tamponade therapy especially for pathologies of the lower retina. The properties, experimental results and new therapeutic potential of HFCL-oligomers will be presented.

PFCLs, HFCLs, HFCL-oligomers: common physical and chemical properties

Common features of PFCLs and HFCLs including the oligomers are biological inertness, immiscibility with water or blood according to the high interfacial tension, and a high gas binding capacity. They are heavier than water with a specific gravity ranging between 1.34 and 2.03 g/cm^3. Both interfacial tension and specific gravity determine the shape of the intraocular substance-droplet ranging between a round, easily rolling bubble or a quickly sinking mass with a horizontal liquid level. The refractive index varies between 1.27 (perfluorooctane) and 1.33 (perfluorophenanthrene). Since these substances are miscible with each other, the refractive index can be adjusted to the demands of the surgeon and the patient between 1.27, clearly distinguishable from that of intraocular fluid or residual vitreous, and 1.34, close to the refractive index of the vitreous. PFCLs and HFCLs for clinical use are highly purified. Differences in the molecular structure of PFCLs, HFCLs, and HFCL-oligomers (Table1) define different physical and chemical properties (Table2) leading to new perspectives for clinical applications.

PFCLs, HFCLs, HFCL-oligomers: specific characteristics, experimental and clinical results

Perfluorocarbon liquids

In PFCLs, all carbon atoms are completely fluorinated. In comparison to the closely related gaseous fully fluorinated fluorocarbons such as C3F8, which are also wide-

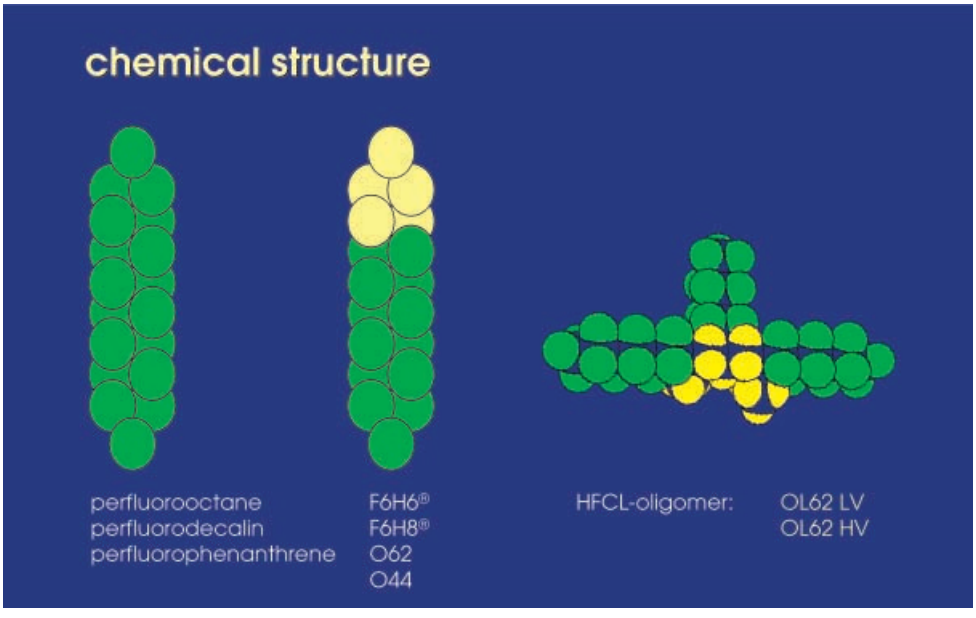
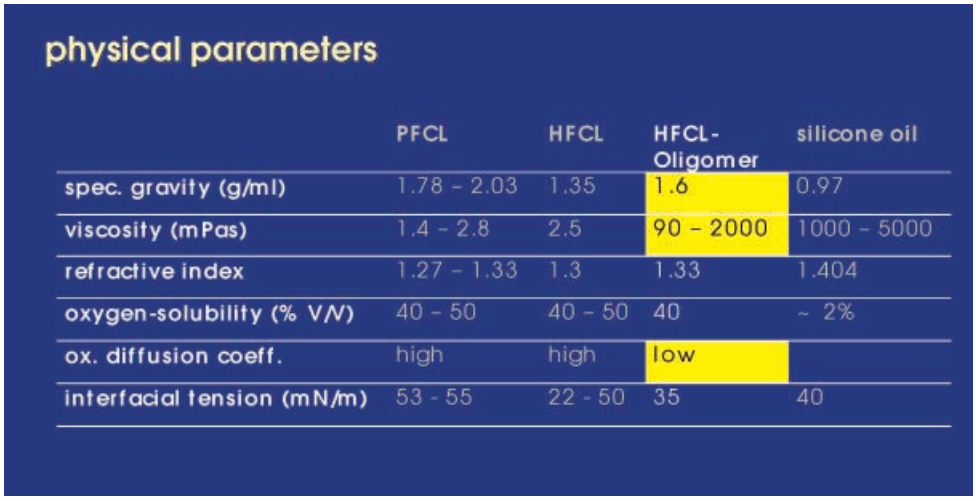


