Vitreous Physiology

IV.A.

Einar Stefánsson

Outline

Keywords

Vitreous • Physiology • Convection currents • Viscosity • Diffusion • Transport • Oxygen • Posterior vitreous detachment • Vitrectomy • Cataract • Neovascularization • Pharmacologic vitreolysis

Key Concepts

1. Vitreous gel modulates the transport of molecules through the vitreous body. The high viscosity of the gel reduces transport by convection currents and diffusion. With age, surgery, or pharmacologic vitreolysis, vitreous viscosity is reduced and the rate of transport of various molecules increases. This physiological change has various clinical consequences, some beneficial and others harmful.
2. Oxygen has been the prime molecule in the study of vitreous physiology and the effect of treatment. Changes in oxygen metabolism explain many of the clinical findings and correlate nicely with the effect of laser and other treatment modalities in the ischemic retinopathies.
3. Vitrectomy and pharmacologic vitreolysis stimulate nuclear sclerosis cataract formation. Posterior vitreous detachment and vitrectomy may protect against macular edema and neovascularization in diabetic and other ischemic retinopathies as well as age-related macular degeneration.

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I. Introduction

Untouchable, Disposable and Invisible

Well into the twentieth century, most ophthalmologists considered the vitreous body to be sacred and that any interference with this structure would have serious consequences for the eye. The vitreous was *untouchable*. Pioneering researchers [1–7] changed this axiom, and towards the end of the century, vitreoretinal surgeons came to think of the vitreous gel almost as an inert substance, which could be freely operated, removed, and replaced for optical and structural reasons, with no consideration for any other functions of this tissue. It became *disposable*. At the same time the vitreous was practically *invisible*; visualizing vitreous detachment with slit lamp biomicroscopy was unreliable, but dramatically improved with ultrasound and optical coherence tomography (OCT). [see chapter II.F. To See the Invisible - the Quest of Imaging Vitreous]

Vitreous surgery and the removal and replacement of vitreous have physiological and clinical consequences for the eye, some beneficial and others detrimental. Several clinical effects have been recognized for decades, and while some of the physiological mechanisms were reported in the early 1980s, it is only recently that vitreoretinal surgeons have opened their eyes to the physiological consequences of vitreoretinal surgery.

This chapter explains the physiological consequences of vitreous surgery, some of which may be predicted from classical laws of physics and physiology. Understanding these physiological mechanisms allows a better rationale in the management of vitreous surgery and its combination with laser treatment and drug injections. Vitreous physiology has moved the vitreous gel to the center of ophthalmology and not just the eye.

II. Physiology

A. Molecular Transport in the Vitreous

The physiological consequences of vitreous gel removal, liquefaction, or replacement are predicted by classical theories of physics. They predict the effect vitrectomy has on transport of molecules within the vitreous chamber and the eye. Molecule transport within the vitreous is by two mechanisms: diffusion and convection currents. Diffusion may be described by the laws of Fick and Stokes–Einstein and fluid currents by the law of Hagen–Poiseuille [8]. Fick's law describes the diffusion flux, J, in terms of the diffusion coefficient, D, and the concentration gradient of the molecule dC/dx:

$$J = D\, dC / dx$$

Stokes and Einstein described the diffusion coefficient, D, in terms of the molar gas constant, R; the temperature in degrees Kelvin, T; the viscosity of medium, η; the radius of diffusing molecule, r; and Avogadro's number, N:

$$D = \frac{RT}{6\pi\eta rN}$$

The diffusion coefficient, D, is inversely related to the viscosity of the medium, η. Consequently, rate of diffusion is also inversely related to the viscosity of the medium.

The Hagen–Poiseuille law describes fluid currents, J, in terms of the pressure difference, ΔP; the length, L; and diameter, d, of a channel and the viscosity of medium, η.

$$J = \pi d^4 \Delta P / 8L\eta$$

Note that convection currents, J, are inversely related to the viscosity of the medium, η.

It is important to note that both diffusion and convection currents are inversely related to the viscosity of the medium. This may be intuitively obvious: diffusion and fluid currents are slower in a highly viscous substance than in a less viscous medium. Since vitrectomy involves the replacement of the vitreous with substances that have different viscosity, this influences the transport of molecules in the vitreous cavity. It is important to keep in mind that this is a general principle that applies to all diffusing molecules, both beneficial and potentially harmful molecules including oxygen and other nutrients, drugs, growth factors, and other cytokines.

1. Viscosity of Vitreous

Ophthalmic surgeons know by experience that the vitreous gel is more viscous than the saline solution that replaces it or the aqueous humor that eventually fills the vitrectomized eye. At the same time the silicone oil, with which we sometimes fill the vitreous chamber has higher viscosity than both vitreous gel and water. The surgeons' impression is confirmed by science [9–11]. While the viscosity of the vitreous gel is variable and depends on species and measurement techniques, it is many times more than water, balanced salt solution, or aqueous humor. Lee et al. [12] found the viscosity of human vitreous gel to be 300–2,000 cP, while the viscosity of water is 1 cP. Gisladottir et al. [13] used a kinetic viscosity meter to measure the viscosity of porcine vitreous and found this to be bimodal; the thinner phase had viscosity of about 5 cP and the thicker about 180 cP (Figure IV.A-1). Also, the diffusion of dexamethasone was found to be about five times greater in saline than in vitreous (Figure IV.A-1). Similarly, Sebag et al. [14] showed that pharmacologic vitreolysis with ocriplasmin increases vitreous diffusion coefficients *in vitro*. It is reasonable to assume that the vitreolysis breaks down vitreous macromolecules and reduces the viscosity of the vitreous gel, resulting in increased diffusion coefficients. Silicone oil that is used for vitreoretinal surgery

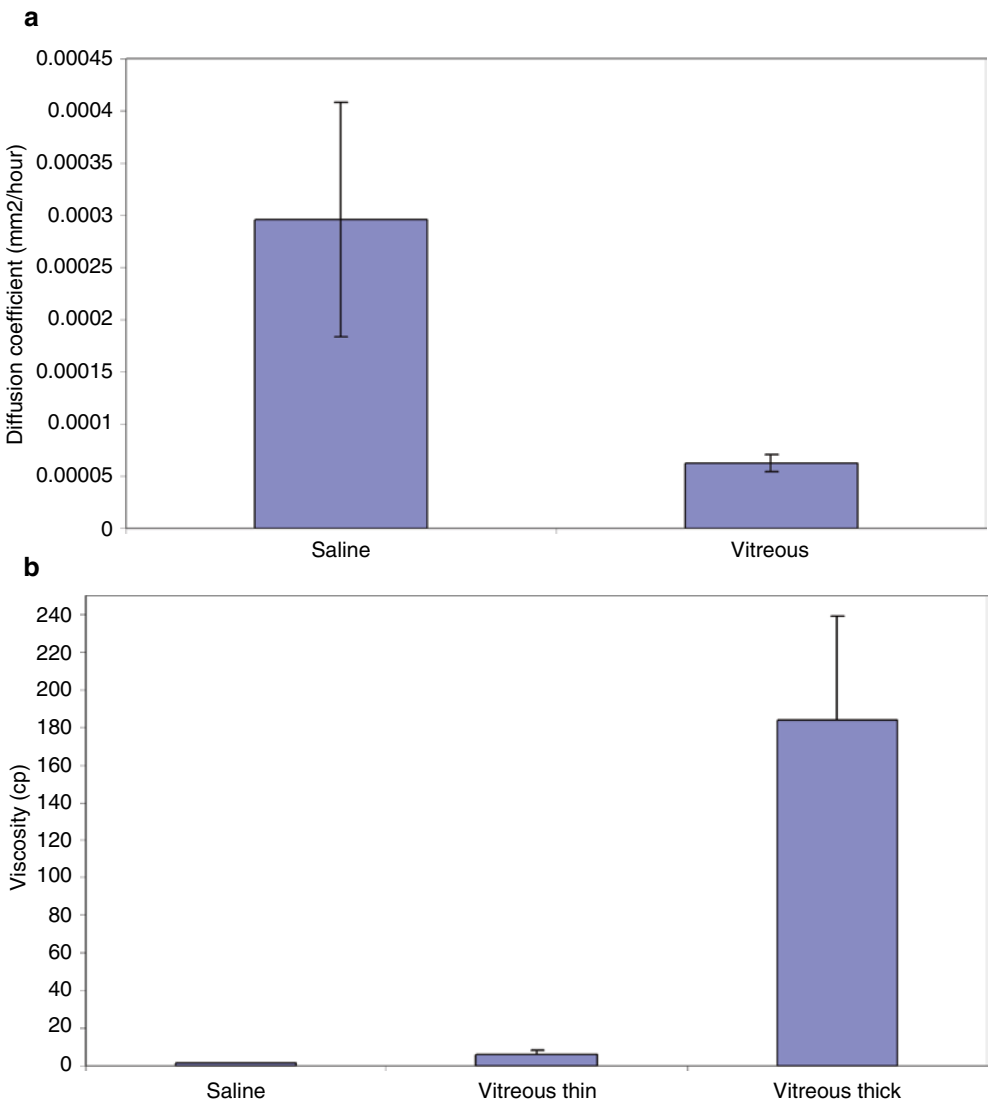

Figure IV.A-1 (**a**) Diffusion of dexamethasone through vitreous gel (**b**) Viscosity of porcine vitreous comparing saline to liquid vitreous (*thin*) and gel vitreous (*thick*) (From Gisladottir et al. [13])

is available in several different viscosities, all of which are considerably more viscous than vitreous gel [15].

The relatively high viscosity of the vitreous gel modulates the transport of molecules within the vitreous body and keeps the rate of transport at a relative low level. This is important for the tissues surrounding the vitreous. With age, the viscosity changes as well as the transport characteristics, and this plays a role in some of the aging diseases in the lens and the retina.

