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REVIEW ARTICLE

Physiology of vitreous surgery

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Abstract Vitreous surgery has various physiological and clinical consequences, both beneficial and harmful. Vitrectomy reduces the risk of retinal neovascularization, while increasing the risk of iris neovascularization, reduces macular edema and stimulates cataract formation. These clinical consequences may be understood with the help of classical laws of physics and physiology. The laws of Fick, Stokes-Einstein and Hagen-Poiseuille state that molecular transport by diffusion or convection is inversely related to the viscosity of the medium. When the vitreous gel is replaced with less viscous saline, the transport of all molecules, including oxygen and cytokines, is facilitated. Oxygen transport to ischemic retinal areas is improved, as is clearance of VEGF and other cytokines from these areas, thus reducing edema and neovascularization. At the same time, oxygen is transported faster down a concentration gradient from the anterior to the posterior segment, while VEGF moves in the opposite direction, making the anterior segment less oxygenated and with more VEGF, stimulating iris neovascularization. Silicone oil is the exception that proves the rule: it is more viscous than vitreous humour, re-establishes the transport barrier to oxygen and VEGF, and reduces the risk for iris neovascularization in the vitrectomized-lentectomized eye. Modern vitreous surgery involves a variety of treatment options in addition to vitrectomy itself, such as photocoagulation, anti-VEGF drugs, intravitreal steroids and release of vitreoretinal traction. A full understanding of these treatment modalities allows sensible combination of treatment options. Retinal photocoagulation has repeatedly been shown to improve retinal oxygenation, as does vitrectomy. Oxygen naturally reduces VEGF production and improves retinal hemodynamics. The VEGF-lowering effect of photocoagulation and vitrectomy can be augmented with anti-VEGF drugs and the permeability effect of VEGF reduced with corticosteroids. Starling's law explains vasogenic edema, which is controlled by osmotic and hydrostatic gradients between vessel and tissue. It explains the effect of VEGF-induced vascular permeability changes on plasma protein leakage and the osmotic gradient between vessel and tissue. At the same time, it takes into account hemodynamic changes that affect the hydrostatic gradient. This includes the influence of arterial blood pressure, and the effect oxygen (laser treatment) has in constricting retinal arterioles, increasing their resistance, and thus reducing the hydrostatic pressure in the microcirculation. Reduced capillary hydrostatic pressure and increased osmotic gradient reduce water fluxes from vessel to tissue and reduce edema. Finally, Newton's third law explains that vitreoretinal traction decreases hydrostatic tissue pressure in the retina, increases the pressure gradient between vessel and tissue, and stimulates water fluxes from vessel into tissue, leading to edema.

Keywords Oxygen · Macular edema · Starling's law · Edema · Water · Laser treatment · Vitrectomy · Vascular endothelial growth factor · Steroids · Viscosity · Diffusion · Convection currents · Fick's law · Stokes-Einstein equation · Newton's third law · Vitreoretinal traction · Silicone oil

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Until about 50 years ago, the vitreous humour was considered by most ophthalmologists as "untouchable" and it was felt that any interference with the vitreous humour would have dire consequences for the eye(1). Unconventional thinkers (2–7) changed this axiom, and soon vitreoretinal surgeons came to think of the vitreous gel almost as an inert substance, which could be freely removed for optical and structural reasons, with no consideration for any other functions of this tissue. Naturally, neither extreme is true.

While the vitreous gel may be safely removed from the eye, vitreous surgery has several long-term physiological and clinical consequences for the eye, which may be either beneficial or detrimental. While various clinical effects have been recognized for decades, and some of the physiological mechanisms were reported in the early 1980s, it is only recently that the eyes of surgeons have opened to the physiological consequences of vitreoretinal surgery.

The aim of this essay is to clarify the physiological consequences of vitreous surgery, some of which may be predicted from classical laws of physics and physiology. Understanding the mechanisms involved in the many aspects of vitreous surgery allows a better rationale in the management of vitreous surgery and its combination with laser and drug injections.

Classical physics

Most of the long-term physiological effects of vitrectomy may be understood in light of the effect it has on transport of molecules within in the vitreous cavity and the eye. Transport of molecules in the vitreous cavity is by two mechanisms only: 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:

$$J = D\frac{dc}{dx}$$

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:

$$D = \frac{R\,T}{6\pi\,\eta\,r\,N}$$

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

$$\mathrm{J} = \pi \mathrm{d}^4 \Delta \mathrm{P} / 8\mathrm{L}\,\eta$$

Both diffusion and convection currents are inversely related to the viscosity of the medium. This is also 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 vitreous humour with substances which 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, including oxygen and other nutrients, growth factors and other cytokines, both beneficial and potentially harmful molecules.

The viscosity of vitreous humour

All vitreous surgeons know by experience that the vitreous gel is more viscous than the balanced salt solution that replaces it or the aqueous humour that presumably fills the vitrectomized eye in the long run. At the same time the silicone oils, with which we sometimes fill the vitreous cavity, have higher viscosity than both vitreous gel and water.

