

Review

# Etiopathogenesis of Macular Diseases in Terms of Glymphatic Fluid Circulation

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**Abstract:** This article is an analysis of theoretical aspects of etiopathogenesis of the macular zone of the eye in terms of glymphatic circulation of tissue fluid. To date, a lot of data has been accumulated on functional and structural changes of the macular zone in normal and in various pathologies. The genesis of macular edema along with subretinal and choroidal neovascularisation could be highlighted and understood from a different point of view if assuming the presence of the glymphatic para- and perivascular fluid flow within the retina, channels in the vitreous body and the choroid. Clinical features of the various eye diseases including hereditary, highlight the paravascular glymphatic outflow routes. As a result of the data analysis, a new theory of disease development in the macular region has been developed for the first time, which explains the pathogenetic mechanisms of occurrence and progression of macular pathology based on the principles of glymphatic current.

**Keywords:** pseudophakic cystoid macular oedema, macular hole, Irvine-Gass syndrome, glymphatic intra-ocular fluid, transient macular oedema, age-related macular degeneration, serous retinal detachment

## 1. Introduction

The etiopathogenesis of Irwin-Gass syndrome or pseudophakic cystic macular oedema (CMO) is not completely clear. It is generally believed that seepage from parafoveal capillaries, which is recorded on fluorescent angiography (FA), leads to the formation of intraretinal cysts mainly in the outer nuclear layer. But macular oedema, observed in such hereditary diseases as X-linked retinoschisis, retinitis pigmentosa and Goldman-Favre syndrome, as a rule, manifests itself without seepage according to FA data [1]. The same absence of dye leakage from the parafoveal capillaries is observed in maculopathy on the background of hypotension [2] and in drug-induced oedema from the action of nicotinic acid [3], drugs of the taxane group [4] and cefuroxime [5]. However, it should be noted that in hereditary degenerative diseases, the pattern of percolation in FA in the macular zone is similar to that observed in aphakia and posterior uveitis [6]. Despite a big step forward in the treatment of wet age-related macular degeneration due to anti-VEGF drugs, there are still unresolved issues concerning the etiopathogenesis of age-related macular degeneration (AMD), relapses of neovascularization and the so-called accumulation of intraretinal fluid [7,8]. There is also no single concept of etiopathogenesis of macular ruptures to date. Glymphatic pathways of fluid circulation in the posterior segment of the eye can answer many questions related to these conditions. Aim of this study is to highlight the macular disorders in terms of glymphatic fluid flow and to generate new theoretical concept of macular diseases.

2. **Methods:** literature review and analysis.

3. **Results**

3.1 **Glymphatic circulation pathways in the eye**



Lymphatic outflow is provided mainly by the conjunctival collectors [9] with the participation of the so-called uveolymphatic pathway [10,11]. At the end of the 20th century, a consensus was reached according to which the vitreous body, the interstitium between the glial cells of the optic nerve, the soft meninges between the septa of the optic nerve, the perivascular spaces and the subarachnoid space of the optic nerve, all together constitute a single pre-lymphatic space [12]. Perivascular channels in the adventitia of cerebral vessels (Virchow-Robin spaces) were described in 1859. In 2012, Iliff and colleagues "rediscovered" these spaces in the form of a single network of interconnected paravascular spaces of arteries and veins that circulate interstitial fluid with the excretion of metabolic products along the processes of astrocytes [13]. So, a new point of view on the exchange of interstitial fluid in the brain arose due to the so-called glymphatic system, which provides fluid exchange between paravascular spaces, nervous tissue and subarachnoid space with the participation of circadian rhythm and pulse wave [13-15]. It has been experimentally shown that the glymphatic outflow pathways of the eye include the vitreous body, the paravascular spaces of the retinal vessels and the suprachoroidal space [16]. Wang and co-authors (2020) proved that in mice with experimental glaucoma, fluid from the vitreal cavity enters directly into the interaxonal space of the optic nerve and moves centripetally, whereas in healthy mice, fluid is absorbed into the paravenous spaces of the retina, from where it flows along the axons of ganglion and amacrine cells along the gradient of hydrostatic pressure and is absorbed into the venous capillaries of the optic nerve membranes [16]. It is important to note that the interaxonal current in the optic nerve in rodents practically stopped when atropine and pilocarpine were instilled and was more pronounced in the light than in the dark [16]. Clinical ophthalmologists have suggested that interstitial glymphatic current in the thickness of the retina is involved in the pathogenesis of microcystic maculopathy at the level of the inner nuclear layer with the participation of Muller cells [17], as well as in the pathogenesis of paravascular posterior uveitis [18,19].