B. Oxygen Physiology

The first studies of vitreous physiology were by-products of studies about oxygen physiology in the retina. In 1972, Alm and Bill [16] showed that oxygen tension in the cat vitreous falls gradually moving anteriorly from the surface of the retina to a minimum behind the crystalline lens. The first physiological studies of vitreous surgery were published in the early 1980s. Stefansson et al. [17, 18] removed the vitreous gel and crystalline lens in cats and found that oxygen transport between the anterior and posterior segments of the eye was increased in the vitrectomized–lensectomized eye compared to the intact eye (Figure IV.A-2). Oxygen was transported at a faster rate from the anterior segment, resulting in a significantly lower PO_2 in the aqueous humor. If the retina was made ischemic and hypoxic with vascular occlusion, the oxygen tension in the anterior segment fell even more (Figure IV.A-2).

de Juan et al. [19] showed that silicone oil is the exception that proves the rule. Using silicone oil that is more viscous than the vitreous humor, they reported that anterior chamber hypoxia in the vitrectomized–lensectomized cat eye is prevented if the vitreous chamber is filled with silicone oil (Figure IV.A-3). The silicone oil is highly viscous, slows the transport of oxygen, and reestablishes a diffusion barrier,

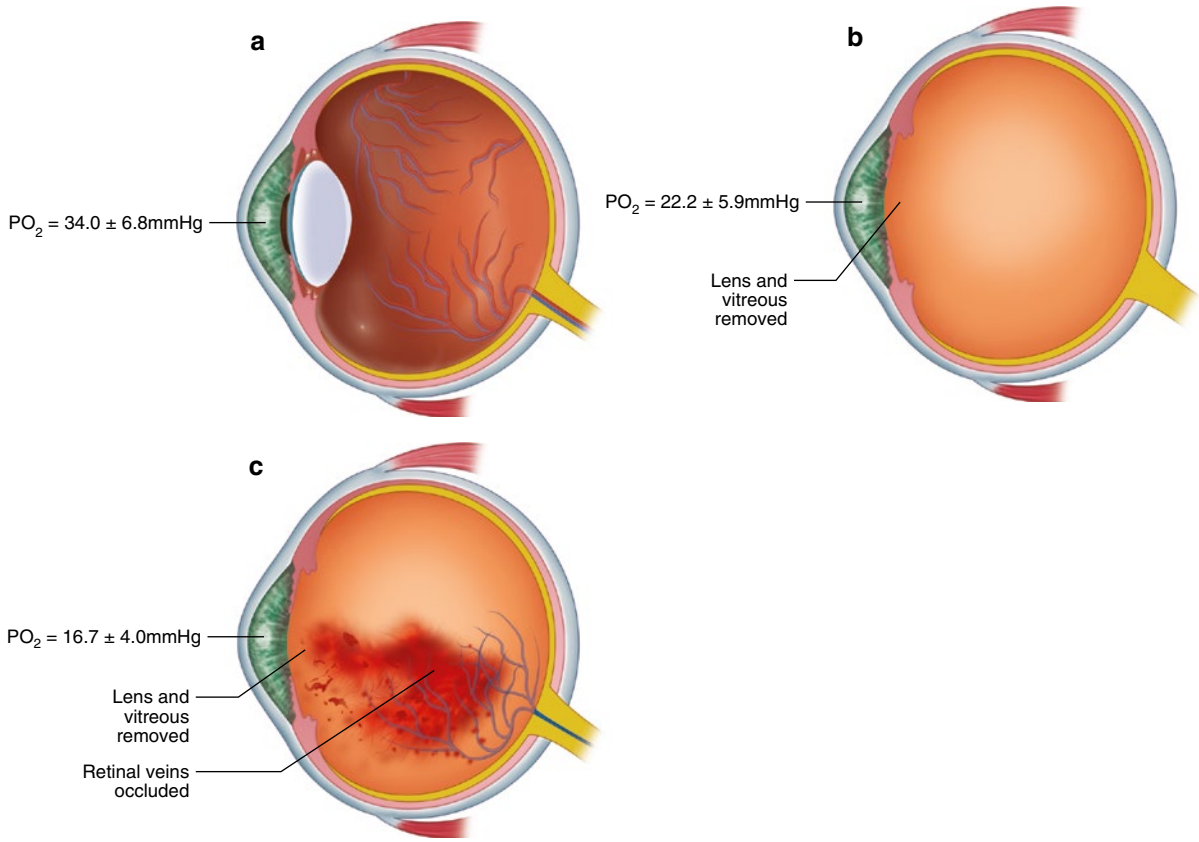

Figure IV.A-2 Stefánsson et al. (1981) reported the oxygen tension in the anterior chamber of cat eyes. The mean anterior chamber oxygen tension is 34 mmHg in the intact eye (**a**), 22 mmHg after vitrectomy and lens extraction (**b**), which is similar to the normal retinal oxygen tension in cats. The anterior chamber oxygen tension falls to 17 mmHg if the retinal veins are occluded in the vitrectomized–lensectomized eye (**c**) (Published with permission from the American Ophthalmological Society)

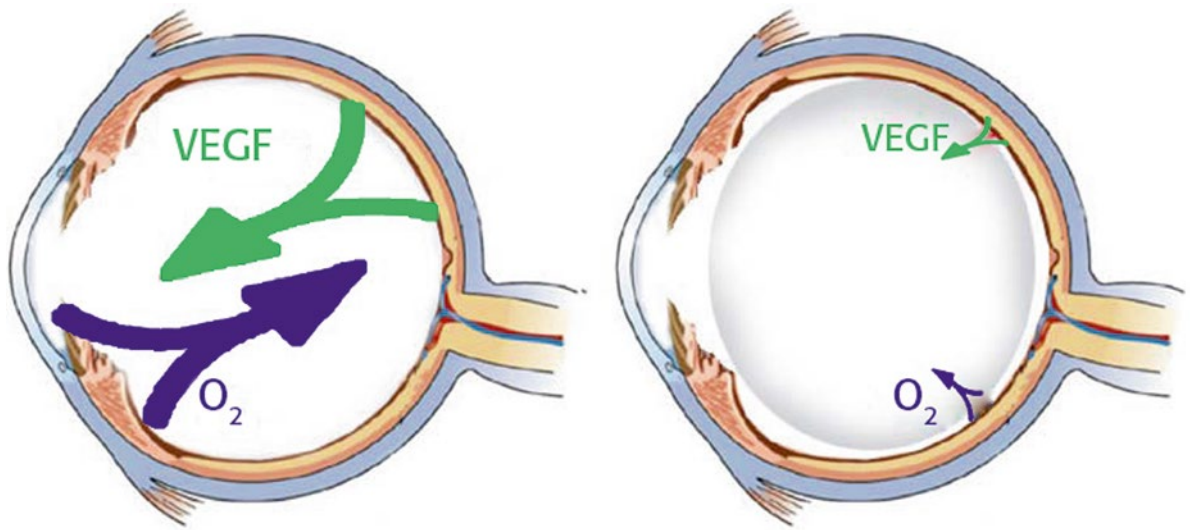

Figure IV.A-3 The schematic drawings show the theoretical fluxes of oxygen and vascular endothelial growth factor (*VEGF*; and any molecule) in the vitrectomized–lensectomized eye (*left*) and silicone oil-filled vitreous chamber (*right*). The low viscosity of the fluid in the vitrectomized eye increases diffusion and convection currents compared with the intact eye. Oxygen is transported from the anterior segment and well-perfused retinal areas to ischemic retinal areas. VEGF is cleared away from the ischemic retinal areas by diffusion and convection at a much higher rate than before vitrectomy. The retina receives oxygen and gets rid of VEGF, and the risk of retinal neovascularization decreases. At the same time, the iris loses oxygen and receives VEGF from the retina, and the risk of iris neovascularization is increased. Silicone oil is more viscous than the vitreous gel, and transport of all molecules is slowed accordingly. It reestablishes the diffusion barrier between the anterior and posterior segments and reduces the risk of iris neovascularization

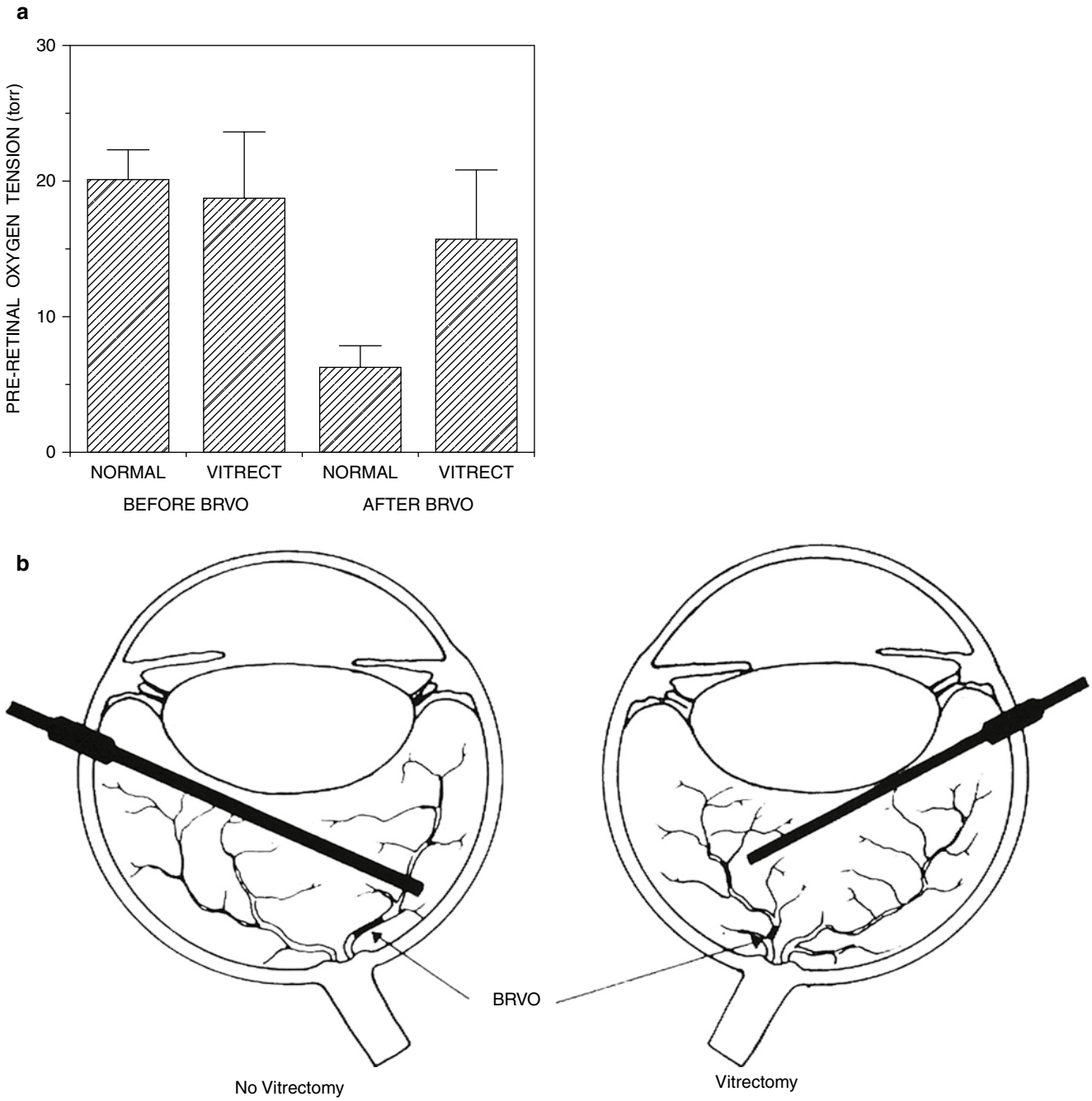

Figure IV.A-4 Stefánsson et al. [20] reported that preretinal oxygen tension falls with branch retinal vein occlusion (*BRVO*) in the intact eye, but vitrectomy prevents retinal hypoxia in this situation. (**a**) Shows the oxygen tension meaurements and figure (**b**) the experimental set-up (Reprinted with permission from IOVS)

compared to the situation in the vitrectomized eye with aqueous humor filling.

