Perfluoropentane in experimental ocular surgery. IAN J. CONSTABLE.

Air has long been advocated as a mechanical aid to both anterior segment1, 2 and retinal detachment surgery.3 However, the fact that air is absorbed within three to four days has lead to the investigation of gases which might last longer in tissues.4-7

One factor which helps determine the absorption rate of gases is aqueous solubility.1-4 Thus, argon lasts longer than the more soluble carbon dioxide,6 but neither outlasts air. A second factor is molecular weight. Hence, two insoluble inorganic gases of large molecular weight, sulfur hexafluoride and octafluorocyclobutane, are both retained in the aqueous and vitreous cavity longer than air.5-9

Many of the family of perfluorinated carbon compounds are highly insoluble. With increasing molecular weight, however, the boiling point drops, so that the six-carbon compounds are liquid at body temperature. However, the five-carbon compounds such as perfluoropentane (C₅F₁₂) have a boiling point of about 30°C, so that they are liquid at room temperature, but gaseous at body temperature.

Liquid volumes ranging from approximately 0.2 µl to 2 µl of perfluoropentane were drawn up in a chilled, sterile microsyringe. These volumes were then immediately injected into the anterior chamber (14 eyes), vitreous cavity (14 eyes), or subconjunctival tissues (6 eyes) of rabbits. The rabbits were anesthetized with pentobarbital sodium and postoperative mydriasis was maintained with atropine. In each situation this minute amount of liquid was immediately heated by the tissues beyond its boiling point and converted into bubbles of gas, which quickly coalesced into one or two large bubbles (Fig. 1). The material was injected from a dependent position, so that the gas bubbles rose away from the injection site.

In the anterior chamber 0.5 to 2 µl of perfluoropentane expanded immediately to occupy one-tenth to one-half the normal aqueous volume. No suture was used, and an immediate rise in intraocular pressure was avoided by displacement of aqueous out the injection site. In each case the gas expanded a further 300 to 600 per cent in volume over the following seven days (Fig. 2), presumably due to the trapping of dissolved tissue gases.6, 10

In four eyes injected with 2 µl of liquid perfluoropentane, secondary expansion of the gas completely replaced the aqueous humor. Each of these eyes developed acute glaucoma, resulting in a cloudy cornea, deepened anterior chamber, posterior synechia, and generalized lens opacities.

In another ten eyes injected with less than 0.5 µl of perfluoropentane, secondary expansion of the gas did not completely fill the anterior chamber, and intraocular pressure did not rise (Fig. 2). Slit-lamp examination revealed fibrin deposits and a flare in the residual aqueous in the first few days in all ten eyes (100 per cent), such as is seen in rabbits after paracentesis alone. After one week, localized corneal haze developed in six eyes (60 per cent) and anterior subcapsular lens opacities in two eyes (20 per cent). In each instance the signs of injury were confined to the area directly in contact with the gas bubble. Corneal haze was not seen in four eyes (40 per cent), and in each of these the bubbles were
Fig. 3. Multiple perfluoropentane gas bubbles in the vitreous cavity of a rabbit eye twelve weeks after injection of 0.5 μl of liquid.

Fig. 4. Subconjunctival perfluoropentane gas four months after injection. There are no signs of irritation, but the gas bubble appears encapsulated.

Injection of 1 to 2 μl of perfluoropentane into the vitreous cavity of six rabbit eyes resulted in a shallow anterior chamber and acute glaucoma in each case (100 per cent). These eyes developed a cloudy cornea and generalized cataract. When 0.5 μl of perfluoropentane was injected into the vitreous (eight eyes), both the immediate and the delayed expansion of the gas was accommodated in all eyes without a rise in intraocular pressure. The gas expanded to a maximum volume in four days of about 20 per cent of the vitreous cavity as judged ophthalmoscopically. The gas volume began to decrease three weeks after injection, to about 10 per cent of the vitreous volume at six weeks, and to less than 3 per cent at twelve weeks (Fig. 3). Several minute gas bubbles persisted in four eyes (50 per cent) after six months. Clinical examination revealed no inflammatory cells, opacities, or scarring formation in the vitreous during the period of observation. No opacities or vacuoles developed in the lens of any of these eyes. Histologic examination of two eyes at four and six months revealed no abnormalities in the lens or retina, and no fibroblastic proliferation in the vitreous.