Clinical manifestations of diabetic maculopathy and retinopathy involving the vitreous body also confirm the great importance of glymphatic intraocular fluid circulation in their pathogenesis. We assumed that the fluid normally enters the premacular bag from the anterior segment of the eye through the central channel and is absorbed along the pressure gradient into the thickness of the retina in the fovea along with tissue fluid secreted by the macular choriocapillary lobule [20]. Further, this fluid flows in the thickness of the glymphatic spaces of the inner layers of the retina, where only the superficial and intermediate vascular networks are surrounded by perivascular astrocytes. The deep vascular plexus is surrounded only by the processes of Muller cells, therefore, excess tissue fluid from the outer layers of the retina is normally excreted through the retinal pigment epithelium (RPE), and with its excess into the vitreous body and into the glymphatic spaces of the inner layers of the retina and into the venous collection of the optic nerve sheaths, as was shown by experiment on rodents [16]. Venules predominate in the capillary network of the optic nerve disc, and there are also many astrocytes in this zone, which suggests the function of glymphatic outflow of tissue fluid in the optic cup area.

### 3.2 Pseudophakic CMO

The frequency of pseudophakic CMO is from 1 to 10%, which is similar to the frequency of transient macular oedema in the early stages after cataract surgery due to the toxic effect of cefuroxime 3.5% [21]. It is assumed that the etiology of the first one is associated with inflammatory factors and an imbalance between the rate of capillary filtration and the rate of fluid outflow from the retina through the perivascular interstitium. The second one is associated with dysfunction of the RPE proton pump and retention of the outflow of tissue fluid between the outer layers of the retina and choriocapillaries (see Fig.1).

It is likely that pseudophakic CMO and central serous chorioretinopathy or detachment (SRD) have common etiopathogenetic pathways of disorder of the water transport function of RPE [22-24]. A defect in the RPE was found between the optic disc and the macula in the FA in a patient with transient macular oedema from cefuroxime, while the authors noted the similarity of the OCT picture of the condition they described with Vogt-Koyanagi-Harada syndrome [5]. It is interesting to note that neovascularization in Vogt-Koyanagi-Harada syndrome is most often located in this zone – juxta-papillary between the optic disc margin and macula, where the perforant artery penetrates into the thickness of the retina.





Figure 1. OCT picture of acute transient oedema after cataract surgery.

In pseudophakic CMO, anatomical and functional recovery is possible in 80% of cases, but in chronic CMO, in addition to cavities in the outer retina, histologically observed: perivascular infiltration by inflammatory cells, Muller cell oedema, mitochondrial oedema in the pre-laminar axons of ganglion cells, astrocyte degeneration and occlusion of surface capillaries of the retina [25,26]. The hydrostatic pressure gradient over the fovea is 3 times higher than over the optic nerve disc [20], which provides a flow of tissue fluid along papillomacular bundle into the lymphatic spaces of the optic nerve in addition to the difference in osmotic pressure of this fluid between the fovea region and the periphery of the retina. This may explain the pathogenesis of pseudophakic CMO and the observed histological changes. The largest and thickest choriocapillary lobule is located under the macula, the RPE cells are the widest and tallest here, and the elastic sieve-like layer of the Bruch membrane is the thinnest here [27].