In the late 1980s, Stefansson et al. [20] induced bilateral branch retinal vein occlusion (BRVO) in cats, where one eye had vitrectomy and the other eye not. BRVO leads to severe regional hypoxia in the retina in non-vitrectomized eyes, whereas vitrectomy reduces or prevents hypoxia in the ischemic retina (Figure IV.A-4). These studies clearly established the physiological effect of vitreous surgery on increased oxygen transport in the eye (Figure IV.A-5).

Blair and colleagues [21, 22] demonstrated in cats that the retina may be oxygenated from the vitreous body by "vitreoperfusion." Maeda and Tano [23] measured oxygen tension in the human vitreous chamber before and after vitrectomy and concluded that "successful diabetic vitrectomy reduces the activity of the neovascular tissue and equalizes

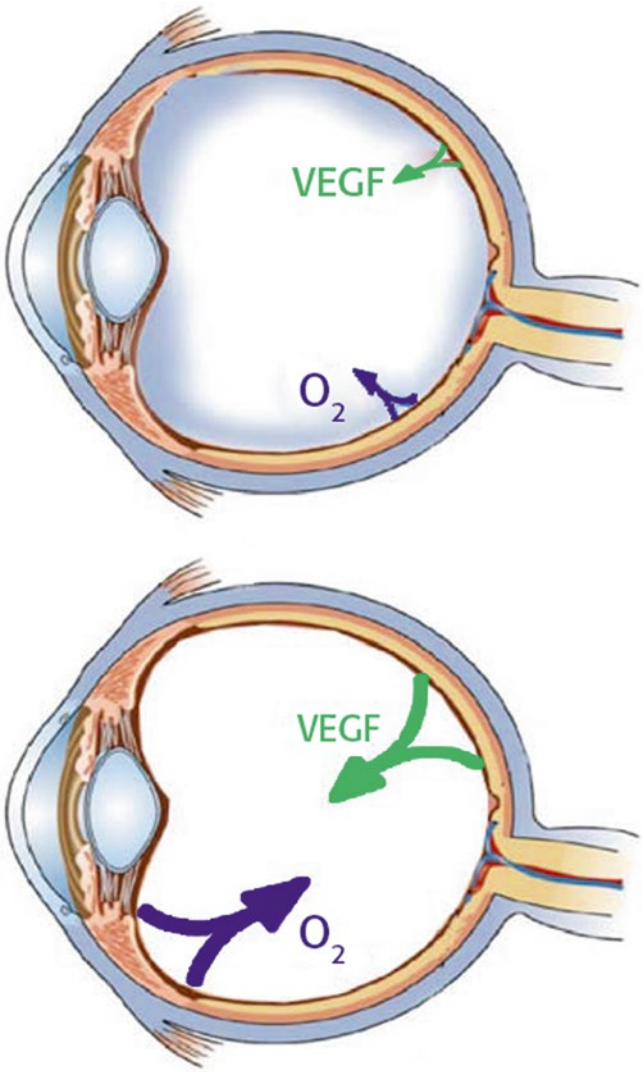

Figure IV.A-5 Schematic drawings showing the diffusion and convection fluxes of oxygen and VEGF (and any molecule) in the intact eye (*top*), vitrectomized eye (*bottom*). The transport of all molecules is relatively slow through the viscous vitreous in the intact eye and much faster when this is replaced with low-viscosity saline or aqueous. In the vitrectomized eye, oxygen diffuses from well-perfused to ischemic retinal areas, thus reducing hypoxia and VEGF production. At the same time, VEGF is cleared away from the retina at a faster rate. Both mechanisms combine to lower VEGF levels in the retina and inhibit neovascularization and edema

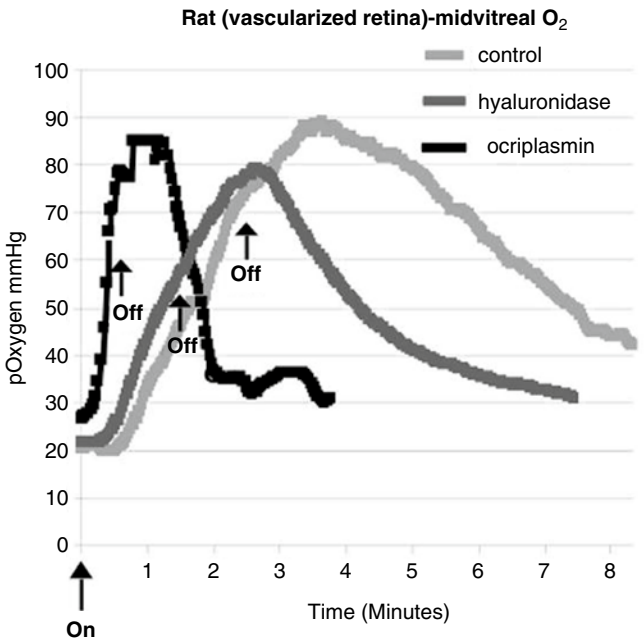

Figure IV.A-6 Comparison of mid-vitreous oxygen levels in control, ocriplasmin-, and hyaluronidase-treated rat eyes over time following exposure to 100 % oxygen. *Arrows* indicate start and stop of 100 % oxygen breathing. Reprinted with permission Quiram et al. [33]

levels of oxygenation in vitreous." Holekamp and Beebe et al. [24] have confirmed in the human eye that vitrectomy facilitates the diffusion of oxygen. In the vitrectomized eye, the oxygen tension gradients are flatter than in the normal eye, and the oxygen flux from the retina to the lens is increased. They have also suggested that oxygen consumption by ascorbic acid in the vitreous gel may play a role in increasing oxygen availability after vitrectomy [25] [see chapter IV.B. Oxygen in vitreo-retinal physiology and pathology]. Several investigators [26–30] have also demonstrated oxygen delivery to the retina through the vitreous body.

Pharmacologic vitreolysis [31, 32] also creates a physiological situation with improved transport of molecules in the vitreous body. Sebag and colleagues [14, 31] demonstrated that ocriplasmin increased the diffusion coefficient of vitreous in a dose-dependent fashion, presumably via breakdown of the macromolecules of the vitreous. Quiram et al [33] showed that pharmacologic vitreolysis speeds oxygen diffusion within the vitreous body (Figure IV.A-6).

More recently, Petropoulos et al. [34] found that oxygen gradients in pig eyes were similar before and after vitrectomy and suggested that diffusion of oxygen was not changed by vitrectomy. They suggested that changes in oxygen transport after vitrectomy were predominantly due to convection currents, which are greater in low-viscosity fluids. Probably, convection currents are much more effective in transport than diffusion. In the completely still eye in an experimental setting, convection may be prevented. In the living mobile eye, convection currents are substantial, influenced by viscosity, and influence molecular transport within the vitreous body.

Simpson et al. [35] used magnetic resonance imaging to measure oxygen tension in the vitreous chamber before and after pars plana vitrectomy (Figure IV.A-7). They confirmed that oxygen tension in the mid-vitreous is significantly higher in vitrectomized eyes than normal. This confirms earlier invasive measurements in animals and humans.

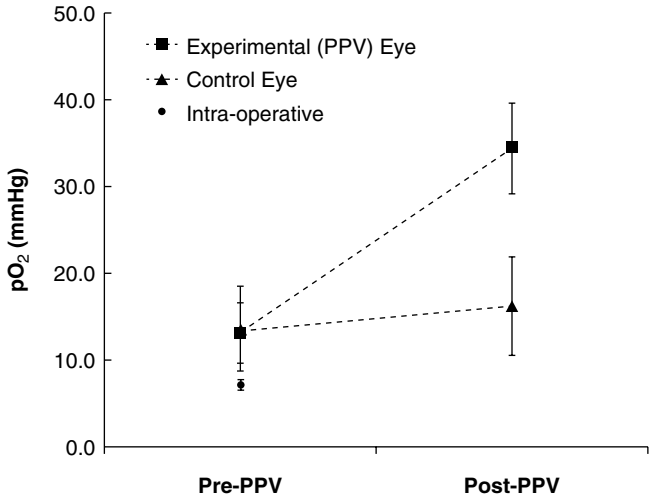

Figure IV.A-7 The effect of pars plana vitrectomy (PPV) on vitreous oxygenation measured with magnetic resonance imaging. Values are mean and error bars are SD. Reprinted with permission Simpson et al. [35]

Sín et al. [36] used noninvasive retinal oximetry (Figure IV.A-8) to measure oxygen saturation in retinal blood vessels before and after vitrectomy. They found higher oxygen saturation in retinal venules after vitrectomy compared to before (Figure IV.A-9). This shows that vitrectomy influences retinal oxygenation.

III. Pathology

When vitrectomy was first introduced, the rationale was entirely structural. Removal of bloody and opaque vitreous was intended solely to restore a clear visual pathway to improve patients' vision, for example, in cases of proliferative diabetic retinopathy. The long-term metabolic consequences came as a surprise – some good, some bad, but all unexpected. The following considers the metabolic effects of aging and various diseases, as well as the metabolic alterations introduced by therapeutic intervention of various types.

