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Schlemm's Canal: The Outflow “Vessel”

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Abstract

The aim of this chapter is to review the knowledge about the aqueous outflow through Schlemm's canal. Morphology of this canal and aqueous humor pathways from the anterior chamber through the trabeculum into suprascleral and conjunctival veins via connector channels are described. Additionally, the role of Schlemm's canal in the development of glaucoma and outflow resistance is discussed. Canalography as a more precise method of assessing the conventional drainage pathway and facilitating localization of an uncollapsed collector and aqueous veins is shown. Attention is also drawn to the relationship between aqueous and suprascleral veins and heartbeat.

Keywords: Schlemm's canal, aqueous humor, conventional drainage pathway, outflow resistance, canalography, glaucoma

1. Introduction

Aqueous humor (AH) is drained from the eye via two physiological pathways. The conventional path begins at the level of the irido-corneal trabecular meshwork (TM) and is responsible for approximately 83–96% of drainage. From the anterior chamber, the aqueous humor moves through the trabecular meshwork to Schlemm's canal (SC) and then to intrascleral collector channels (CCs), which lead to the intrascleral venous plexus, aqueous vessels, and venous vessels of the suprascleral space. Aqueous vessels begin as collector channels in the exterior wall of Schlemm's canal and can be seen on the surface of the eye in the corneal limbus.

Aqueous humor flows out of the anterior chamber as a mass stream regulated by a pressure gradient. In healthy human eyes, outflow facility has a value of 0.40 at 10 mmHg and is reduced with age. From a physiological perspective, the trabeculum, particularly the interior wall of

Schlemm's canal, and the trabecular meshwork near collector channels are the main sources of resistance to aqueous outflow, and the remaining part of resistance is located in the exterior wall and surrounding tissues. Elevated IOP in glaucoma is caused by an increase in aqueous outflow resistance on its drainage pathways, not by an increase in aqueous production. Many authors believe that the source of outflow resistance in correct eyes is found close to or in the area of the interior wall of Schlemm's canal. Outflow resistance is not constant but a function of IOP and rises as IOP rises.

The aqueous humor flows out of Schlemm's canal through one of 30 collector channels and aqueous veins (AVs) and then to the system of suprascleral veins, ophthalmic veins, and general circulation. According to Poiseuille's law, the resistance of aqueous veins should be insignificant if they are not collapsed or compressed. Provocative gonioscopy, during which blood reflux into Schlemm's canal is observed, is the simplest method of assessing the conventional drainage pathway and facilitating localization of an uncollapsed collector and aqueous vein. Assessment of the distribution of aqueous veins in canalography is a more precise method. Studies by Grieshaber et al. showed a relationship between postoperative intraocular pressure (IOP) level and the presence of reflux in Schlemm's canal before surgery and between the degree to which water veins were filled. Zou introduced the trabeculum bypass theory, which reduces resistance in this part of the drainage route. He observed increased flow through Schlemm's canal only in the quadrant where the implant was applied, and intraocular pressure reduction was dependent on initial pressure.

Aqueous and suprascleral veins oscillate according to heartbeat. These oscillations enable continuous lamellar flow. Pressure in aqueous veins is sufficiently high and enables reverse lamellar flow from suprascleral veins at cardiac diastole. At cardiac systole, pressure in aqueous veins increases and reverses the direction of aqueous flow with simultaneous blood reflux.

2. Schlemm's canal

Schlemm's canal (SC) was named in honor of the German anatomist, Friedrich Schlemm, who, in 1830, discovered the canal in the anterior chamber angle, draining aqueous humor (AH) into the bloodstream [1, 2]. It is a ring-like canal with a length of 36–40 mm encircling the cornea [3, 4] and directly adjacent to the juxtacanalicular trabecular meshwork (JCT) [5], and together with the trabecular meshwork (TM), it forms the conventional outflow pathway, which accounts for 50–90% of AH flow [6, 7]. Its cross-section has the shape of an elongated ellipse, with its longer axis measuring 150–350 μm . Three-dimensional visualizations have made it possible to take precise measurements of the canal, the cross-sectional area of which ranges from 4064 to 7164 μm^2 [8–12]. Rarely, the canal may be bi- or tripartite [13], and it may sometimes contain septa [14]. One of the primary functions of SC is to drain aqueous humor from the trabeculum to collector channels (CCs).