In pseudophakic CMO, glymphatic flow in the macula probably fails because of weakened fluid flow through the central channel into the premacular sac and increased fluid secretion from the choriocapillaries or because of retention of its outflow towards the choroid. As a result, fluid accumulates in the outer retina. It does not have time to be transported by Muller cells into the vitreous body due to the presence of an ionic gradient limit and accumulates around retinal vessels for outflow through perivascular glymphatic spaces. The opening of the endothelium of retinal capillaries is probably compensatory and adaptive in order to improve the outflow of accumulated tissue fluid in the outer retina. With normalization of the functioning of the proton pump, the described imbalance of flow of tissue fluid from the choriocapillaries is restored. This is confirmed by the positive effect of carboanhydrase inhibitors in the course of cystic CMO. Muller cells, forming a framework in the foveolar zone, contain receptors for carboanhydrase inhibitors on their membrane, regulate the composition of extracellular fluid due to voltage-dependent ion channels, and also due to the presence of glutamate and GABA receptors, regulate depolarization of neurons and intracellular calcium levels [28].

Thus, we assume that it is the activation of the perivascular lymphatic outflow of fluid that causes the appearance of a cystic pattern and the leakage of the dye during FA. Only in this case there is an outflow of tissue fluid into the perivascular space and further into the paracellular spaces of the optic nerve. That is why diffuse macular oedema in uveitis is a poor prognostic sign, because there is no activation of the outflow of interstitial fluid. It which accumulates excessively in the thickness of the retina due to RPE dysfunction. The absence of normal tissue metabolism leads to the death of retinal neurons, followed by a decrease in central vision.

The lens contains melanopsin [29], a protein that is also expressed in the macular retina on specialized melanopsin-containing ganglion cells involved in the regulation of circadian rhythm through the suprachiasmatic nucleus and epiphysis. Also, in the thickness of the retina in the outer nuclear and ganglion layers, MT1 melatonin receptors are expressed [30]. The absence of which leads in mice to an increase in intraocular tone by 5 mmHg at night and to the death of up to 30%



of ganglion cells with age [31]. The protein dystrophin, also expressed in the macular zone and in the thickness of the lens, also affects the intraocular pressure. The absence of this gene in mice leads to a decrease in intraocular tone and is also associated with Alzheimer's disease. It is known that the transmembrane protein BEST 1 belongs to the family of calcium-activated anion channels regulating transepithelial transport of chlorides, is associated with the  $\beta$ -subunit of  $\text{Ca}^{2+}$  channels and is located on the basolateral membrane of the RPE [32].

Thus, there is a circulation of tissue and intra-ocular fluid (IOF) in the thickness of the retina, the optic nerve and the central channel of the vitreous body. At the same time, at night, there is an outflow of tissue fluid in the thickness of the retina from the macular zone towards the optic nerve along a pressure gradient, probably mainly in the thickness of the ganglion nerve fibre layer. This glymphatic outflow, which occurs only at night, depends on pressure gradients, head position, pulse pressure and the coordinated functioning of aquaporin-4 and G-protein receptors in the glial spaces of the retina. In the brain, for example, perivascular glymphatic spaces expand at night in order to increase the inflow of cerebrospinal fluid, followed by outflow together with tissue glymphatic fluid [33]. It has been established in rodents that aquaporin-4 on Muller cells and astrocytes is highly expressed, mainly along the border between the inner limiting membrane (ILM) and vitreous body. In the process, networks in the inner and outer plexiform layers opposite the capillary networks and is less expressed on fibrous astrocytes of the optic nerve and its soft sheaths [34].

The relationship between cataract surgery and macular pathology has been noticed for a long time. It was found that in the early stages (maximum values after 1 month) after uncomplicated cataract surgery, there is a thickening of the ganglion cell complex-the inner plexiform layer [35]. CMO in patients with ophthalmohypertension in the background of prostaglandin intake can occur on the arthphakic eye even 9 months after cataract surgery [36] and even 24 months later [37], as well as against the background of drug withdrawal in refractory operated glaucoma [38]. I.e., in some circumstances, there is a direct relationship between the values of IOP and the thickness of the retina in the macular area. We also observed appearance of CMO in several clinical cases when using prostaglandin analogues in patients with arthphakia, which resorbed when they were cancelled with an increase in IOP. Given the presence of prostaglandin receptors in the retina [39], these observations are quite understandable.