The surgeons' impression is confirmed by chemical studies (9–12). 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 humour. Lee et al. (13) found the viscosity of human vitreous gel to be 300–2,000 cP, while the viscosity of water is 1 cP. Gísladóttir et al. (14) 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. Also, the diffusion of dexamethasone was found to be about five times greater in saline than in vitreous humour. Similarly, Sebag et al. (15) showed that pharmacologic vitreolysis with human recombinant microplasmin increases vitreous diffusion coefficients in vitro. It is reasonable to assume that the vitreolysis reduces the viscosity of the vitreous gel, resulting in increased diffusion coefficients. Silicone oil that is used for vitreoretinal surgery is available in several different viscosities, which are considerably more viscous that vitreous gel (16).

Physiology studies

The first physiological studies of vitreous surgery were published in the early 1980s. Stefánsson, Landers and Wolbarsht (17, 18) performed vitrectomy and lens extraction in cats, and found that the oxygen transport between the anterior and posterior segments of the eye were increased in the vitrectomized–lentectomized eye compared to the intact eye (Fig. 1). Oxygen was transported at a faster rate from the anterior segment, resulting in a significantly lower PO_2 in the aqueous humour, especially if the retina

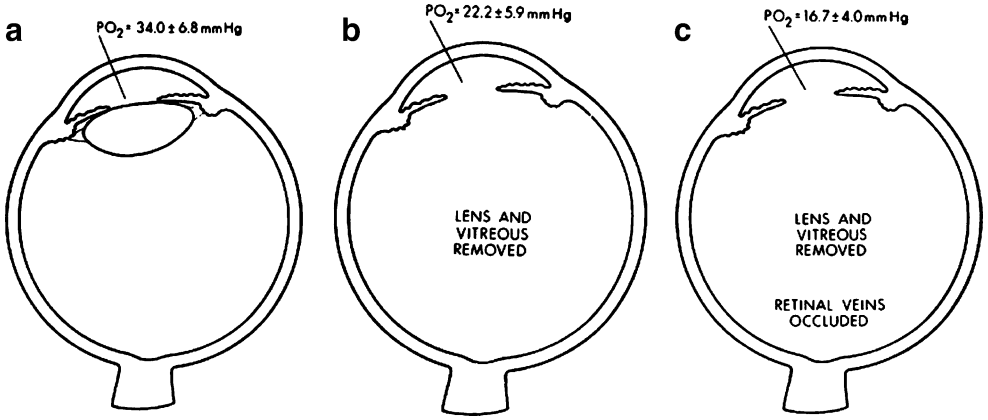

Fig. 1 Stefánsson et al. (1981) reported the oxygen tension in the anterior chamber of cat eyes. The mean anterior chamber oxygen tension in 34 mmHg in the intact eye, 22 mmHg after vitrectomy and lens extraction, which is similar to the normal retinal oxygen tension in cats. The anterior chamber oxygen tension falls to 17 mmHg if the retinal veins are occluded in the vitrectomized, lentectomized eye. Published with permission from The American Ophthalmological Society

was made ischemic and hypoxic with vascular occlusion (Figs. 1, 2).

de Juan et al. (19) showed that silicone oil is the exception that proves the rule. Using silicon oil that is more viscous than vitreous humour, they reported that anterior chamber hypoxia in the vitrectomized-lentectomized cat eye is prevented if the vitreous cavity is filled with silicon oil (Fig. 2). The silicone oil is highly viscous, slows the transport of oxygen and re-establishes a diffusion barrier, compared to the situation in the vitrectomized eye with aqueous humour filling.

In the late 1980s, we induced bilateral branch retinal vein occlusion (BRVO) in cats, where one eye had vitrectomy and the other eye not. BRVO leads to severe retinal hypoxia in the non-vitrectomized eye, whereas vitrectomy prevents hypoxia in the ischemic retina (Figs. 3, 4). These studies clearly established the physiological effect of vitreous surgery on increased oxygen transport in the eye. Blair (20, 21) confirmed in cats that the retina may be oxygenated from the vitreous cavity by "vitreoperfusion". Maeda and Tano (22) measured oxygen tension in the human vitreous cavity before and after vitrectomy, and concluded that "successful diabetic vitrectomy reduces the activity of the neovascular tissue and equalizes levels of oxygenation in the tissue of the vitreous cavity". Holekamp, Beebe et al. (23) have confirmed in the human eye that

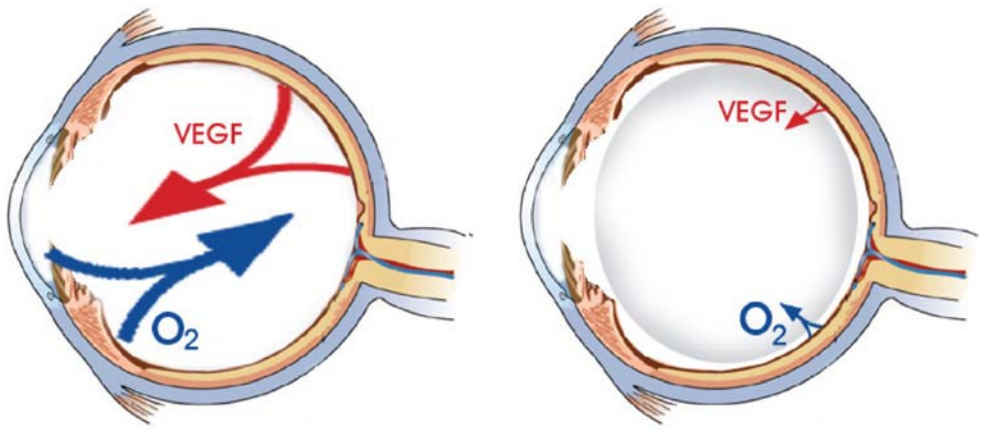

Fig. 2 The schematic drawing shows the theoretical fluxes of oxygen and VEGF (and any molecule) in the vitrectomized, lentectomized eye (*left*) and silicone oil filled vitreous cavity (*right*). The low viscosity of the fluid increases diffusion and convection currents compared with the intact eye. Oxygen will be transported from the anterior segment and well-perfused retinal areas to ischemic retinal areas. VEGF will be 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 vitreous gel, and transport of all molecules is slowed accordingly. It re-establishes the diffusion barrier between the anterior and posterior segments, and reduces the risk of iris neovascularization