Table 1 Chemical structure of fluorocarbon liquids (FCLs), PFCLs, HFCLs, and HFCL-oligomers (yellow: hydrogen;green: fluorine) HFCLs, for example the octane O62, are obtained by partial fluorination of hydrocarbon liquids. Two to maximal four O62 molecules can be oligomerised to OL62 LV (low viscosity) or OL62 HV (high viscosity)

Table 2 Physical and chemical properties of PFCLs, HFCLs, and HFCL-oligomers as compared to silicone oil



physical parameters

	PFCL	HFCL	HFCL-Oligomer	silicone oil
spec. gravity (g/ml)	1.78 – 2.03	1.35	1.6	0.97
viscosity (mPas)	1.4 – 2.8	2.5	90 – 2000	1000 – 5000
refractive index	1.27 – 1.33	1.3	1.33	1.404
oxygen-solubility (% V/V)	40 – 50	40 – 50	40	~ 2%
ox. diffusion coeff.	high	high	low	
interfacial tension (mN/m)	53 - 55	22 - 50	35	40

ly used in ophthalmology, they possess a higher molecular weight and consist of more than five carbon atoms. PFCLs are hydrophobic and lipophobic. They have a very low viscosity and, due to the heavy fluorine atoms, a high specific gravity (Table2).

PFCLs are used as soft tools to manipulate, unfold and reappose the retina intraoperatively in cases of complicated retinal detachment, during macular rotation, or for removal of dislocated lenses [5, 6, 9, 15, 29, 33, 34, 36, 37, 39, 40, 50]. However, at present complete removal of the substance at the end of surgery is recommended because intraocular long-term tolerance is unsatisfactory as demonstrated in animal experiments or described in clinical reports after use in humans [7, 12, 13, 14, 16, 22, 32, 35, 41, 46]. Intraocular droplet formation does occur within the first few days, demonstrated here in a rabbit eye 5 days after injection. Simultaneously, flakey white precipitates appear in the residual vitreous and build membrane like structures around the bubbles, which may prevent reconfluence and indicate disturbance of the blood retinal barrier and leakage of protein (Fig.1) [20]. Experimentally, functional and morphological alterations of the retinal blood supply were found in two respects: first, an immediate vasoconstriction with an up to 30% reduction in retinal blood flow was measured in rabbit eyes after injection of PFCL [25]. Measurements of both pO_2 and pCO_2 in the PFCL before injection and than intraocularly after injection of PFCLs revealed high pO_2 (160 mm Hg) and low pCO_2 (3 mm Hg) levels in comparison to normal intravitreal values (pO_2 15 mm Hg, pCO_2 50 mm Hg). Consequently we suggested that vasoconstriction could be explained as an additive vasoconstrictive effect due to high pO_2 together with low pCO_2 in PFCLs, when injected intravitreally. The fact that vasoconstriction could be avoided or blood flow even increased by adaption of pO_2 and pCO_2 in PFCLs to normal values or to reduced pO_2 and increased pCO_2 levels, further supports our hypothesis [17, 25].