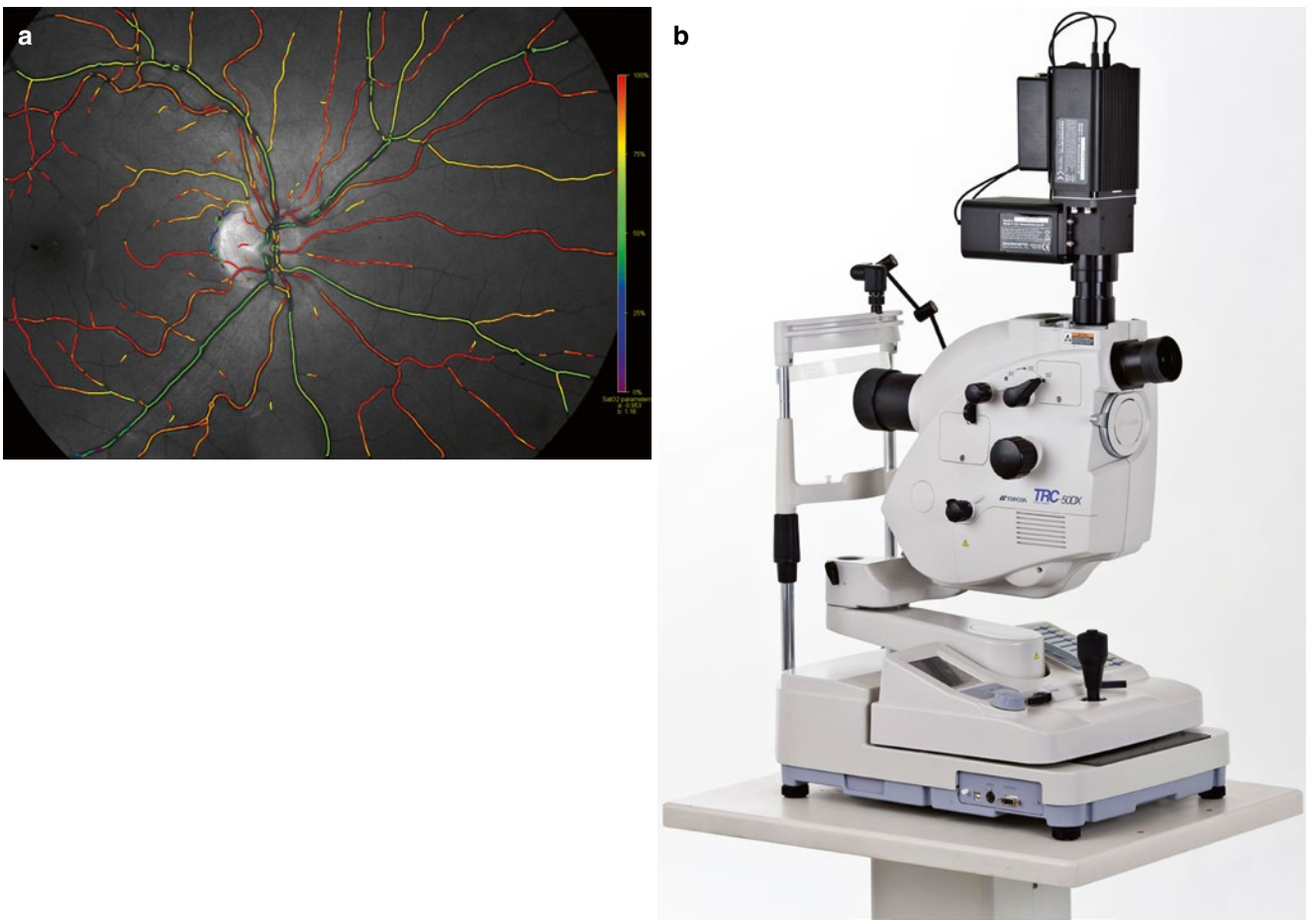

Figure IV.A-8 Pseudocolor retinal oximetry image (**a**) and spectrophotometric retinal oximeter (**b**). The oximetry image shows oxygen saturation in retinal vessels. The pseudocolor scale indicates oxygen saturation; *red* is 100 % saturation and *violet* is 0 %

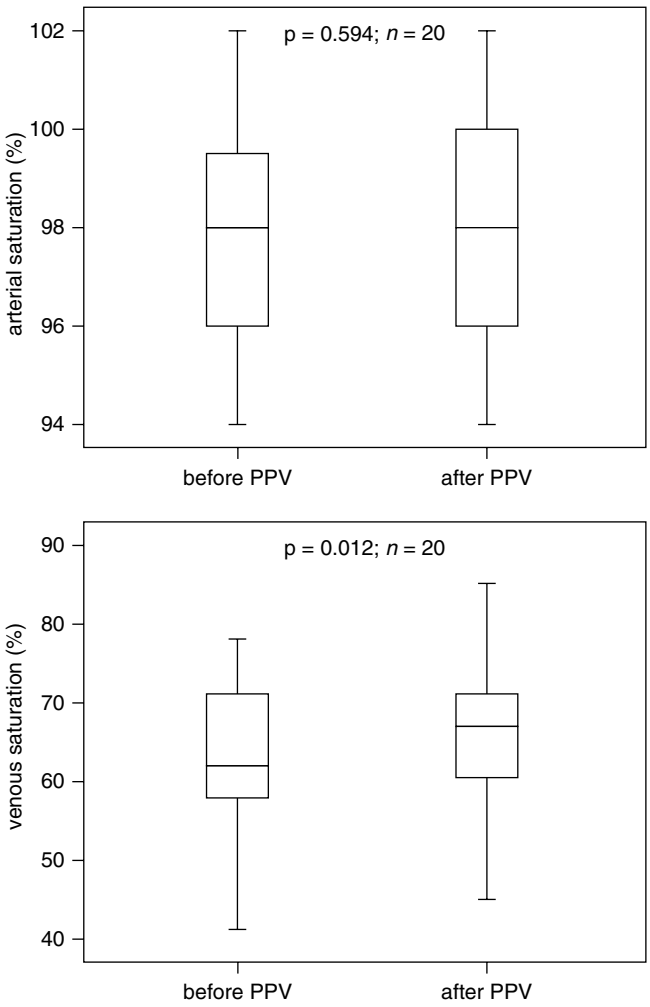

Figure IV.A-9 *Box graphs* comparing average arterial and venous saturation before and 45 days after pars plana vitrectomy (*PPV*) measured by automatic retinal oximetry. The *box* shows the distance between the quartiles, with the median marked as a *line*, and the whiskers show the maximum and the minimum. Paired t-tests were used for statistical analyses. Reprinted with permission Sín et al. [36]

A. Vitreous Aging

Changes in vitreous viscosity often result from natural degeneration [see chapter II.C. Vitreous aging and posterior vitreous detachment]. Sebag describes a *spectrum* from the fully attached, homogenous vitreous gel in a young healthy eye, through the various stages of vitreous liquefaction [37] and posterior vitreous detachment, partially vitrectomized eye, and pharmacologic vitreolysis to the totally vitrectomized eye on the other extreme [38]. Some of the same clinical consequences of vitrectomy may be seen in eyes with age-related vitreous liquefaction and posterior vitreous detachment. The development of posterior vitreous detachment in midlife may indeed reduce the risk of some aging diseases of the retina in older age, including exudative age-related macular degeneration and diabetic retinopathy, while at the same time increase the risk of others, such as peripheral retinal tears and nuclear sclerotic cataract. These changes will be considered for a physiological perspective.

1. Clearance of Molecules in the Vitreous

The principle of increased transport with reduced viscosity of the medium applies to all molecules. It also applies to postoperative conditions following the replacement of the vitreous gel with saline, pharmacologic vitreolysis, and physiological degeneration of the vitreous gel and posterior vitreous detachment. This means that following vitrectomy, vitreolysis, or a posterior vitreous detachment, the transport of all molecules to and from the retina is increased (Figures IV.A-3 and IV.A-5). Molecules that are produced in the retina, such as vascular endothelial growth factor (VEGF), may be cleared into the fluid vitreous chamber at a higher rate following vitrectomy or posterior vitreous detachment. This serves to reduce the VEGF concentration in the retina (Figure IV.A-5) and may be helpful in several diseases. Obviously, the clearance of VEGF and other cytokines helps prevent macular edema and retinal neovascularization in ischemic retinopathies, such as diabetic retinopathy and retinal vein occlusions. The possible role of this phenomenon in age-related macular degeneration and diabetic macular edema will be discussed later. The positive or negative effect of clearance of molecules from the retina into the vitreous chamber following vitrectomy, vitreolysis, or posterior vitreous detachment needs further study in a variety of eye diseases.

Vitreous clearance of VEGF may have the same effect as the presence of VEGF antibodies in the vitreous body. VEGF, which is produced in the retina, diffuses from the retina into the vitreous body. If VEGF is constantly removed through clearance by diffusion, convection, binding with an antibody, or other mechanisms, the removal of VEGF from the retina will increase and the concentration of VEGF in (and under) the retina decrease.

B. Iris Neovascularization

Soon after the invention of vitrectomy, surgeons noticed increased risk of iris neovascularization following vitrectomy in diabetic retinopathy eyes, particularly if the lens had also been removed [39, 40]. In light of the previously described vitreous physiology, this is easy to understand [see chapter IV.C. Vitreous and iris neovascularization]. In the vitrectomized eye, and in particular in the vitrectomized–lensectomized eye, both oxygen and various growth [24] factors/cytokines are transported faster through the vitreous chamber (Figures IV.A-2 and IV.A-3). Oxygen is transported by diffusion and convection from the anterior chamber

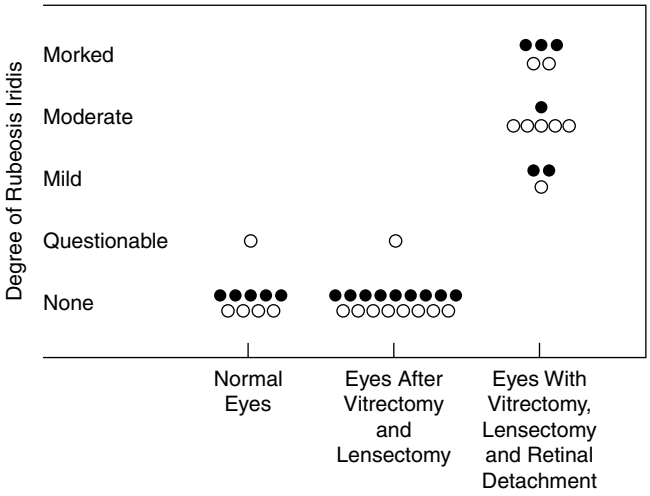

Figure IV.A-10 Vitrectomy, lens extraction, and retinal detachment create iris neovascularization in the cat. *Open circles* denote the clinical diagnosis made at the slit lamp 6–12 months after the onset of the experiments. The histologic diagnosis made by light microscopy of the enucleated eyes 6–12 months after the onset of the experiments is shown in *filled circles*. In both the clinical and histologic evaluation, an arbitrary scale of "no-questionable-mild-moderate-marked" rubeosis iridis was created. Reprinted with permission Stefansson et al. [41]

(where the PO_2 is normally higher than at the retina) to the posterior segment, resulting in anterior segment and iris hypoxia (Figures IV.A-2 and IV.A-3). At the same time, growth factors such as vascular endothelial growth factor (VEGF) are transported faster from the retina to the iris. Anterior segment hypoxia and additional VEGF from the retina will stimulate neovascularization on the iris. Experimentally, iris neovascularization could be induced in healthy cats by removing the vitreous gel and lens and creating a retinal detachment, which makes the retina hypoxic (Figure IV.A-10) [41].

Retinal laser therapy during vitreous surgery helped reduce iris neovascularization, as the photocoagulation reduced retinal hypoxia [42, 17, 43–51] and VEGF production, thus decreasing concentration gradients and transport of both oxygen and VEGF between anterior and posterior segments. Wakabayashi et al. [52] found a strong correlation between neovascular glaucoma and VEGF levels in the vitreous following diabetic vitrectomy. The same was true for vitreous hemorrhages after vitrectomy.