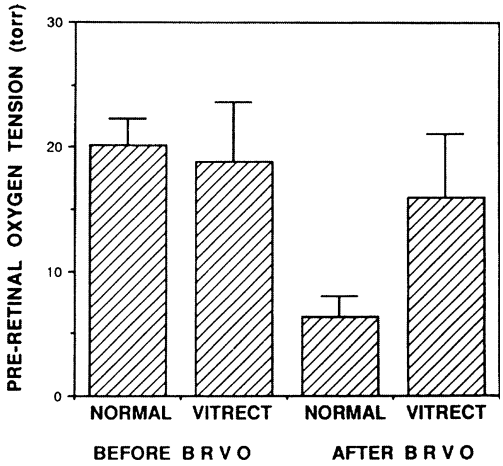

Fig. 3 Stefánsson et al. (1990) reported that pre-retinal oxygen tension falls with branch retinal vein occlusion, BRVO, in the intact eye, but vitrectomy prevents retinal hypoxia in this situation. Published with permission from IOVS

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 (24). Jampol (25) Ben-Nun et al. (26), Wilson et al. (27, 28) and Cringle et al. (29) have also demonstrated oxygen delivery to the retina through the vitreous cavity.

Vitreous liquefaction and posterior vitreous detachment

Presumably, the physiological situation in a vitrectomized eye and an eye with posterior vitreous detachment are related. In all probability, there is a spectrum from the fully attached, homogenous vitreous gel in a young healthy eye, through the various stages of vitreous liquefaction (30) and posterior vitreous detachment, the partially vitrectomized eye, to the totally vitrectomized eye on the other extreme (31).

Some of the clinical consequences of vitrectomy may be seen in eyes with vitreous liquefaction and posterior vitreous detachment. Pharmacologic enzymatic vitreolysis (15, 32–34) may also contribute to a physiological situation with improved transport of molecules in the vitreous cavity. Quiram et al. (35) showed that pharmacologic vitreolysis improves oxygen diffusion within the vitreous cavity.

Clearance in vitreous cavity

The physiological studies have focused on oxygen, but the principle of increased transport following the replacement of vitreous gel with saline includes all molecules. This means that following vitrectomy or a posterior vitreous detachment, the transport of all molecules to and from the retina is increased (Figs. 2, 4). Molecules that are produced in the retina, such as vascular endothelial growth factor, VEGF, may be cleared into the fluid vitreous cavity at a higher rate following vitrectomy or posterior vitreous detachment. This serves to reduce the VEGF concentration (Fig. 4), and may be important in several diseases. Obviously, the clearance of VEGF and other cytokines may help 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 will be discussed later. The positive or negative effect of clearance of molecules from the retina into the vitreous cavity following vitrectomy or posterior vitreous detachment needs further study in a variety of eye diseases.

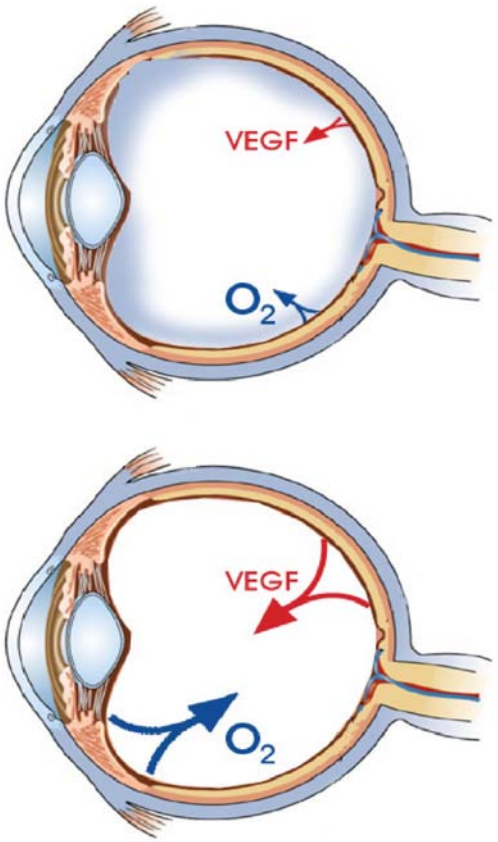

Fig. 4 Schematic drawings showing the diffusion and convection fluxes of oxygen and VEGF (and any molecule) in the intact eye (*top*); vitrectomized eye (*bottom*). The transport of all molecules is relatively slow through the viscous vitreous humor in the intact eye, and much faster when this is replaced with low viscosity saline or aqueous humour. 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

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

The clinical consequences of vitrectomy

The initial rationale for vitrectomy was entirely structural. Removal of bloody and opaque vitreous humour would restore a clear visual pathway and the patients' vision, for example in cases of vitreous hemorrhage. The long-term consequences came as a surprise.