### 3.3 AMD

Deposition of pigment granules from RPE in the thickness of the neuroepithelium occurs in maculopathy against the background of tamoxifen [40], as well as in the late stages of age-related macular degeneration. It is known that retinal vessels radially diverge on average of  $8.9 \pm 0.23$  around the foveola, and arterioles are usually located above the venules [41]. There are more diverting venules in the parafoveolar zone than arterioles. I.e., there are about 8 channels located radially around the foveola, and one vertical from the central channel of the vitreous. Moreover, the latter plays one of the leading roles in the pathogenesis of macular diseases, since posterior vitreous detachment (PVD) is reliably a factor of protection against both pseudophakic cystic macular oedema [42] and AMD [43]. It has also been found that in diabetes mellitus, partial PVD contributes to increased proliferation, and full PVD causes a stop of the proliferative process [44].

In patients with AMD, when stimulated by a light wavelength of 488 nm, increased emission is observed with autofluorescence at the level of the Bruch membrane and subretinal deposits, in contrast to the control group without AMD [45]. This indicates an altered chemical composition of the intercellular fluid in this zone, probably due to a primary change in the outflow rate of the interstitial fluid, followed by the activation of inflammatory factors on such metabolic products as beta-amyloid, etc.

The macula has a high density of green and red cones that express carbohydase, but in the foveola there are only blue cones that do not express carbohydase receptors [46] and a special type of Muller astrocytic cells on the roof of the foveolar fossa. These data may indicate that through the foveola, there is normally an outflow of tissue and intraocular fluid towards the RPE and into the thickness of the retina at night and an influx during the day from the choriocapillaries to cool the RPE and remove metabolic products.

Carboanhydase inhibitors in some patients with primary glaucoma cause choroidal effusion, which may indicate a significant outflow of intra-ocular fluid through the retina into the suprachoroidal space in these patients, especially given the presence of carboanhydase receptors in the RPE and glia [47]. It is known that the perichoroidal space, behind on the nasal side of the eyeball, ends 2-3 mm from the exit point of the optic nerve. On the temporal side – at the central fossa of the retina, and in front – at the attachment point of the ciliary body to the scleral spur. The lymphatic vessels of the conjunctiva are maximally developed from below-inside the eyeball and have nasal-ventral and temporal-dorsal polarization [8]. The number of vortucose veins collecting blood from the choroid clearly does not allow taking the entire volume of tissue fluid, and part of the tissue fluid goes through the suprachoroidea and sclera into the lymphatic collectors of the face



and neck [9]. But the central region of the retina has an additional, autonomous glymphatic outflow of tissue fluid along the glial spaces of the retina itself into the thickness of the optic nerve and its para-sheaths space.

The shape of the drusen with the convex side up indicates that the delay of tissue current and fluid stasis occurs precisely in the direction from under the RPE towards the vitreous body. The etiopathogenesis of AMD is unknown for certain changes in the structure of choriocapillaries, etc., although much is clear about the pathogenesis of this disease, including activation of the complement system and cytokines. We assume that the triggering moment of AMD is not just physiological photo-oxidative stress in the central zone of the retina, namely, a decrease in the rate of hydrodynamic flows in the macula and the occurrence of fluid stasis. A decrease in the metabolic rate in this zone and the accumulation of detritus: intralaminar basal deposits, soft and dry drusens also occur. Figure 2 shows the accumulation of fluid in the perithyroidal pocket, which is located between the Bruch membrane and hyperreflective deposits in the thickness of the detached retinal pigment epithelium which correlates with the activity of the neovascular membrane in AMD [8]. The process of neovascularization in AMD itself may be the primary adaptive factor for eliminating excess interstitial fluid accumulating in this zone through newly formed "fenestrated" vessels. It has been proven that endothelial vascular growth factor (VEGF) is the main element for the pathogenesis of wet AMD, and it also reduces the hydraulic bandwidth throughout RPE [48].