Silicone oil, which is highly viscous and reduces transport of oxygen and growth factors between anterior and posterior segments of the eye, reduces the risk of iris neovascularization in vitrectomized eyes (Figure IV.A-3). In 1986, de Juan et al. [19] showed that silicone oil filling of the vitreous chamber reestablishes a diffusion barrier between the anterior and posterior segments, thus reducing the exchange of oxygen and VEGF. Silicone oil filling also reduces the risk of iris neovascularization following vitrectomy.

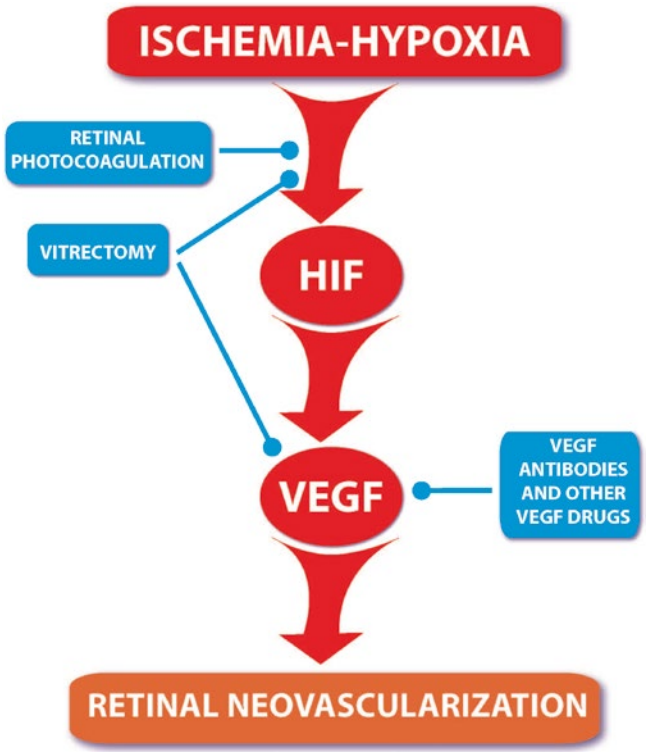

Figure IV.A-11 Vascular endothelial growth factor (*VEGF*) is a major stimulus for retinal neovascularization. VEGF production is controlled by oxygen tension, and therefore retinal photocoagulation, vitrectomy, and oxygen breathing can reduce VEGF production. VEGF can be cleared away from the retina into low-viscosity fluid in the vitrectomized eye or in an eye with posterior vitreous separation. VEGF antibodies in the vitreous gel will also remove VEGF from the solution and similarly clear it away from the retina. Hypoxia-inducible factor (*HIF*) allows the cell to sense hypoxia

C. Retinal Neovascularization

Machemer and Blankenship [53] observed that diabetic patients who underwent successful vitrectomy did not have recurrent retinal neovascularization. This can be explained by the physiological principles stated above. In vitrectomized eyes, oxygen is transported from well-perfused areas to ischemic zones [20, 24] reducing local hypoxia and decreasing VEGF production (Figure IV.A-5). VEGF and other cytokines will be cleared away from the ischemic retina faster than before. Consequently, VEGF levels will be reduced both from reduced production and increased clearance into the vitreous chamber (Figure IV.A-5). Retinal laser photocoagulation helps further by also relieving hypoxia of remaining retinal cells and thus reducing VEGF production [17, 23, 42–51]. The physiological principles provide a rational foundation to combine treatment, as laser treatment and vitrectomy have synergistic and similar effects on the ischemic retina (Figure IV.A-11). Vascular endothelial growth factor (VEGF) is an important (but not the only) stimulus for retinal neovascularization. VEGF production

is primarily controlled by oxygen tension, and therefore retinal photocoagulation, vitrectomy/vitreolysis, and oxygen breathing can reduce VEGF production. VEGF can be cleared away from the retina into low-viscosity fluid in the vitrectomized eye or in an eye with posterior vitreous detachment. VEGF antibodies in the vitreous gel also remove VEGF from the solution and similarly clear it away from the retina (Figure IV.A-11). Recent support for this thesis comes from experimental work in rats by Li et al. [54] who found that pharmacologic vitreolysis increases oxygen concentration in the vitreous and reduces expression of HIF-1α and VEGF, thus alleviating the progression of diabetic retinopathy. Similarly, Lange et al. [55] found hypoxia in mid-vitreous in eyes with proliferative retinopathy, and these eyes also had high levels of several cytokines in the vitreous, including VEGF.

D. Macular Edema

Edema is swelling of soft tissues due to an abnormal accumulation of fluid, i.e., water. Edema may be cytotoxic or vasogenic in origin. In cytotoxic or ischemic edema, the abnormal water accumulation and swelling occurs within cells [56], whereas in vasogenic edema the water accumulates in the interstitial space between cells. While retinal edema may be either cytotoxic or vasogenic, Starling's law applies to the vasogenic edema, which presumably is the most frequent and important form of edema in vascular retinopathies. With abnormal accumulation of water in the retina, the tissue volume increases and the retina thickens. The thickening may be measured with optical coherence tomography (OCT) [57].

1. Origins of Macular Edema

To fully understand the effect of the vitreous on retinal edema, we must understand the pathophysiology of edema, which follows Starling's law [58]. The general law explaining the formation or disappearance of edema in any tissue of the body was formulated in the nineteenth century by Ernest Henry Starling (1866–1927). In 1896, Starling described the transport of fluid between the microcirculation and a tissue, including edema formation: "…there must be a balance between the hydrostatic pressure of the blood in the capillaries and the osmotic attraction of the blood for the surrounding fluids.... and whereas capillary pressure determines transudation, the osmotic pressure of the proteins of the serum determines absorption." In other words, the hydrostatic pressure forcing fluids from the vessel into the tissue must be balanced by the osmotic pressure, generated by the colloidal protein solutions in the capillary, forcing absorption of the fluid from the tissues [59]. The four Starling's forces that govern the transport of water between the vascular compartment and the tissue compartment are:

- Hydrostatic pressure in the capillary (P_c)
- Hydrostatic pressure in the tissue interstitium (P_i)
- Osmotic (oncotic) pressure exerted by plasma proteins in the capillary (Q_c)
- Osmotic pressure exerted by proteins in the interstitial fluid (Q_i)

The balance of these forces allows the calculation of the net driving pressure for filtration:

$$Net\ Driving\ Pressure = (P_c - P_i) - (Q_c - Q_i)$$

The hydrostatic pressure, which originates in the heart, is higher in the vessel than in tissue, and this drives water from the vessel into the tissue. The hydrostatic pressure gradient, ΔP, must be balanced by the osmotic pressure gradient, ΔQ, where osmotic pressure is higher in blood than in interstitial fluid, and this pulls water back into blood vessels. If the hydrostatic pressure gradient and the osmotic pressure gradient are equal, no net transport of water takes place, and edema is neither formed nor resolved. Starling's law is frequently shown in this form as:

$$\Delta P - \Delta Q = 0$$

which describes the steady state of the equal and opposing hydrostatic, ΔP, and osmotic pressure, ΔQ, pressure gradients [59].

Starling's law has been generally accepted in medicine and physiology for more than a century as the fundamental rule governing the formation and disappearance of vasogenic edema in the body. It is reasonable to believe that the ocular tissues follow the same general laws of physiology and physics as the rest of the body, and those who believe otherwise should be burdened with the duty to disprove Starling's law in the eye [8, 60, 61]. According to Starling's law, edema will form if the hydrostatic pressure gradient between the vessel and tissue is increased or the osmotic pressure gradient is decreased. The hydrostatic gradient increases if the blood pressure in the microcirculation rises or the tissue pressure decreases. The osmotic pressure gradient decreases if proteins accumulate in the interstitium to increase the osmotic pressure in the tissue and also if the osmotic pressure in the blood goes down. Osmotic pressure changes in the retina as a result of increased vascular leakage, which allows macromolecules to escape from plasma into tissue interstitial space. VEGF is the main instigator of vascular leakage.

a. Increased Hydrostatic Pressure Gradient

The hydrostatic pressure in the microcirculation, capillaries, and venules is a function of the work of the heart, arterial blood pressure, and resistance and pressure fall in the arterioles. Arterial hypertension tends to increase the hydrostatic

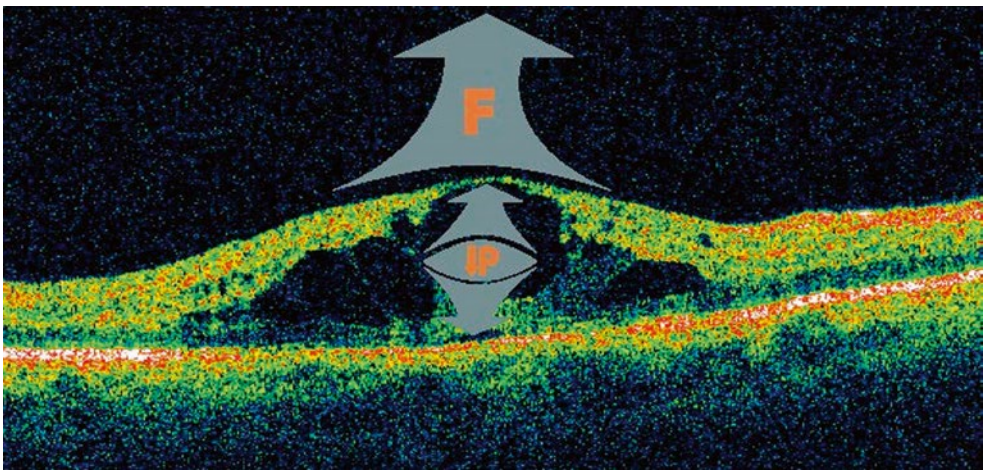

Figure IV.A-12 An axial vitreoretinal traction force (*F*) is indicated with the *large gray arrow*. Inside the retinal tissue, the two *smaller arrows* indicate force and counterforce according to Newton's third law. The counteracting forces result in lowering of the hydrostatic tissue pressure, indicated by *P*. The lowered tissue pressure will increase the pressure gradient between vascular and tissue compartments and stimulate fluid flux from vessel to tissue resulting in edema accumulation according to Starling's law. *F* Force, *P* pressure

pressure in the capillaries and is a well-known risk factor for diabetic macular edema [62, 63]. Diabetic macular edema tends to improve if arterial hypertension is successfully treated [64]. The resistance in the retinal arterioles, and thereby the pressure drop in the arterioles, is a function of the diameter of the arterioles. The resistance to flow is described by the Hagen–Poiseuille law, where the resistance is inversely related to the fourth power of the vessel radius [59]. If the arterioles dilate, as they do in hypoxia, the resistance in the arterioles decreases, and the hydrostatic pressure in the capillary bed rises [8, 17, 65]. This is also seen in diabetic retinopathy, where progressive dilatation of the retinal blood vessels has been observed during the development of diabetic macular edema [41, 66].