Second, after long-term intraocular application of PFCLs, vascular damage was evident in FLA findings. Vascular occlusions, avascular zones, aneurysms and leakage of dye are demonstrated as compared to the same vascular area before treatment (Fig.2). Trypsin digested flat mounts of the vessels [28] show loss of pericytes and endothelial cells [24]. Similar vascular alterations have been related to oxygen toxicity [1, 44]. We conclude, based on our hypothesis, that these vascular alterations can be caused by high pO_2 and low CO_2 levels. Histologically, alterations of the retina were more striking in the lower retina, the area of permanent contact with the PFCL, as compared with the upper retina (Fig.3). Preretinal foam cells containing optically empty vacuoles were found along the inner side of the retina, mainly around the vessels. Retinal thinning and penetration of all retinal layers by vacuoles was occasionally noted. Hypertrophy of Müller cells and structural disturbances in the plexiform layers was observed.

Hydrofluorocarbon liquids

The hypothesis that the high specific gravity of PFCLs is a causative factor for long-term intraocular tissue damage led to the development of HFCLs with reduced specific gravity [42]. In HFCLs, reduction of the specific gravity is accomplished by only partial replacement of hydrogen atoms by fluorine atoms. Corresponding to the number of carbon atoms, which are either fluorinated or hydrogenated, the substances are called F6H6 (perfluorohexane), F6H8 (perfluorohexyl-octane), O62 (perfluorohexyl-ethane) or O44 (perfluorobutyl-butane). Partial fluorination leads to a stepwise reduction in specific gravity, from 2.03 g/cm^3 (perfluorophenanthren) to 1.32 g/cm^3 (F6H8). Simultaneously, hydrogenation causes augmented polarisation leading to increased lipophilic, silicone-solvent properties of the substances. Thus, rep-