Iris neovascularization

The first unexpected clinical consequence of vitreous surgery was the increased risk of iris neovascularization following vitrectomy in diabetic retinopathy eyes, in particular if the lens had also been removed (36, 37). In light of the previously described physiology this is easy to understand. In the vitrectomzed eye, and in particular in the vitrectomized-lentectomized eye, both oxygen and various growth factors/cytokines will be transported faster through the vitreous cavity (Figs. 1 and 2). Oxygen will be transported by diffusion and convection from the anterior chamber (where the PO_2 is normally higher than at the retina) to the posterior segment, resulting in anterior segment and iris hypoxia (Figs. 1 and 2). At the same time, growth factors such as vascular endothelial growth factor (VEGF) will be transported more readily from the retina to the iris. Anterior segment hypoxia and additional VEGF from the retina will stimulate neovascularisation on the iris. The practice of endophotocoagulation during vitreous surgery helped reduce this threat, as the photocoagulation reduced retinal hypoxia (17, 22, 38–50) and VEGF production, thus decreasing concentration gradients and transport of both oxygen and VEGF between anterior and posterior segments.

Silicone oil, which is highly viscous and reduces transport of oxygen and growth factors between anterior and posterior segments of the eye, is known to reduce the risk of iris neovascularisation in vitrectomized eyes (Fig. 2). de Juan et al. (19) showed that silicone oil filling of the vitreous cavity re-establishes a diffusion barrier between the anterior and posterior segments, thus reducing the exchange of oxygen and VEGF and reducing risk of iris neovascularization.

Retinal neovascularisation

The next clinical observation was a positive one. Two pioneers in vitreous surgery, Blankenship and Machemer, observed that diabetic patients who underwent successful vitrectomy did not have recurrent retinal neovascularization (51). This is also easily understandable in light of the physiological principles stated above. In the vitrectomized eye, oxygen will be transported from well-perfused areas to the ischemic zones (23, 52), relieving the local hypoxia and decreasing VEGF production (Fig. 4). At the same time, VEGF and other cytokines will be cleared away from the ischemic retina faster than before. Thus, VEGF levels will be reduced both from reduced production and increased clearing into the vitreous cavity (Fig. 4). Naturally, laser photocoagulation will contribute to this by also relieving hypoxia of remaining retinal cells and thus reducing VEGF production (8, 17, 22, 38–50)

Understanding the physiological principles makes it possible to combine treatment modalities in a sensible way (Fig. 5). Vascular endothelial growth factor (VEGF) is a major (but not the only) stimulus for retinal neovascularization. VEGF production is controlled by oxygen tension, and therefore retinal photocoagulation, vitrectomy and oxygen breathing can reduce VEGF production (Fig. 5). 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 will also remove VEGF from the solution and similarly clear it away from the retina.

Diabetic macular edema

Nasrallah et al. (53) showed 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. Similarly, Sivaprasad et al. (2008) suggested that posterior vitreous detachment plays a role in reducing diabetic macular edema following intravitreal injections (54).

Lewis et al. (55–57) were the first to note that vitrectomy is beneficial in diabetic macular edema. He emphasized the use of vitrectomy and membrane peeling in cases where vitreo-retinal traction contributed to 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 (58–64). Hoerle et al. (65) reported therapeutic effects of vitrectomy on diabetic macular edema in patients with proliferative diabetic retinopathy. Terasaki et al. (66) found improved vision and electroretinographic activity and thinning of retina