The hydrostatic pressure gradient between the vessel and tissue is the difference between the hydrostatic pressure in the microcirculation and the intraocular pressure. In ocular hypotony, where the intraocular pressure is low, the hydrostatic pressure gradient in Starling's law will increase. Ocular hypotony is associated with retinal edema, which may improve if the intraocular pressure increases [67–69]. Hydrostatic pressure in the tissue also decreases if there is vitreous traction on the retina, which decreases the hydrostatic tissue pressure, according to Newton's third law (Figure IV.A-12). Relieving such traction will restore the tissue pressure to normal and decrease the hydrostatic pressure gradient between the vessel and tissue.

b. Decreased Osmotic Pressure Gradient

The traditional example of a decrease in the osmotic pressure in blood is in hypoalbuminemia, which may be seen in nephrotic syndrome or starvation with severe generalized edema. A more frequent cause of decreased osmotic pressure gradients between the vessel and tissue comes from capillary leakage, where plasma proteins leak from the capillaries and venules into the tissue. The accumulation of plasma proteins in the tissue increases the osmotic pressure in the tissue and thereby decreases the osmotic pressure difference between the vessel and the tissue compartment. The reduction of the osmotic pressure gradient reduces water movement from the tissue into the vessel and leads to edema formation [8]. Funatsu et al. [70] demonstrated the close correlation between macular edema and VEGF, which is a potent stimulator of capillary leakage [71]. Retinal edema, such as in diabetic retinopathy and branch retinal vein occlusion, is highly associated with retinal capillary leakage [60, 72, 73]. Fluorescein angiography and fluorophotometry have shown a close association between retinal and macular edema formation and fluorescein leakage, and this has indeed been one of the most frequently used clinical tools to evaluate retinal edema [74–79]. It is the leakage of plasma proteins that matters, due to their effect on osmotic pressure. The leakage of fluorescein itself is naturally not involved in the pathophysiology of edema, and the capillaries are naturally permeable to water. It is important to realize that Starling's law takes into account both the osmotic pressure gradient and the hydrostatic pressure gradient. It is the balance between the two that governs water movement and the formation and disappearance of edema.

2. Diabetic Macular Edema

Vitreous physiology plays a significant role in the development of diabetic macular edema [see chapter III.K. Vitreous in retino-vascular diseases and diabetic macular edema]. Full understanding of the pathophysiology of diabetic macular

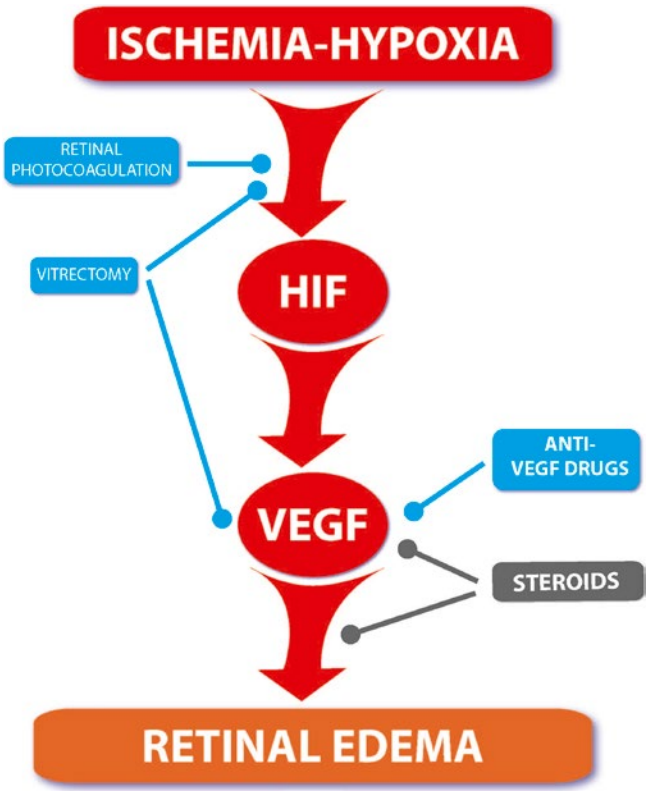

Figure IV.A-13 Ischemia leads to hypoxia. The cells sense hypoxia through hypoxia-inducible factor, HIF. Laser treatment reduces retinal hypoxia (through reduced consumption), and vitrectomy can also improve retinal oxygen supply in hypoxic areas. HIF activation promotes vascular endothelial growth factor (*VEGF*) formation, which increases vascular permeability and induces edema. Vitrectomy and vitreous detachment allows clearance of VEGF away from the retina into the vitreous chamber and VEGF antibodies have essentially the same effect. Corticosteroids reduce VEGF formation and also reduce their permeability effect

edema involves Starling's law, which is discussed above. Nasrallah et al. [80] reported that posterior vitreous adhesion plays a major role in the development of macular edema in diabetic retinopathy. We may deduce that a posterior vitreous detachment tends to prevent diabetic macular edema, in the same fashion as vitrectomy does (Figure IV.A-13). Similarly, Sivaprasad et al. [81] suggested that posterior vitreous detachment plays a role in reducing diabetic macular edema following intravitreal injections.

Lewis et al. [82, 83] were the first to note that vitrectomy is beneficial in diabetic macular edema. Thus they promoted the use of vitrectomy and membrane peeling in cases where vitreoretinal traction contributes to macular edema [see chapter V.A.5. Surgery of diabetic vitreo-retinopathy and diabetic macular edema]. While this issue is still controversial, other experts have since reported that vitrectomy also successfully decreases macular edema in cases where no vitreoretinal traction can be detected [71, 84–89]. Both the physiology of diabetic macular edema with and without vitreoretinal traction are explained by principles described above (Figure IV.A-3). In the vitrectomized eye or eye with posterior vitreous detachment, oxygen is transported from well-perfused areas to ischemic retinal zones to reduce hypoxia and VEGF production (Figures IV.A-4, IV.A-5, IV.A-11, and IV.A-13) [20, 24]. At the same time, VEGF and other cytokines will be transported faster away from the hypoxic area (Figure IV.A-5). Improved oxygenation and reduced VEGF concentration will reduce stimulus for edema formation (Figures IV.A-4, IV.A-11, and IV.A-13).

This works both through the osmotic and hydrodynamic arms of Starling's law [8] [see chapter IV.B. Oxygen in vitreo-retinal physiology and pathology].

Hoerle et al. [90] reported therapeutic effects of vitrectomy on diabetic macular edema in patients with proliferative diabetic retinopathy. Terasaki et al. [91] found improved vision and electroretinographic activity as well as thinning of edematous and thickened retina following vitrectomy in patients with diabetic macular edema. Yamamoto et al. [92] proposed that the creation of a posterior vitreous detachment is critical in order to influence diabetic macular edema through vitreous surgery. In all reports there is structural improvement of macular edema following vitrectomy, but visual improvement is variable and in some cases either minimal or transient [71, 93, 94]. Vitrectomy clearly has effects on retinal edema in diabetes, but in many cases the treatment is instituted late in the disease, and permanent tissue damage prevents visual improvement, even though the retinal thickness and edema per se are reduced (Figure IV.A-13).

Retinal photocoagulation also reduces diabetic macular edema [95] and has to some degree similar physiological effects as vitrectomy. Photocoagulation improves retinal oxygenation [17, 42–51], reduces VEGF production, and constricts retinal arterioles to influence both the osmotic and hydrodynamic arms of Starling's law [72, 96–99].

3. Macular Edema in Retinal Vein Occlusions

Hikichi et al. [100] reported that partial posterior vitreous attachment contributes to edema development in patients with central retinal vein occlusion, while complete posterior vitreous detachment is protective. According to the laws of physics, posterior vitreous detachment should help to prevent macular edema and retinal neovascularization in all vein occlusions. Indeed, similar observation has been made in branch retinal vein occlusion [101], where the incidence of macular edema was significantly higher in eyes with vitreomacular adhesion (93 %) than in eyes with posterior vitreous detachment (41 %, $P = .009$).

Charbonnel et al. [102]) suggested that vitrectomy with posterior vitreous separation and sheathotomy [see chapter V.A.6. Vitreous surgery of arterial and venous retinovascular

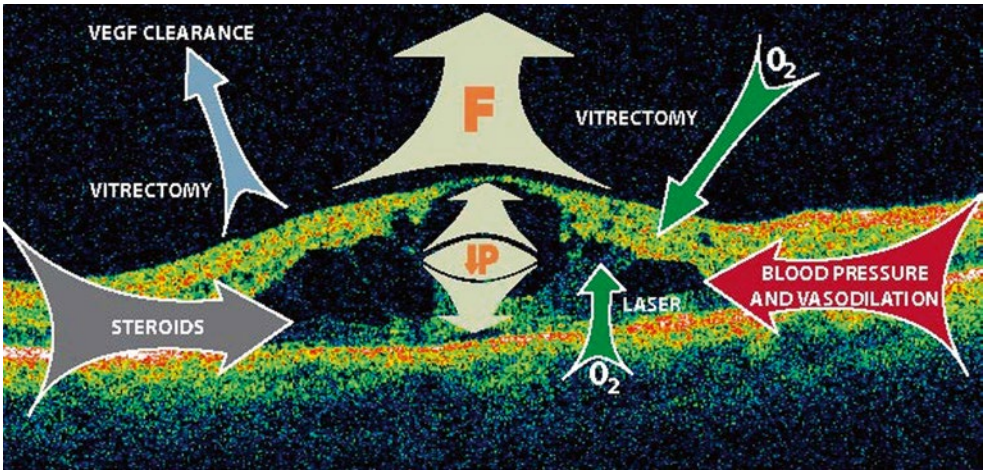

Figure IV.A-14 The figure indicates the several ways macular edema may be treated. Releasing vitreoretinal traction (*F*) will increase the tissue pressure (*P*), reduce the hydrostatic pressure gradient between the vessel and tissue, and reduce edema according to Starling's law. Vitrectomy (or posterior vitreous detachment) will increase oxygen delivery to the retina and reduce hypoxia and VEGF production (*green upper right-hand arrow*). Vitrectomy (or posterior vitreous detachment) will clear VEGF and other cytokines from the retina, due to increased diffusion and convection currents (*blue upper left-hand arrow*). VEGF antibodies in the vitreous would similarly increase VEGF clearance from the retina. Retinal photocoagulation decreases outer retinal oxygen consumption, increases oxygen delivery to the inner retina, and reduces hypoxia and VEGF production (*green lower arrow*). Steroids reduce permeability of retinal blood vessels, reduce leakage of proteins into the tissue, and help restore the osmotic gradient between the blood and tissue, thus reducing edema (*gray left horizontal arrow*). Lowering of arterial blood pressure or constriction of retinal arterioles (oxygen, photocoagulation, vitrectomy) will reduce the hydrostatic pressure in the microcirculation, reduce hydrostatic pressure gradient between the vessel and tissue, and reduce edema according to Starling's law (*red right horizontal arrow*). *F* Force, *P* pressure

diseases] was helpful in reducing macular edema in branch retinal vein occlusion. It may be that the former is the actual therapeutic act as opposed to the sheathotomy. Indeed, Kumagai et al. [103] suggested that the vitrectomy is critical in treatment of branch retinal vein occlusion, and sheathotomy may or may not have an additional effect. Hvarfner and Larsson [104] observed that vitrectomy reduces macular edema in central retinal vein occlusion. All these observations agree with the physiological effect of posterior vitreous detachment in improving oxygen transport and cytokine clearance (Figure IV.A-13).