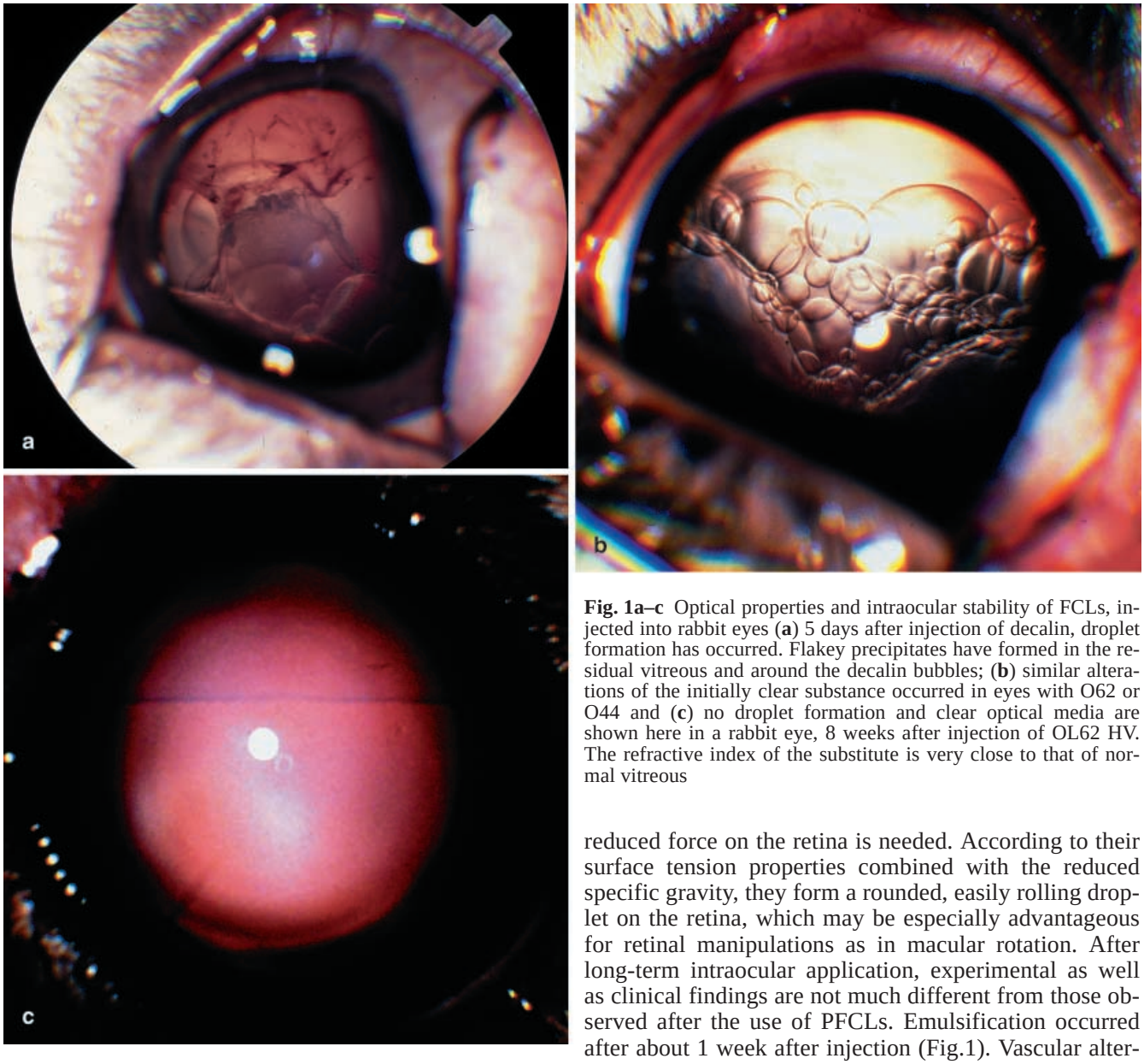


Fig. 1a–c Optical properties and intraocular stability of FCLs, injected into rabbit eyes (**a**) 5 days after injection of decalin, droplet formation has occurred. Flakey precipitates have formed in the residual vitreous and around the decalin bubbles; (**b**) similar alterations of the initially clear substance occurred in eyes with O62 or O44 and (**c**) no droplet formation and clear optical media are shown here in a rabbit eye, 8 weeks after injection of OL62 HV. The refractive index of the substitute is very close to that of normal vitreous

resenting the first biocompatible intraocular silicone solvent, HFCLs potentially allow removal of silicone oil remnants from the eye or wash out of silicone oil contaminations from intraocular lenses. Initial clinical applications have been reported [51]. However, if PFCLs, HFCLs and silicone oil are used in succession intraopertaively, “silicone oil in HFCL solutions” can build dense opacifications which may obscure the vision of the surgeon and are difficult to remove [23]. Therefore, for combined intraocular use, a definite sequence of application and exact knowledge of solubility properties is mandatory for the surgeon.

For clinical intraoperative short-term application, HFCLs offer advantages over PFCLs in cases where a reduced force on the retina is needed. According to their surface tension properties combined with the reduced specific gravity, they form a rounded, easily rolling droplet on the retina, which may be especially advantageous for retinal manipulations as in macular rotation. After long-term intraocular application, experimental as well as clinical findings are not much different from those observed after the use of PFCLs. Emulsification occurred after about 1 week after injection (Fig.1). Vascular alterations, an immediate vasoconstrictive effect and long-term structural damage, are shown in Fig.2, 6 weeks after injection of O62.

Histology of the inferior retina revealed structural alterations similar to those observed after application of PFCLs, despite the lower specific gravity of HFCLs (Fig.3) [18]. Based on calculations, the downward force of intraocular PFCLs cannot exceed 1–2 mm Hg and thus remains within the normal range of intraocular tension. So both histological findings and calculations do not support the hypothesis that the specific gravity of PFCLs is a major factor for retinal damage [17, 18, 42, 48]. At present, the long-term tolerance of HFCLs in human eyes is under investigation in a clinical study. Thus, for further optimisation of an intraocular tamponade