Thus, we assume that a decrease in the hydrodynamic parameters of the rate of transition of HCV into the interstitial fluid of the inner layers of the retina, as well as a decrease in the rate of tissue fluid exchange between the choriocapillary lobule and the outer layers of the retina are the main glymphatic components of the etiopathogenesis of age-related degenerative diseases of the macular zone. The hydrostatic pressure gradient between the vitreous, sensorineural and pigment epithelium, calculated in the area of the foveolar fossa, is about  $\Delta 5$  mm Hg. [20], which is confirmed by experimental data [49], therefore, even a slight decrease in the rate of inflow of IOF through the central channel into the macular sac and/or a decrease in the rate of fluid outflow through the RPE towards the choroid can lead to stasis of the interstitial fluid in this zone. The main reason for the decrease in the rate, is probably age-related in the production of IOF by ciliary processes and altered regulation of the transport of tissue fluid in the macula. A change in osmotic gradients between the external hematophthalmic barrier and the interphotoreceptor space, leading to fluid stasis under RPE and "intoxication" by products of the exchange of choriocapillaries, RPE cells and photoreceptors, also occurs. It is important to note that damage to ganglion cells in AMD occurs much more significantly in the exudative form of AMD than in the non-exudative form.

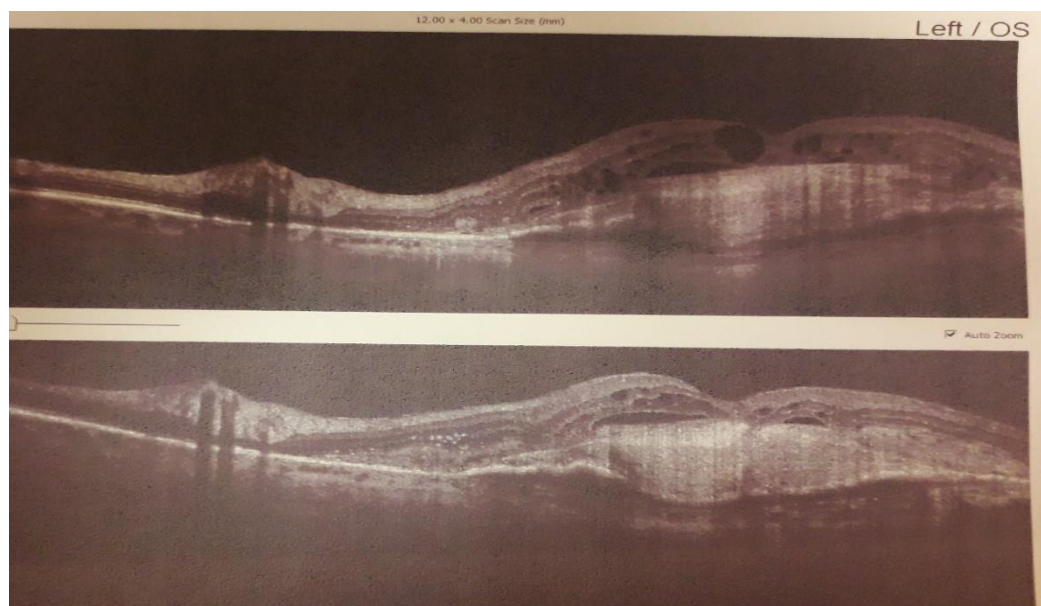


Figure 2. OCT picture of a patient with a wet form of AMD after 3 injections of anti-VEGF therapy with the presence of a prechioroidal pocket and accumulation of fluid around the scar

Age-related cataract is also probably associated with impaired circulation of IOF around the lens capsule and the Bergson space towards the posterior segment of the eye. The development of



age-related posterior capsular cataracts in the native vitreous body may indicate either the presence of excess oxygen in IOF behind the lens, which occurs predominantly preretinally in the posterior segment of the eye, or the stasis of the fluid washing the lens in the Bergson space. This is probably due to the low throughput of the foveolar radial outflow path of glymphatic fluid, as well as direct reverse absorption to the choroid through the RPE.

Confocal microscopy of cadaveric eyes revealed an additional silent vessel in the avascular zone of the retina in 2 out of 9 cases, which adds to the understanding of the etiopathogenesis of the wet form of AMD [41].