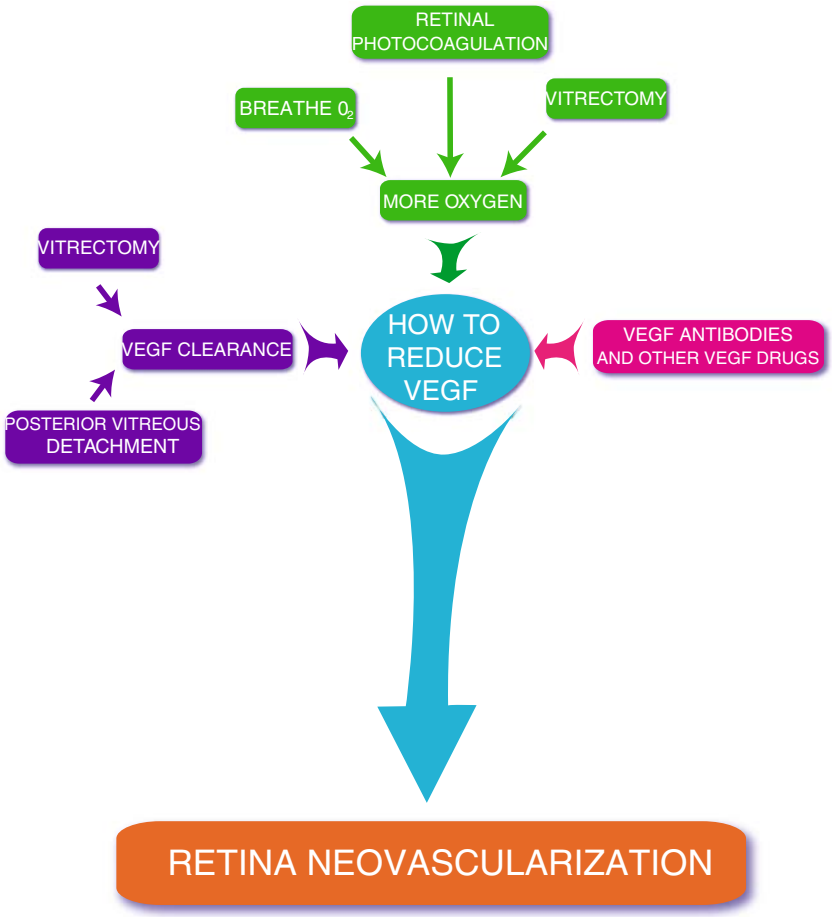

Fig. 5 Vascular endothelial growth factor (VEGF) is a major stimulus for retinal neovascularization. VEGF production is controlled by oxygen tension (*green arrows*), and therefore retinal photocoagulation, vitrectomy and oxygen breathing can reduce VEGF production. VEGF can be cleared away from the retina into low viscosity fluid in the vitrectomized eye or in an eye with posterior vitreous separation (*purple arrows*). VEGF antibodies in the vitreous gel will also remove VEGF from the solution and similarly clear it away from the retina (*red arrow*)

following vitrectomy in patients with diabetic macular edema. Yamamoto et al. (67) 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 (60, 68, 69). The improvement in macular edema following vitrectomy has been reported with and without the presence of vitreoretinal traction (57–64). Both situations are easily understandable in light of the physiological principles above and laws of physics (see "Traction" below and Fig. 6).

In the vitrectomized eye, oxygen will be transported from well-perfused areas to ischemic retinal zones to reduce hypoxia and VEGF production (Fig. 4) (23, 52). At the same time, VEGF and other cytokines will be transported faster away from the hypoxic area (Fig. 4). The improved oxygenation and reduced VEGF concentration will reduce stimulus for edema formation. This works both through the osmotic and hydrodynamic arms of Starling's law, which will be discussed below (47).

Retinal photocoagulation also reduces diabetic macular edema (70). Photocoagulation improves retinal oxygenation (17, 22, 38–50), reduces VEGF production and constricts retinal arterioles to influence both the osmotic and hydrodynamic arms of Starling's law (8, 71–74).

Macular edema in retinal vein occlusions

Hikichi et al. (75) suggested that posterior vitreous attachment contributes to edema develoment in patients with central retinal vein occlusion, and conversely that posterior vitreous detachment helps to prevent macular edema and retinal neovascularization in central retinal vein occlusion. Takahashi et al. (76) made a similar observation in branch retinal vein occlusion, and Charbonnel et al. (77) suggested that vitrecomy with posterior vitreous separation (and sheathotomy) was helpful in reducing macular edema in branch retinal vein occlusion. Kumagai et al. (78) 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 (79) suggested that vitrectomy

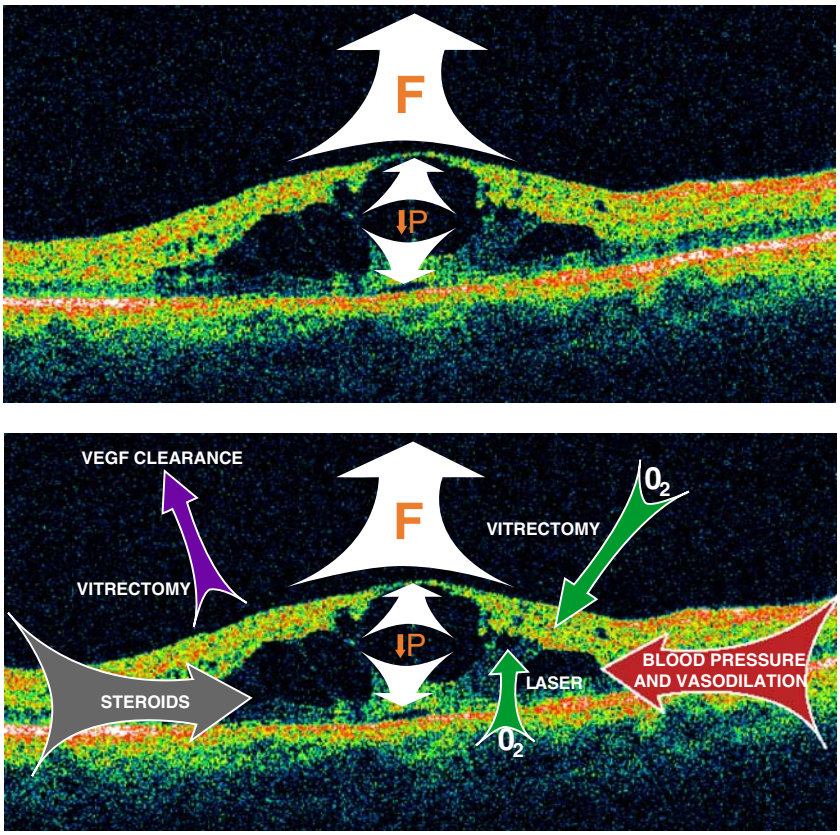

Fig. 6 *Top*: a vitreoretinal traction force is indicated with the *large white arrow*. Inside the retinal tissue, the *two smaller arrows* indicate force and counterforce according to Newton's third law. The counter-acting forces result in lowering of the hydrostatic tissue pressure, indicated by *P*. 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. Bottom: this figure indicates the several ways macular edema may be treated. Releasing vitreoretinal traction will increase the tissue pressure, reduce hydrostatic pressure gradient between vessel and tissue and reduce edema according to Starling's law (*white central arrows*). 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 (*purple upper left-hand arrow*). VEGF antibodies (bevacizumab) in the vitreous cavity 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 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 vessel and tissue and reduce edema according to Starling's law (*red right horizontal arrow*)

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.