Subconjunctival injection of perfluoropentane (six eyes) resulted in extensive ballooning of these tissues. Gas migrated right around the limbus and posteriorly into the orbit. Again, the gas caused no clinical signs of irritation, and was slowly resolved in each case over six months. The residual subconjunctival gas at four months was localized in a bleb (Fig. 4) in three eyes (50 per cent), but was no longer present in any animals at six months.

These preliminary studies show that perfluoropentane will persist in biological tissues and cavities for much longer than other gases reported. It causes very little inflammation, but is definitely irritative to the corneal endothelium and lens if in immobile direct contact. A similar irritative effect has been noted with air and other gases. However, when the gas bubbles are able to move around in the aqueous or vitreous cavities, evidence of toxicity is not seen clinically. This previously observed fact is also true for perfluoropentane, even though it persists for months.

Expansion of sulfur hexafluoride in the vitreous can be controlled by admixture with air. To test this hypothesis with perfluoropentane, the liquid was added to air in a syringe in a cold room (4° C.) in concentrations of 1 and 5 μl per cubic centimeter of air. After warming to 37° C. in an incubator, a small bubble of each concentration was injected into the anterior chamber (four eyes) and vitreous cavity (four eyes) of rabbits. The bubbles were examined and photographed daily.

Perfluoropentane in a concentration of 1 μl per cubic centimeter of air showed no clinical evidence of expansion in any of the eyes. The gas bubble only began to decrease in size after three weeks. In concentrations of 5 μl per cubic centimeter, the bubble expanded 200 to 300 per cent in volume over three days in all eyes, in both the aqueous and vitreous.
Attempts to add perfluoropentane directly to an air bubble already injected into the aqueous or vitreous proved unreliable. It was not possible to measure such small amounts of the perfluoropentane in these situations.

Long-term evaluation is necessary to determine if perfluoropentane is sufficiently nontoxic for clinical use. However, these experiments suggest important principles in the search for an inert chemical of relatively high molecular weight which will vaporize below 37°C. C. might be expected to persist in a gaseous phase in the body for a prolonged period of time.


Key words: perfluoropentane, anterior chamber, vitreous, subconjunctival tissues, vaporization, toxicity.

REFERENCES

A model of anisotropic factors contributing to retinal venous nicking. B. Carroll, Smiley, Jonathan D. Wirtschafter, and James F. Lafferty.

A laboratory model consisting of fluid flow through Penrose tubing arrangements in a pressure chamber was used to explain the “nicking” phenomenon. The effects of various forces possibly at play in the regions of arteriovenous crossings were considered. The triangular or “shark’s tooth” shape of the underlying vein observed by investigators can be produced by the forces generated by the movement of a hypertensive artery. The narrowed lumen of the vein and, therefore, the narrowed blood column at the crossings can explain the ophthalmoscopic appearance of “nicking.”

This investigation determined, in a laboratory model, the effects of various forces which may act to deform the veins in the region of retinal arteriovenous crossings. Histopathologic reconstructions from eyes with hypertensive retinopathy have revealed progressive changes in the shape of the cross-section of nicked retinal veins.\(^1\)\(^2\) At such crossings, the veins have triangular or shark tooth-shaped cross-sections instead of the indented cylinders normally seen. These deformations extend for essentially equal distances both proximal and distal to the crossings. The shape of the cross-section undergoes progressive translation from triangular through elliptical to circular. The axis of the ellipse is at right angles to the internal limiting membrane of the retina. In this study the retinal vein was treated as a collapsible tube and the question asked was what forces were necessary to produce the observed deformations.

Previous laboratory studies of collapsible tubes have dealt with water flowing through circular rubber tubes rigidly supported at either end of a pressure chamber.\(^3\)\(^4\) In such models the wall properties of the tube were essentially uniform around the circumference while the wall properties of the retinal veins are not uniform because 20 per cent of the circumference of the venous perimeter is attached to the overlying, stiffer artery at the crossing. Such inequality of directional properties is known as anisotropy. In addition, the retinal vein is not suspended in a homogeneous media but is embedded in and attached to the retinal structures which are also likely to subject the vein to anisotropic forces. The deformed shape of the venous cross-section may result from the interaction of anisotropic forces exerted by the hypertensive artery on the anisotropic structure of the vein and the surrounding retina.

A collapsible piece of rubber tubing was connected to fittings at either end of clear Lucite cylinder 20 cm. long and 8 cm. in diameter (Fig. \(A\), B).