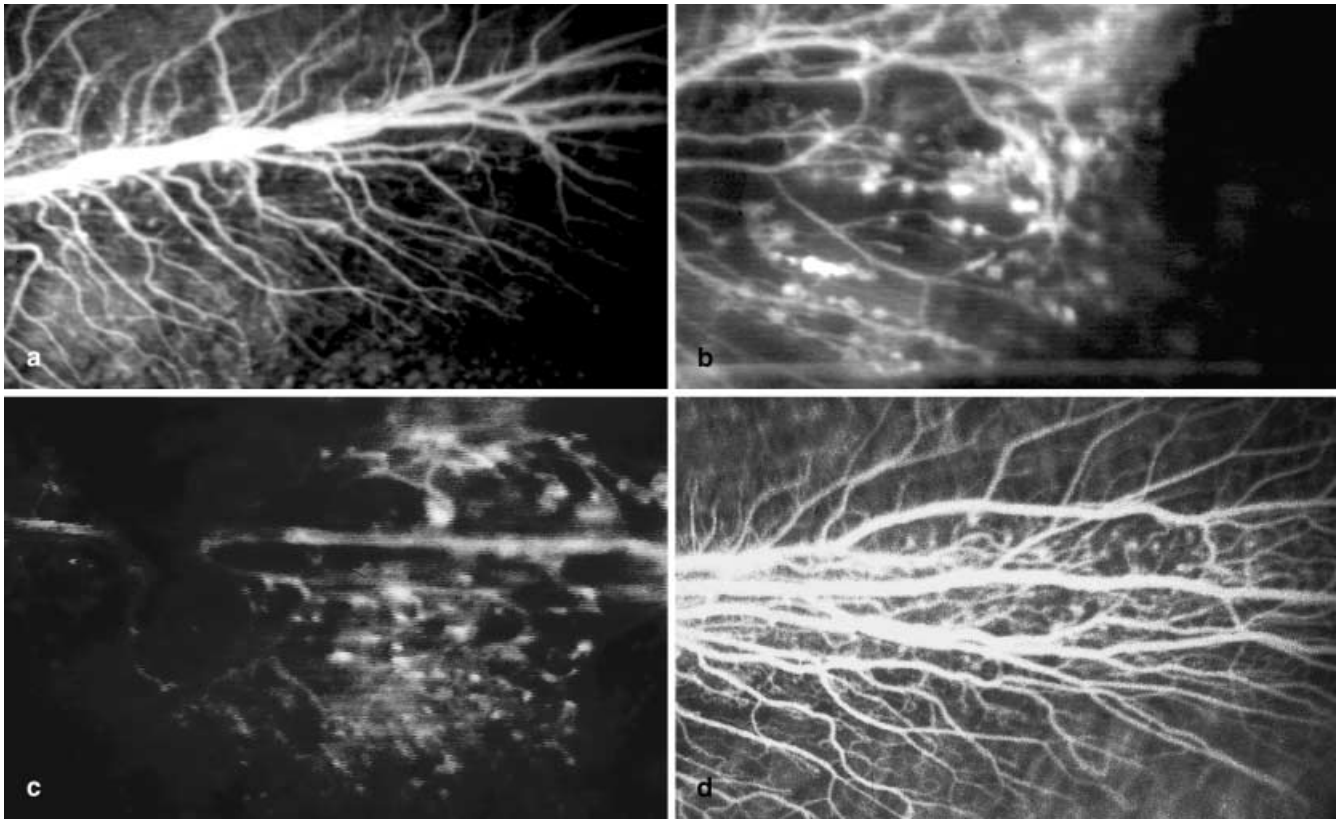


Fig. 2a–d Fluorescein angiography of the rabbit's retinal blood vessels (**a**) before and after injection of (**b**) PFCL (identical area of the vascular system),(**c**) HFCL and (**d**) OL62 HV. As compared to the normal, untreated contralateral eye (**a**), vascular occlusions, rarefication, aneurysms and leakage of dye have developed 6 weeks after injection of PFCL (**b**) or O62 (**c**), whereas the vascular system appears normal 8 weeks after OL62HV-injection (**d**)

therapy, in particular for the lower retina, as an alternative to silicone oil, the major goals remain to improve the optical properties of the substitute by avoiding intraocular droplet formation and to reduce intraocular side-effects.