Vitreoretinal traction

Vitreoretinal traction has been associated with macular edema in diabetic retinopathy (55–57) and following complicated cataract surgery (Irvine–Gass syndrome), and the removal of such traction through vitreoretinal surgery has been found to be useful. What might be the mechanism through which vitreoretinal traction influences edema formation?

The effect of traction on retinal edema is understandable in light of Newton's third law (80, 81): to any action (force) there is always an opposite and equal reaction (counter-force); 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 (Fig. 6). 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 (47). 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 below).

Starling's law and macular edema

Ernest Henry Starling (1866–1927, Fig. 7) discovered the first hormone, formulated the law of the function of the heart which bears his name, and described the transport of fluid between the microcirculation and a tissue, including edema formation. Starling stated in 1896: "...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 an absorption of the fluid from the tissues (82).

The four Starling's forces that govern the transport of water between the vascular compartment and the tissue compartment are the following:

1. Hydrostatic pressure in the capillary (Pc).
2. Hydrostatic pressure in the tissue interstitium (Pi)
3. Osmotic (oncotic) pressure exerted by plasma proteins in the capillary (Qc).
4. Osmotic pressure exerted by proteins in the interstitial fluid (Qi)

Fig. 7 Ernest Henry Starling (1866–1927). English physician and physiologist

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

$$\text{Net Driving Pressure} = (Pc - Pi) - (Qc - Qi)$$

The hydrostatic pressure, which originates in the heart, is higher in the vessel than in the 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 the osmotic pressure is higher in the blood than in the interstitial fluid, and this pulls water back into the blood vessel. 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

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

describing the steady state of the equal and opposing hydrostatic, ΔP, and osmotic pressure, ΔQ, pressure gradients. (82).

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 (47, 83, 84).

Edema

Edema is the 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 (85), 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 ocular coherent tomography (OCT) (86). At the same time, the specific gravity of the tissue is decreased proportionally with the increased water content (87–90).

What creates edema?

According to Starling's law, edema will form if the hydrostatic pressure gradient between 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 blood goes down.

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 the resistance and pressure fall in the arterioles. Arterial hypertension tends to increase the hydrostatic pressure in the capillaries and is a well-known risk factor for diabetic macular edema (91, 92). Diabetic macular edema tends to improve if arterial hypertension is successfully treated (93, 94).

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 (82). If the arterioles dilate, as they do in hypoxia, the resistance in the arterioles decreases and the hydrostatic pressure in the capillary bed rises (17, 47, 95). 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 (96, 97).

The hydrostatic pressure gradient between 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 (98–100). The hydrostatic pressure in the tissue also decreases if there is vitreal traction on the retina, which decreases the hydrostatic tissue pressure, according to Newton's third law (Fig. 6). Relieving such traction will restore the tissue pressure to normal, and decrease the hydrostatic pressure gradient between the vessel and tissue (55–57).

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 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 tissue into the vessel and leads to edema formation (47). Funatsu et al. (101) demonstrated the close correlation between macular edema and vascular endothelial growth factor, which is a potent stimulator of capillary leakage (102). Retinal edema, such as in diabetic retinopathy and branch retinal vein occlusion, is highly associated with retinal capillary leakage (47, 83, 84, 103). 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 (104–109). It is the leakage of plasma proteins that matters, due to the effect they have 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.

How do we treat 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 vessel and tissue, or by increasing/restoring the osmotic pressure gradient between vessel and tissue (Fig. 8).

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 (93, 110). 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 which has been shown to constrict retinal blood vessels and reduce diabetic macular edema (111–114). Retinal oxygenation may also be improved by scattered laser treatment, which destroys a part of the retina and thereby reduces its oxygen consumption (17, 22, 38–50). 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 improves retinal oxygen tension (17, 38–46, 48–50, 115, 116) and leads to constriction of retinal blood vessels (71–74). Retinal vessel constriction has been shown with oxygen breathing and laser treatment, and the vasoconstriction goes hand in hand with the resolution of