4. Vitreoretinal Traction and Edema

Vitreoretinal traction has been associated with macular edema in diabetic retinopathy (Figure IV.A-12 and IV.A-14) [84, 83, 82] and following complicated cataract surgery (Irvine–Gass syndrome). Removal of such traction through vitreoretinal surgery has been found to be useful. The effect of traction on retinal edema is understandable in light of Newton's third law [105]: *to any action* (*force*) *there is always an equal and opposite reaction* (*counterforce*). In other words, a force is always met by an equal force, in the opposite direction. The force of vitreoretinal traction will be met by an equal and opposite force in the retina, and these tend to pull the tissue apart. This results in a lowering of the tissue pressure in the retina (Figure IV.A-14). The lowered tissue pressure increases the difference between the hydrostatic pressure in the blood vessels and the tissue and contributes to edema formation according to Starling's law [8, 58]. Releasing the traction will increase tissue pressure and thus lower the hydrostatic pressure gradient and reduce the water flux from blood vessels into retinal tissue and edema formation (see Starling's law above).

5. Treating Macular Edema

It should be obvious from the previous discussion that according to Starling's law retinal edema may be treated either by decreasing the hydrostatic pressure gradient between the vessel and tissue or by increasing/restoring the osmotic pressure gradient between the vessel and tissue (Figure IV.A-13).

a. Decreasing Hydrostatic Pressure Gradient

Treatment of arterial hypertension is a well-established method for treating diabetic macular edema and is certainly beneficial in some cases [64, 106]. Another way to reduce the hydrostatic pressure in the microcirculation is to constrict the arterioles. This may be done simply by breathing oxygen-enriched air, an approach that has been shown to constrict retinal blood vessels and reduce diabetic macular edema [107–110].

Retinal oxygenation may also be improved by scattered laser treatment, which destroys a part of the retina and thereby reduces its oxygen consumption and by vitrectomy [17]. Retinal laser treatment destroys some of the photoreceptors and allows oxygen to diffuse from the choroid through the laser scars into the inner retina, where it increases retinal

oxygen tension [17, 23, 42–47, 49–51, 111–113], and leads to constriction of retinal blood vessels [96–99]. Interestingly, intravitreal bevacizumab [114] and triamcinolone [115] have been reported to constrict retinal blood vessels, suggesting that these drugs may have a hemodynamic effect, in addition to their role of reducing VEGF-induced permeability. This is possibly related to the role of VEGF in inflammation, where the anti-VEGF drugs would decrease inflammation and therefore constrict the retinal blood vessels.

Retinal vein occlusions are an obvious case of elevated hydrostatic pressure, due to the occlusion of the central retinal vein or a branch retinal venule. The high hydrostatic pressure in the venule is obvious from the dilatation and tortuosity, which reflects the increased transmural pressure difference according to the law of Laplace [41, 116–118]. Laser treatment has been shown to reduce the vessel diameter in branch retinal vein occlusion and resolve the macular edema at the same time [96–98]. Presumably this involves a reduction in the intravascular hydrostatic pressure. It may be presumed that other methods to relieve the high intravascular pressure, such as the creation of shunt vessels or resolution of the occlusion, for example, with sheathotomy, would have the same effect [119–123]. [see chapter V.A.6. Vitreous surgery of arterial and venous retinovascular diseases].

Since the hydrostatic pressure gradient is the difference between the blood pressure in the microcirculation and the intraocular pressure, this is increased in ocular hypotony, which may be associated with retinal edema as was previously mentioned [69]. Such edema may be successfully treated simply by raising the intraocular pressure [124]. It is less clear whether intraocular pressure changes have a function when the intraocular pressure is in the normal range and whether the intraocular pressure should be considered in patients with macular edema and normal or high intraocular pressure. Vitreoretinal traction decreases tissue hydrostatic pressure (Figure IV.A-12), as discussed earlier, and increases the hydrostatic pressure difference between blood and tissue compartments. This stimulates water flux from the vessel to tissue and edema formation, and relieving the vitreoretinal traction reduces the water flux and retinal edema.

b. Increasing Osmotic Pressure Gradient

Leaking capillaries and venules in the retina are closely associated with retinal and macular edema [74–76, 78]. Fluorescein leakage has been used for diagnostic purposes in macular edema. The leaky blood vessels presumably leak plasma proteins from the blood into the interstitial tissue compartment, thus decreasing the osmotic pressure gradient between the two compartments. The protein leakage may be influenced by administering drugs that reduce vascular endothelial growth factor, which is one of the most powerful agents known to induce capillary leakage [125, 126].

Reducing hypoxia is a natural way to reduce VEGF production, and this may be achieved through retinal photocoagulation or vitrectomy (Figure IV.A-13). Corticosteroids such as triamcinolone and dexamethasone also stabilize capillaries and tend to reduce capillary leakage [127–130]. These treatment modalities will decrease the leakage of proteins into the interstitial tissue compartment and help to restore the osmotic gradient between blood and tissue compartments. This will resolve edema formation according to Starling's law [131–133] (Figure IV.A-13).

c. The Central Role of Oxygen

Oxygen plays an important role in influencing both the hydrostatic and the osmotic arms of Starling's equation. On one hand, oxygen controls the diameter of retinal arterioles and thereby the hydrostatic pressure in the microcirculation. On the other hand, oxygen is a major regulator of the production of vascular endothelial growth factor and other hypoxia-induced growth factors and exerts influence on capillary leakage. Vascular endothelial growth factor is produced in hypoxia, and oxygen is the natural anti-VEGF factor [134]. Retinal oxygenation may be improved by breathing oxygen. Retinal photocoagulation, as well as vitreous surgery, improves retinal oxygenation [17, 72]. Retinal photocoagulation and vitreous surgery improve oxygenation and thereby influence the hemodynamic consequences of hypoxia, as well as the hypoxia-induced VEGF. If these measures do not correct the hypoxia, it is possible to decrease the effect of the hypoxia with anti-VEGF drugs, and with corticosteroids, which decrease the permeability effect of VEGF. All these actions are easily understood in the light of Starling's law, keeping in mind the hydrodynamic and osmotic arms of the law (Figure IV.A-15) [see chapter IV.B. Oxygen in vitreoretinal physiology and pathology].

E. Age-Related Macular Degeneration (AMD)

Based upon observations made during sub-macular surgery for AMD, Krebs et al. [135] suggested that vitreoretinal adhesion contributes to exudative AMD [see chapter III.G. Vitreous in age-related macular degeneration]. The physiological considerations above suggest a possible mechanism for this effect. VEGF and other cytokines are important in the development of exudative AMD, and the improved clearance of the cytokines following posterior vitreous detachment or vitrectomy would offer protection from the development or persistence of exudative AMD [136] (Figure IV.A-16). Adherent vitreous over the macula does not allow VEGF and other cytokines to be cleared away into the vitreous body (Figures IV.A-14 and IV.A-17).With a posterior vitreous detachment or vitrectomy, the clearance of the cytokines is increased and VEGF load in

Figure IV.A-15 Physiological principles explain the combination of various treatment modalities, including vitrectomy, for diabetic macular edema and edema in other ischemic retinopathies, such as vein occlusions. Starling's law governs the formation of vasogenic edema, based on osmotic and hydrostatic gradients between the microcirculation and tissue. The osmotic gradient is influenced by vascular endothelial growth factor (VEGF), which controls the leakage of osmotically active proteins into the tissue compartment (*blue balloon*). VEGF is controlled by oxygen tension. Laser treatment, vitrectomy, and oxygen breathing can increase retinal oxygen tension and thereby reduce VEGF production (*green arrows*). Vitrectomy and posterior vitreous detachment (*purple*) increase diffusion and convection in the vitreous chamber and increase clearance of VEGF (and other cytokines) from the retina, thus reducing VEGF concentration in the retina. VEGF antibodies in the vitreous also remove VEGF from the retinal surface and decrease VEGF concentration in the retina by clearance (*red arrows*). The permeability effect of VEGF can be reduced by the administration of steroids (*gray bar*). The hydrostatic arm of Starling's law is indicated by the *dark red arrows*. The hydrostatic gradient between the microcirculation and tissue may be reduced through several mechanisms. Releasing vitreoretinal traction will increase the tissue pressure, reduce hydrostatic pressure gradient between the vessel and tissue, and reduce edema according to Starling's law. Treating ocular hypotony by raising intraocular pressure will do the same. Reduction of arterial blood pressure will reduce hydrostatic pressure in the microcirculation and thus reduce the hydrostatic gradient between the vessel and tissue and reduce edema. Finally, improved retinal oxygenation through laser treatment or vitrectomy constricts the retinal arterioles, increases their resistance, and reduces hydrostatic pressure in the microcirculation, thus reducing the hydrostatic gradient between the vessel and tissue and edema

the macula decreased. Oxygenation would also improve and reduce VEGF production. Krebs et al. [135] found a close correlation between vitreoretinal adhesion on OCT and choroidal neovascularization in AMD. It is the experience of many experienced vitreoretinal surgeons that vitrectomized eyes do not as a rule develop exudative AMD. This clinical observation has not been studied systematically and must be taken with some caution. Nonetheless, physiological considerations suggest that such a mechanism may be present. Improved clearance of growth factors from the retina after vitrectomy or posterior vitreous detachment, along with improved oxygenation, might help prevent exudative AMD. Recurrence of neovascularization after macular translocation surgery for exudative AMD [see chapter V.A.1. AMD Surgery] is an exception here, but may be a wound-healing response in severely diseased eyes and not representative of prevention in less advanced AMD. Schulze et al. (2008) reviewed the role of the vitreous in AMD and suggest that "incomplete or