### 3.4 Macular rupture

To date, there are several theories of the development of macular ruptures. The theory of Gass (1973), based on the disorder of the skeleton functions of Muller cells located Z-shaped in the thickness of the macular zone, is complemented by the traction theory. Alpatov (2005) proved that cystic retinal oedema with subsequent trophic disorder forms the basis of structural and functional disorders around the rupture, and epiretinal membranes can also form at the last stage of rupture formation, after the development of complete PVD [50].

The initial or first stage (1a) of idiopathic age-related macular rupture presupposes the elevation of the neuroepithelium under the foveola. i.e., the influx of fluid from under the RPE secreted by the choriocapillary lobule exceeds its absorption rate into the thickness of the retina. Further excess inflow of tissue fluid can lead to the formation of intraretinal cysts when local compensation pathways are activated by Muller cells and ILM astrocytes, but eventually leads to a divergence of the retina in the radial direction. It is known that macular ruptures most often primarily manifest in the morning. During the night, fluid accumulates in the thickness of the retina, which could not be "pumped" along the perivascular outflow pathways, as well as due to a violation of the physiological process of vertical outflow of tissue fluid towards the choroid due to a violation of the transport function of the RPE. Therefore, an excess of tissue fluid is formed, aiming to "go down the sides" into the thickness of the retina, while the entry point is the foveola. Hydrodynamic flows of interstitial fluid rushing along the gradient of hydrostatic pressure towards the optic disc along the axons of the ganglion cells of the papillo-macular bundle and below in the plexiform layers are normally carried out due to the processes of Muller cells and glial astrocytes, as well as convection. But when certain conditions are combined: degenerative glial changes and/or functional disorders (failure of regulation by the dopamine-melatonin system in the retina, decreased blood flow in the macular choroidal lobule, etc.), these outflow pathways are disrupted, and a macular rupture occurs.

OCT images of the macular zone of the operated macular rupture show that fluid accumulation in the early postoperative period (up to 1 month) occurs in the same "spaces" as in CMO: in the cystic cavities in the outer plexiform and nuclear layers (Fig. 3 and 4) and directly under the foveola (see Fig.3).

Thus, convection in the foveolar zone, which increases during the day under the influence of light and chemical reactions, leads to the formation of cysts with violations in the glymphatic outflow at night against the background of a malfunction in the functioning of the RPE. The dopamine-melatonin system of macular RPE and neuroepithelium performs a regulatory role and depends on circadian rhythms on the day-night principle. At night, the outflow of tissue fluid goes through the glymphatic paravascular spaces of the retina and optic nerve (central vascular bundle and venules of meningeal membranes). During the day, under the influence of light, the glymphatic current flows along the axons of ganglion cells and mainly through retinal veins, as well as through the capillary network of the choroid, ciliary body and optic nerve into venous and lymphatic collectors. The production of a residence permit occurs in the ciliary processes and choriocapillary lobules mainly at night and in the morning in order to activate the circulation of tissue fluid with which it is mixed.