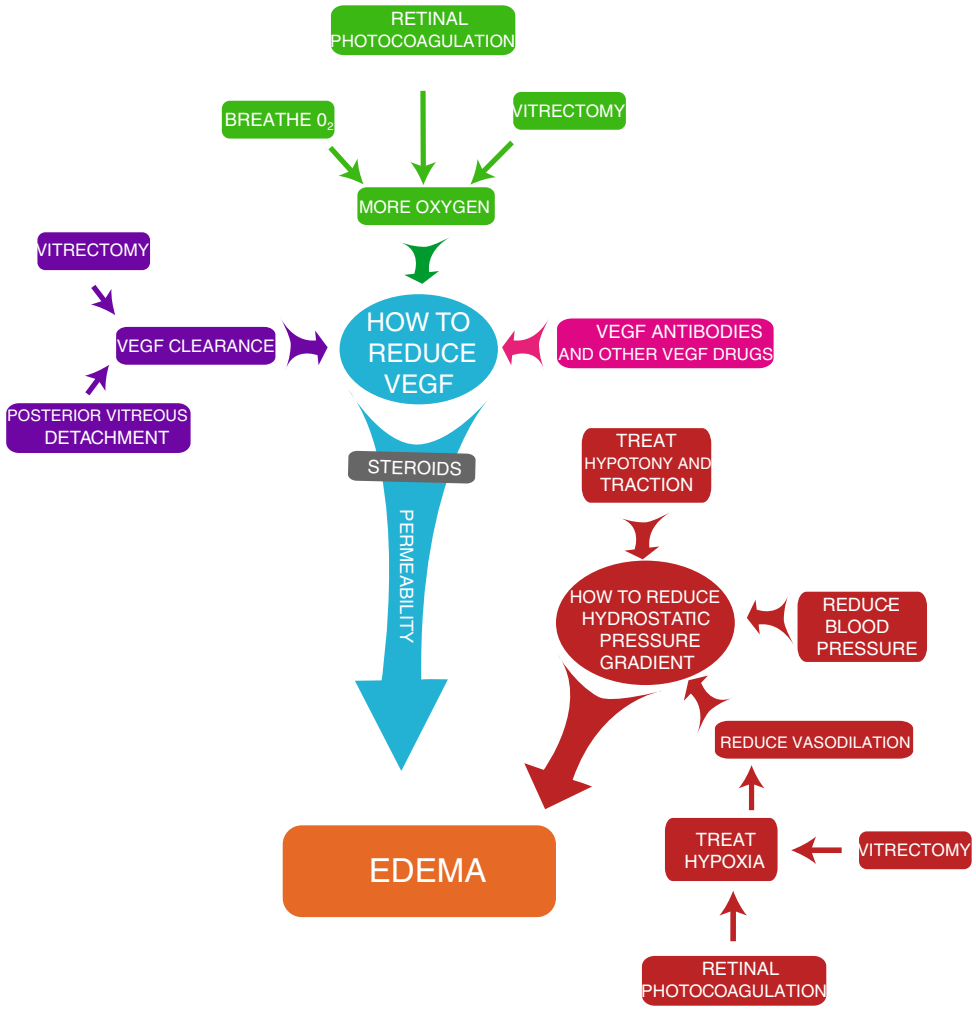

Fig. 8 Physiological principles explain the combination of various treatment modalities for diabetic macular edema and edema in other ischemic retinopathies, such as vein occlusions. Starling's law governs the formation of vasogenic edema, based on osmotic and hydrostatic gradients between microcirculation 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 arrows*) increase diffusion and convection in the vitreous cavity and increase clearance of VEGF (and other cytokines) from the retina, thus reducing VEFG concentration in the retina. VEGF antibodies in the vitreous cavity also remove VEGF from the retinal surface and decrease VEFG concentration in the retina by clearance (*red arrows*). The permeability effect of VEGF can be reduced by the administration of steroids (*grey bar*). The hydrostatic arm of Starling's law is indicated by the *brownish-red arrows*. The hydrostatic gradient between microcirculation and tissue may be reduced through several mechanisms. Releasing vitreoretinal traction will increase the tissue pressure, reduce hydrostatic pressure gradient between vessel and tissue and reduce edema according to Starling's law (see also Fig. 6). 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 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 vessel and tissue and edema

retinal edema, both in diabetic retinopathy and branch retinal vein occlusion (71, 73). Vitrectomy also improves the oxygenation of the retina, as was discussed earlier in this essay.

Interestingly, intravitreal bevacizumab (117) and triamcinolone (118) have been reported to constrict retinal blood vessels, suggesting that these drugs may have a hemodynamic effect, in addition to their main 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 high 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 (97, 119–121). Laser treatment has been shown to reduce the vessel diameter in branch retinal vein occlusion and resolve the macular edema at the same time (71–73). 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 (122–126).

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 (100). Such edema may be successfully treated simply by raising the intraocular pressure (127). 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 (Fig. 6), as discussed earlier, and increases the hydrostatic pressure difference between blood and tissue compartments. This stimulates water flux from vessel to tissue and edema formation and releaving the vitreoretinal traction reduces the water flux and retinal edema.

Increasing osmotic pressure gradient

Leaking capillaries and venules in the retina are closely associated with retinal and macular edema (104–109). Fluorescein leakage has been used for diagnostic purposes in macular edema. The leaky blood vessels presumably leak plasma proteins from 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 (128, 129). Reducing hypoxia is a natural way to reduce VEGF production, and this may be achieved through retinal photocoagulation or vitrectomy. Corticosteroids such as triamcinolone and dexametasone also stabilize capillaries and tend to reduce capillary leakage (130–133). 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 (134–136) (Fig. 8).

The central role of oxygen

Oxygen plays an important role in influencing both the hydrostatic and the osmotic forms 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 (137). At the same time, we should keep in mind that hypoxia is not the only stimulant for VEGF production.

Retinal oxygenation may be improved by breathing oxygen. Retinal photocoagulation, as well as vitreous surgery, improve retinal oxygenation (17, 22, 38–50) as discussed above. The mechanism by which retinal photocoagulation improves retinal oxygenation has recently been reviewed (47, 95) and the reader is referred to these review papers as well as reports from a number of laboratories (17, 38–46, 48–50). 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 (Fig. 8).