Hydrofluorocarbon oligomers

With the idea that higher viscosity can improve the mechanical properties of an intraocular tamponade and thus reduce emulsification and intraocular complications, we have developed HFCL-oligomers. By joining two to maximal four HFCL molecules, viscosity reaches values ranging between 90 (OL62 LV, low viscosity) and 1750 mPas (OL62 HV, high viscosity), which still guarantee an easy handling and injectability through fine needles but can improve intraocular stability and reduce droplet formation. Due to the star-shaped molecular structure with the polar, hydrogenated end of the molecule in the centre, HFCL-oligomers represent a new class of compounds. They differ from HFCLs in many respects such as surface properties and lipophilic properties. The specific gravity of these substances, 1.62, is very suitable for tamponade of the lower retina. The refractive index is almost identical with that of normal vitreous, which is an advantage for the patient but may make it difficult for the surgeon to distinguish the intraocular oligomer bubble from intraocular fluid. For special surgical demands, in case of removal, better visualisation can be achieved by mixing the oligomer with a PFCL, which has a different refractive index.

The intraocular compatibility of two HFCL-oligomers with different viscosity, OL62 LV of 90 mPas and OL62 HV of 1750 mPas respectively, was evaluated in rabbit eyes. After gas compression of the vitreous [43], 1.2 ml of either substance was injected intravitreally. The eyes were observed for up to 3 months and examined by slit lamp, ophthalmoscopy, and fluorescence angiography (n=4 in each group). ERGs were performed with the substance in the eye and after removal of the oligomer. At the end of the observation time, the eyes were enucleated and processed for light and electron microscopy.

Both substances were easy to handle. They were tolerated without any inflammatory reaction. Droplet formation did not occur in any eye during the whole observation period. The substance, the residual vitreous and all optical media remained clear, as shown in Fig.1, 8