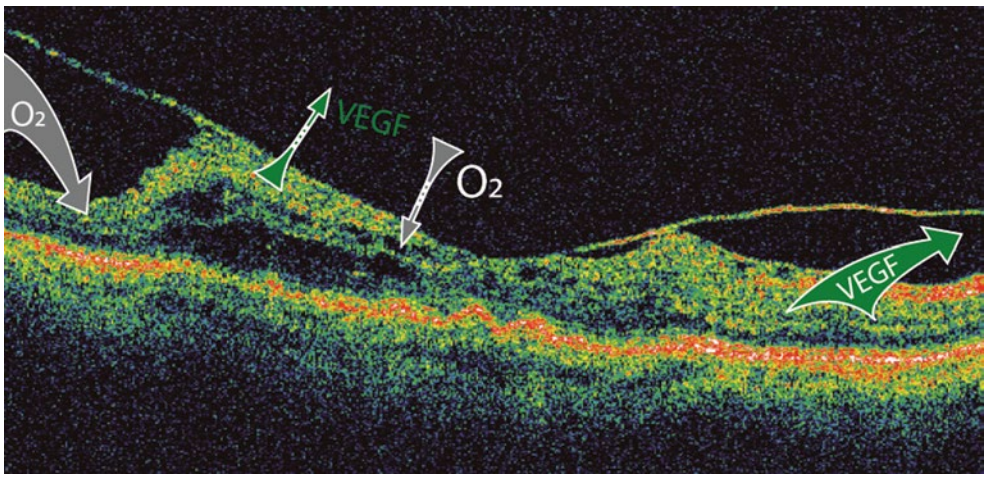

Figure IV.A-16 The schematic drawing on top of an OCT image indicates that where the posterior vitreous cortex is attached, oxygen delivery from the vitreous body is slow and VEGF cannot easily escape. Conversely, where the posterior vitreous cortex is detached, oxygen supply to hypoxic retina is possible, and VEGF and other cytokines may be cleared into the vitreous body

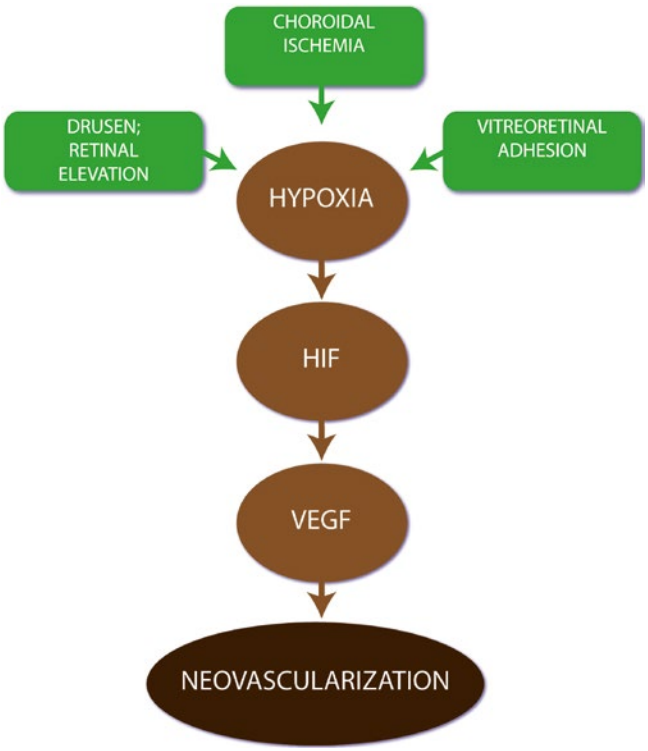

Figure IV.A-17 A schematic drawing showing how choroidal ischemia, drusen, and vitreoretinal adhesion can contribute to retinal hypoxia, resulting in VEGF accumulation and neovascularization (See Stefánsson et al. [136])

anomalous posterior vitreous detachment is suspected to play a crucial role in the pathogenesis of different forms of age-related macular degeneration." They reviewed several studies that have found vitreoretinal adhesion in patients with AMD. Schulze et al. [137] went on to study patients who had unilateral vitrectomy. In 0 of 21 vitrectomized eyes, there were signs of early AMD, while in 5 of 21 non-vitrectomized eyes (24 %), there were AMD-like changes on angiography and slit-lamp examinations.

Some studies [138, 139] found a higher rate of posterior vitreous attachment in patients with AMD, and others [140] found vitreoretinal attachment in 80 % of patients undergoing vitrectomy for subretinal neovascularization in AMD. Schmidt et al. [141] reported a high incidence of vitreoretinal traction in recurrent subretinal neovascularization, suggesting that a complete posterior vitreous separation (or vitrectomy) would be protective in AMD. Schmidt et al. [141] and Meyer and Toth [142] suggested that vitreomacular traction might play a role in the development of pigment epithelial detachments, and Gross-Jendroska et al. [143] reported that pigment epithelial detachments flatten following an intravitreal gas bubble.

In summary, with a posterior vitreous detachment or vitrectomy, the clearance of cytokines from the retina is increased, and the oxygenation of the retina is improved (Figures IV.A-11, IV.A-12, IV.A-13, IV.A-14, and IV.A-15). Both mechanisms will reduce the concentration of VEGF and other cytokines in and under the retina, and this may reduce the development of neovascularization and edema. In addition, traction will reduce tissue pressure in the retina (Figures IV.A-12 and IV.A-14) and possibly also in a pigment epithelial detachment and contribute to edema formation and fluid accumulation. Release of such traction should reduce edema and fluid accumulation, for example, in a pigment epithelial detachment.

F. Vitrectomy and Cataract

The effect of vitreous gel on cataract formation is the subject of much research. Liang et al. [144] reported that vitrectomy may increase the oxygen delivery to the lens in the rabbit. Holekamp et al. [24, 145] have shown in the human eye that the transport of oxygen through the vitreous chamber to the lens is increased after vitrectomy, and the increased oxygen tension of the lens contributes to nuclear sclerosis cataract

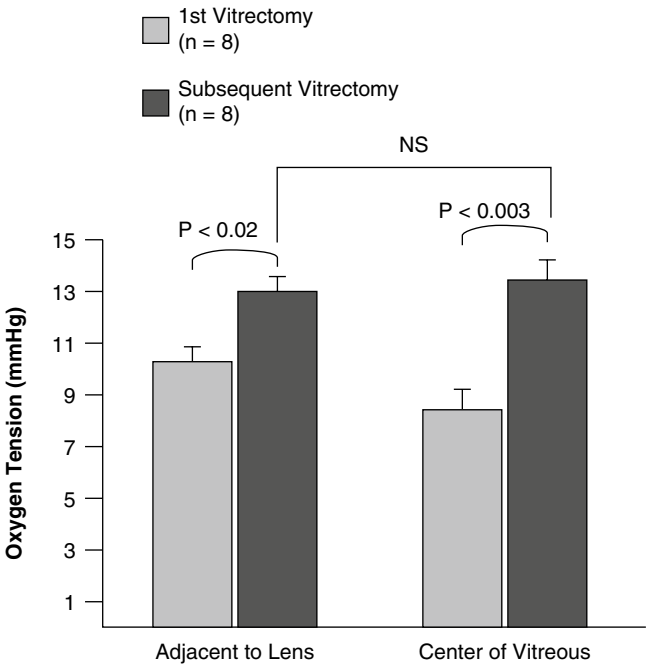

Figure IV.A-18 Oxygen tension measurements made before the first vitrectomy and before the subsequent surgery. Values adjacent to the lens and in the center of the vitreous body were significantly higher in eyes with a previous history of vitrectomy [24]

(Figure IV.A-18). Posterior vitreous detachment also increases pO_2 levels [see chapter IV.B. Oxygen in vitreoretinal physiology and pathology]. Another factor to consider is that the vitreous gel contains antioxidants that act as free radical scavengers mitigating the untoward effects of elevated oxygen levels. Thus, human studies employing minimally invasive vitrectomy without surgical induction of PVD have found a significantly lower incidence of postoperative cataract surgery [see chapter V.B.8. Floaters and vision – current concepts and management paradigms]. This fits perfectly with the physical and physiological principles stated above and confirms the principles previously demonstrated in animal studies (Figures IV.A-2, IV.A-3, IV.A-4, and IV.A-5) [17, 20]. It is likely that the nuclear sclerosis cataract frequently seen following trabeculectomy surgery for glaucoma may be of similar nature [146]. The increased flow rate of aqueous humor following glaucoma filtration surgery is very likely to increase the oxygen delivery to the lens and may contribute to nuclear sclerosis cataract formation [147–153].

G. Vitrectomy and Glaucoma

Studies [154] have suggested that there is an increased risk of open-angle glaucoma after vitrectomy, especially if the crystalline lens has also been removed, presumably via oxidative stress in the trabecular meshwork as the pathogenesis. Koreen et al. [155] observed that 12 % of 285 vitrectomized eyes later developed open-angle glaucoma, and the incidence rose to 15 % in non-phakic eyes. However, these clinical findings have been disputed. Yu et al. [156] followed 441 eyes after vitrectomy for about 7 years and found only 4 % who developed glaucoma and 4 % ocular hypertension, which was not significantly different than the control group (3 % in both categories). Also, they found no effect from lens extraction. In another study, Lalezary al. [157] audited 101 eyes after vitrectomy and did not see increased risk for glaucoma. Vitrectomized eyes may not have increased risks of glaucoma. On the other hand, Siegfried et al. [158] measured oxygen distribution with a fiberoptic probe beneath the central cornea, in the mid-anterior chamber, and in the anterior chamber angle. They found that eyes which had undergone both vitrectomy and previous cataract surgery had increased oxygen tension in the posterior chamber, anterior to the IOL, and in the anterior chamber angle compared with non-vitrectomized eyes. They concluded that vitrectomy and cataract surgery increase oxygen tension in the anterior chamber angle, potentially damaging trabecular meshwork cells. These findings are different from early measurements in cats [17, 43] where oxygen tension was found to be lower in the anterior chamber of cats following vitrectomy and lens extraction (Figure IV.A-2). Thus, the hypothesis, that vitrectomy leads to glaucoma, still enjoys some controversy, both clinically and experimentally. Thus, this question deserves further study, and other molecules that move freely from the retina towards the trabecular meshwork after vitrectomy may be worth exploring.

Abbreviations

AMD	Age-related Macular Degeneration
BRVO	Branch Retinal Vein Occlusion
HIF	Hypoxia inducible factor
OCT	Ocular coherence tomography
Pc	Hydrostatic pressure in the capillary
Pi	Hydrostatic pressure in the tissue interstitium
PO_2	Partial pressure of oxygen
PPV	Pars plana vitrectomy
PVD	Posterior vitreous detachment
Qc	Osmotic (oncotic) pressure exerted by plasma proteins in the capillary
Qi	Osmotic pressure exerted by proteins in the interstitial fluid
VEGF	Vascular endothelial growth factor

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