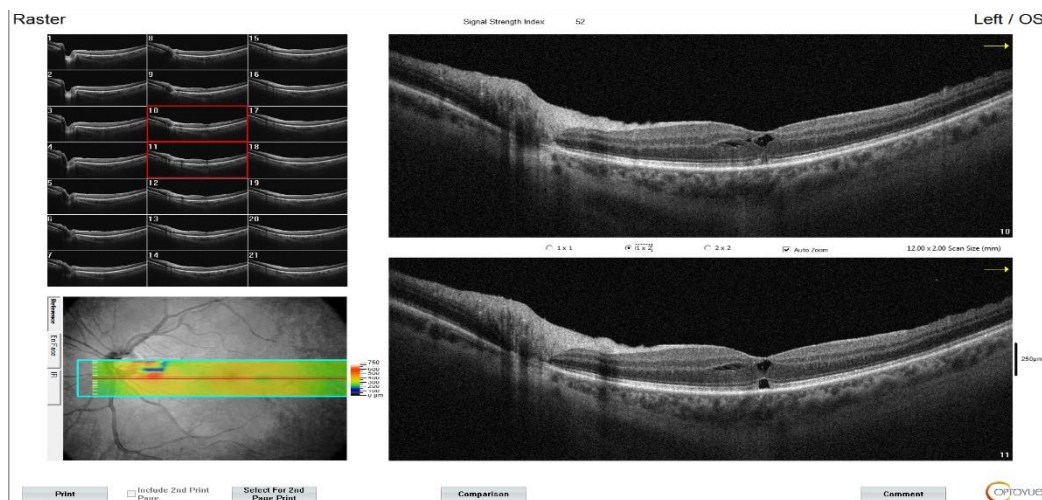


Figure 3. OCT picture of the macular interface in the early postoperative period of macular rupture surgery.

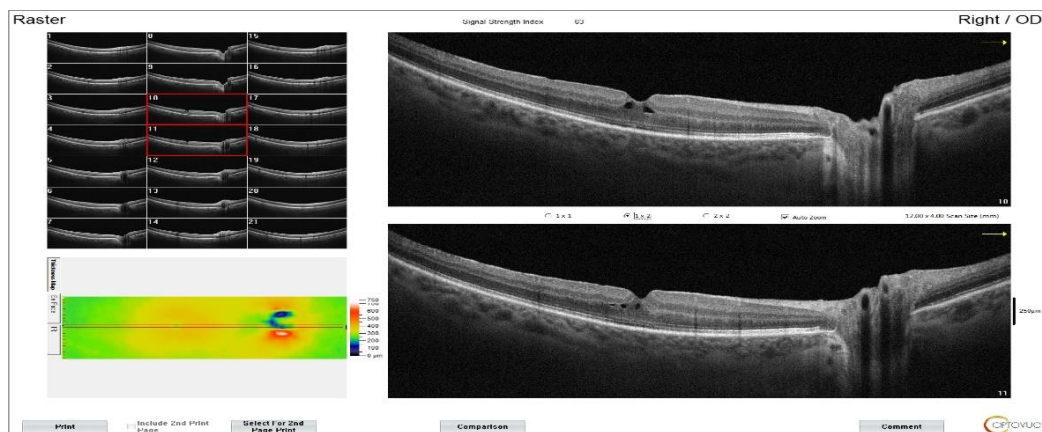


Fig. 4. OCT picture of operated macular rupture with cavities in the outer layers of the retina in the early postoperative period

In the macular zone there is a "crossroads" regulated by the dopamine-melatonin system through the suprachiasmatic nucleus, which, thanks to the RPE, Muller cells, glial astrocytes and paravasal spaces, provides a bidirectional fluid flow in the thickness of the retina in two planes: longitudinally radial and transversely through the thickness of the retina. A schematic representation of the circulation of tissue fluid in the central zone is shown in Fig. 5.