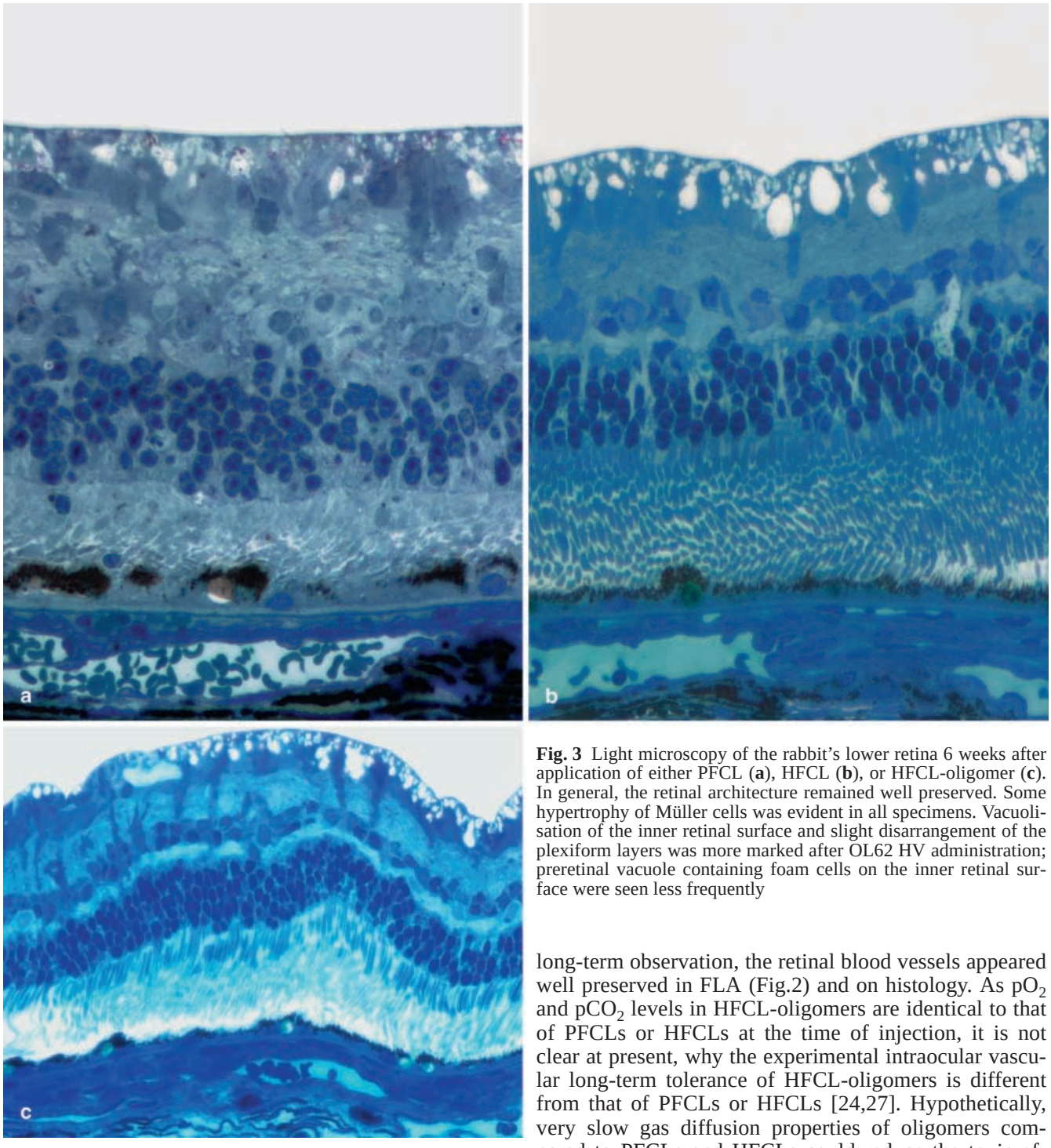


Fig. 3 Light microscopy of the rabbit's lower retina 6 weeks after application of either PFCL (**a**), HFCL (**b**), or HFCL-oligomer (**c**). In general, the retinal architecture remained well preserved. Some hypertrophy of Müller cells was evident in all specimens. Vacuolisation of the inner retinal surface and slight disarrangement of the plexiform layers was more marked after OL62 HV administration; preretinal vacuole containing foam cells on the inner retinal surface were seen less frequently

weeks after injection of OL62 HV. In contrast, droplet formation and precipitates were demonstrated 5 days after injection of decalin and 7 days after injection of O62 (Fig. 1). The interface between the oligomer and the residual vitreous was visible as a fine line (Fig.1). Vascular constriction was noticed briefly after injection, but after long-term observation, the retinal blood vessels appeared well preserved in FLA (Fig.2) and on histology. As pO_2 and pCO_2 levels in HFCL-oligomers are identical to that of PFCLs or HFCLs at the time of injection, it is not clear at present, why the experimental intraocular vascular long-term tolerance of HFCL-oligomers is different from that of PFCLs or HFCLs [24,27]. Hypothetically, very slow gas diffusion properties of oligomers compared to PFCLs and HFCLs could reduce the toxic effects of oxygen to the retinal vessels.

While the oligomer was in the eye, ERGs showed a general reduction in amplitude of about 30% as compared to the contralateral untreated eye (n=2), which is in accordance with the known insulating properties of FCLs. Ten days after removal of the oligomer from the rabbit eye, the ERG had returned to the normal value of

the control eye (n=2; data not shown). Histological alterations of the lower retina were comparable to those after PFCL or HFCL application or to those that have been described in the upper retina after long-term administration of silicone oil [19, 24, 31]. They consisted in hypertrophy of Müller cells, structural disturbance of the outer plexiform layer, and occasional foam cells and vacuolisation on the inner retinal surface (Fig. 3) [27]. Currently, oligomers are being evaluated in porcine eyes before clinical trials are planned.

Conclusions

For the future, PFCLs, HFCLs, and HFCL-oligomers may represent a group of substances which can be employed and combined favourably according to special surgical needs. High gas-binding capacities of PFCLs, HFCLs, and oligomers offer new perspectives for the treatment of the ischaemic retina [25, 38, 49]. HFCLs with reduced specific gravity are presently introduced into clinical use for intraoperative management of the detached retina, but also for extended term application or for removal of intraocular silicone oil remnants. HFCL-oligomers with increased viscosity proved stable against intraocular emulsification. The appropriate physical and chemical properties and the excellent experimental long-term biocompatibility and biostability point towards a very good suitability of the oligomers for tamponade of the lower retina and as a long-term vitreous substitute. At present, clear guidelines and indications for an application of HFCL-oligomers in human eyes have to be determined in clinical trials.

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