Age-related macular degeneration (AMD)

Krebs et al. (138) have recently suggested that vitreoretinal adhesion contributes to exudative AMD. The physiological considerations above suggest a possible mechanism for this effect. The presence of adherent vitreous over the macula will not allow VEGF and other cytokines to be cleared away into the vitreous cavity. Following a posterior vitreous detachment or vitrectomy, the clearance of the cytokines will be vastly increased and the VEGF load in the macular area be decreased. The oxygenation may also improve, and this would reduce the VEGF production. It is reasonable to presume that VEGF and other cytokines may be important in the development of exudative AMD, and the improved clearance of the cytokines following posterior vitreous detachment or vitrectomy would offer some protection from the development of exudative AMD.

It is the experience of several 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. However, the physiological principles suggest that

such a mechanism may be present. Improved clearance of growth factors from the macular area after vitrectomy or posterior vitreous detachment, along with improved oxygenation, might help prevent exudative AMD. The recurrence of neovascularization after retinal rotation surgery for exudative AMD 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. (1) reviewed the role of the vitreous in AMD and suggest that "incomplete or anomalous posterior vitreous detachment is suspected to play a crucial role in the pathogenesis of different forms of age-related macular degeneration." They review several studies that have show vitreoretinal adhesion in patients with AMD. Weber-Krause and Eckardt (139) showed a higher rate of posterior vitreous attachment in patients with AMD, and Ondes et al. (140) and Hayreh and Jonas (141) reported similar findings. Lambert et al. (142) found vitreoretinal attachment in 80% of patients undergoing vitrectomy for subretinal neovascularization in AMD. Schmidt et al. (143) 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. Meyer and Toth (144) suggested that vitreomacular traction might play a role in the development of pigment epithelial detachments, and Gross-Jendroska et al. (145) reported that pigment epithelial detachments flatten following an intravitreal gas bubble.

In the light of the previous discussion about vitreous physiology, it is reasonable to speculate that with a posterior vitreous detachment or vitrectomy, the clearance of cytokines from the retina will be increased and the oxygenation of the retina improved. Both mechanisms will reduce the concentration of VEGF and other cytokines in and under the retina, and this may hinder the development of neovascularization and edema. In addition, traction will reduce tissue pressure in the retina 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.

Cataract

Liang et al. (146) reported that vitrectomy may increase the oxygen delivery to the lens in the rabbit. Holekamp et al. (23, 147) have shown in the human eye that the transport of oxygen through the vitreous cavity to the lens in increased after vitrectomy, and propose that the increased oxygen tension of the lens contributes to nuclear sclerosis cataract. This fits perfectly with the physical and physiological principles stated above, and confirms the principles previously demonstrated in animal studies (20, 52).

It is likely that the nuclear sclerosis cataract frequently seen following trabeculectomies for glaucoma may be of similar nature. The increased flow rate of aqueous humour following glaucoma filtration surgery in very likely to increase the oxygen delivery to the lens, and may contribute to nuclear sclerosis cataract formation (148–154).

Glaucoma

Chang observed that there is an increased risk of open-angle glaucoma after vitrectomy, especially if the crystalline lens has also been removed. He suggested that oxidative stress in the trabecular meshwork may have a role in the pathogenesis (155). However, the oxygen tension in the anterior chamber has been shown to decrease, not increase, following vitrectomy and lens extraction (Fig. 1) (17, 18). The reason for this is that the oxygen tension is normally higher in the aqueous humour than in the retina and vitreous cavity. When the vitreous gel and lens are removed and oxygen moves freely throughout the one-chamber eye, the oxygen tension is reduced to the normal level of the retina, which in the cat is about 20 mmHg compared to 34 mmHg in the normal anterior chamber (Fig. 1) (17, 18). Helbig et al. (156, 157), Sakaue et al. (158) and Wilson et al. (159) reported comparable findings in the human eye. The oxidative stress hypothesis may be doubtful as the mechanism of glaucoma development following vitrectomy, but other molecules that move freely from the retina towards the trabecular meshwork may be worth considering to explain this phenomenon (155).

Conclusion

The vitreous humour regulates the transport of molecules within the vitreous cavity. This transport will increase when the vitreous gel liquifies with advancing age, with a posterior vitreous detachment and vitrectomy. The change in transport patterns will involve all molecules that dissolve in the vitreous cavity fluids. Some molecules will be cleared away from the retina and others will be transported to distant sites, such as the lens or distant parts of the retina. The physiological effects may be variable. Ischemic retinal areas may benefit from the added supply of oxygen, while the lens suffers from the same. Ischemic tissue may benefit from VEGF clearance, while other tissues may lose necessary molecules, that are cleared away by low viscosity fluid in the vitreous cavity. Is it possible that some of the degenerative diseases in the posterior segment of the eye, that start after middle age, may be due to vitreous liquifaction and separation, leading either to harmful loss

of molecules from some tissues or harmful abundance in other tissues?

While this paper presents a general theory for the physiologic and pharmacologic processes in vitreous surgery, retinal laser treatment and drug treatment, it leaves out some important aspects. Inflammation, wound healing and perhaps other processes also play a role, and their influence can hopefully be added to the physiological theory.

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