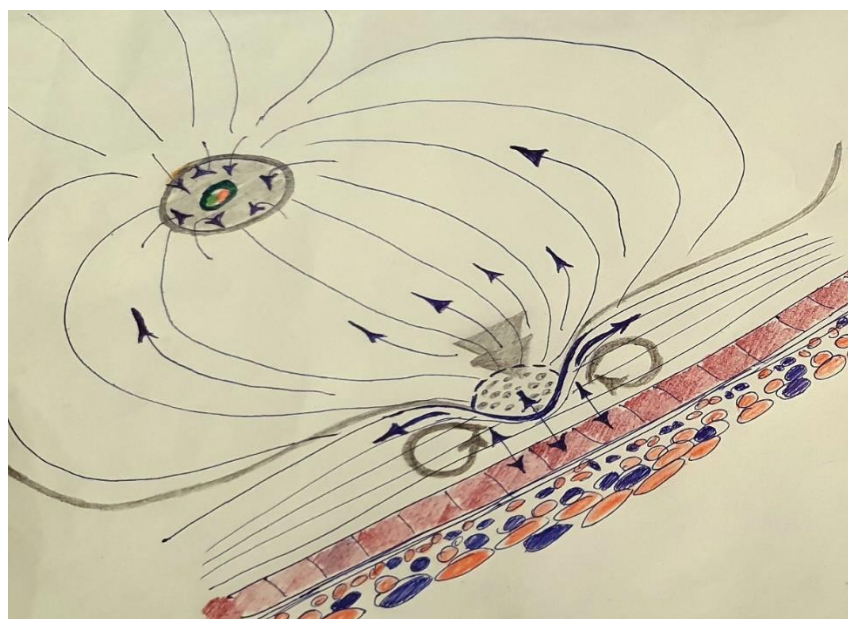


Fig. 5 Schematic representation of tissue fluid circulation in the central area of the retina. The blue arrows represent the interaxonal fluid flow (along the surface capillary network). The gray thick arrow above the foveola is the HCV current from the central channel through the thickness of the retina. Gray arrows around the foveola in the thickness of the retina – the direction of fluid flow under the action of convection.

#### 4.1 Hydrodynamic theory of the development of macular diseases

1. Idiopathic degenerative/age-related macular ruptures from a hydrodynamic point of view can be explained by a violation of the flow of tissue fluid through the thickness of the retina at the point of entry into the fovea both from the premacular bag and from under the RPE. In this case, a rupture in the fovea occurs with a sharp increase in the flow rate of the interstitial fluid in the thickness of the retina in the radial direction against the background of an increase in the contractile activity of the processes of Muller cells. Macular rupture is detected, as a rule, in the morning after sleeping in a horizontal position, in particular, and on the first day after phacoemulsification, which confirms the hypothesis of a radial-longitudinal glymphatic flow of tissue fluid in the inner layers of the retina in the macula.

2. Age-related macular degeneration manifests itself with a decrease in the flow rate of lymphatic tissue fluid in the thickness of the retina and from under the REM in this area. A decrease in the flow of glymphatic fluid occurs with age with a decrease in heat production in the retinal pigment epithelium, which leads to a decrease in convection and circulation of tissue fluid in the foveolar zone, accumulation of metabolic products and deposition of retinal and subretinal druzens. The fact that in macular ruptures, as a rule, there are no concomitant macular druzens indirectly confirms paragraphs 1 and 2.

3. Epiretinal fibrosis occurs with a decrease in the rate of outflow of IOF diffused from front to back towards the retinal RPE and choriocapillaries along the posterior hyaloid membrane into the thickness of the inner layers of the retina. Stagnation of tissue fluid, coupled with an increase in the concentration of proinflammatory factors and protein fractions that have passed through the external hematophthalmic and/or hematopoietic barriers, leads to the deposition of inflammatory products on the surface of the posterior hyaloid and/or internal boundary membranes. Thus, idiopathic epiretinal fibrosis occurs as an "attempt" to suspend the amount of diffused fluid from the vitreous body into the thickness of the retina and RPE, as well as in the opposite direction during inflammatory and infectious processes of the posterior segment.

#### 5. Conclusions

In the posterior segment of the eye, in addition to a slight fluid flow from front to back towards the RPE, there are two ways of tissue fluid flow: the first is radial, which is caused by fluid flow along the axons of ganglion cells along the paravasal pathways of the superficial capillary network into the thickness of the axons of the optic nerve. The second is longitudinal in the outer layers of the retina, draining into the paravascular glymphatic spaces of the optic nerve and to a lesser extent under the RPE in the choriocapillaries. The first one functions mainly at night in a





horizontal position under the influence of gravity and hydrodynamic gradients of the bags and channels of the vitreous body and the pressure of the cerebrospinal fluid, and the second direction of the tissue fluid flow occurs during the day and is due to the electrochemical potential of the visual act, i.e. heating of the retina in the macular zone and the difference in temperatures in different parts of the retina, i.e. convection. Gravitational (gravispin) forces and the hydrodynamics of a charged fluid are two forces that cause the circulation of the interstitial and IOF.

Thus, the totality of data on various eye diseases, as well as the revealed clinical features of their course based on the latest scientific data and glymphatic flow in the nervous tissue allowed us to make assumptions about the presence of new physiological patterns of fluid flow in the posterior segment of the eye and formulate a new concept of the development of macular diseases.

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**The use of artificial intelligence:** the article is written without the use of artificial intelligence technologies.

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