Due to its direct adjacency to the trabeculum, not all SC cells are identical [5, 15]. Owing to the canal's microanatomy, we can distinguish between the inner and outer wall, each built of a

continuous, single-cell layer of endothelium. The cells of both walls differ in terms of morphology [16], the presence of different marker expressions, cell organelles, and function [17]. The inner wall is more frequently analyzed because it presents the greatest resistance to drainage of AH [18–20]. Endothelial cells of the inner wall are shaped like paver stones, while the cells of the outer wall are smooth and flat [15]. Tight junctions of VE-cadherin as well as characteristic giant vacuoles and pores are the markers for cells of the inner wall. Desmin, reactivity to Factor VIII-related antigen, and the presence of Weibel-Palade bodies are the markers for cells of the outer wall [6, 21–26].

2.1. Embryogenesis

Schlemm's canal is a highly specialized vessel. Despite many similarities to vascular endothelium, the canal's embryonic origin and progression of its development have still not been precisely determined [5]. Earlier research suggested a vascular origin of cells [24, 27–29], but recent publications have classified them as unique endothelial cells with phenotypical traits of the endothelial cells of both blood and lymphatic vessels [30–33]. In humans, the prenatal development of SC begins with development of the trabeculum in the 17th week [15]; in the 24th week, the canal is already defined and encircles the limbus over 360°; and in the 36th week, the canal and collector channels are fully developed [34].

The organogenesis of SC was described by Kizhatil as a combination of the vascular developmental factors of angiogenesis and lymphangiogenesis. He termed this process "*canalogenesis*," which begins from the limbal vascular plexus [30]. The development of SC can be divided into four stages, starting from differentiation of the canal's precursor cells, proliferation and migration of frontal cells, formation of the canal's lumen, and separation from the venous vascular system [5]. PROX1 and VEGFR-3 expression is required for division of frontal cells and shaping them into the canal.

2.2. Genetics

PROX1 (*prospero homeobox protein 1*) is the main regulator of lymphangiogenesis, and its expression is critical in transforming cells of the vascular endothelium into cells of the lymphatic endothelium [5, 30, 32]. Truong was the first to demonstrate a high level of expression of the PROX1 lymphatic transcription factor in the canal's endothelial cells, thus showing the similarity to lymphatic endothelial cells [7]. VEGFR-3 (*vascular endothelial growth factor receptor 3*), or FLT4, is a receptor belonging to the RTKs-KDR (*kinase insert domain-containing receptor*) family; it binds the VEGF-C and VEGF-D vascular endothelial growth factors, and its expression is typical of endothelium in lymphatic vessels [35]. Aspelund et al. [31] and Park et al. [32] presented the properties of the precursor cells of Schlemm's canal as well as key molecular mechanisms required for differentiation of these cells into the mature cells of the canal [31, 32]. Aspelund demonstrated that the VEGF-C vascular endothelial growth factor is necessary for activating migration of vascular endothelial cells and their further formation from transscleral venous vessels. He also demonstrated that precursor cells are, in essence, vascular endothelial cells with VEGFR-2 and TIE-2 (*tunica interna endothelial cell kinase*) expression. Precursor cells then gain PROX1 expression in order to create and form

the canal's lumen and also VEGFR-3 for later maturing of the canal's cells [31, 32]. Both aqueous humor and VEGF-C are required for proper SC development. A reduction in AH in mice resulted in the loss of elements of canal cells' lymphatic identity [32]. The direct relationship of the SC endothelium with JCT and the fact that the development of TM precedes the development of SC allow for the hypothesis that soluble factors from JCT cells may be of critical significance for obtaining phenotypical traits of SC cells. Because the inner wall of SC is in direct contact with the TM over a 360° circumference, modern canal surgery provides access to the entire inner wall of SC and the juxtacanalicular region without affecting the cornea, iris, and ciliary body. Canaloplasty may be used to deliver transgenic SC/TM vectors in glaucoma gene therapy [36].

2.3. Role of NO

Several studies have also documented the influence of cytokines (tumor necrosis factor (TNF)- α , interleukin (IL)-1- α , IL- β , IL-8) released by TM cells on SC cells, as well as their influence on regulation of aqueous drainage [37, 38]. Nitrogen oxide (NO) was widely studied from the perspective of its role in modulating the behavior of SC cells and regulating aqueous flow [39, 40]. Stresses in the SC endothelium trigger no production in SC cells, similarly as in other vascular endothelial cells [39]. Nitrogen oxide also mediates volume reduction in SC cells, which is linked to facilitation of AH drainage [40].

2.4. Biomechanics

The hydraulic conductivity of the conventional aqueous drainage pathway amounts to approximately $10^{-7} \text{ cm}^2 \text{ s}^{-1} \text{ g}^{-1}$, and this value also sets the lower limit for hydraulic conductivity of the SC endothelium, which is 2–5 times greater than the hydraulic conductivity of brain endothelium and the greatest in the entire human body [41]. In SC, the biomechanical conditions acting on endothelial cells resemble the microenvironment in a lymphatic vessel [30]. In SC endothelial cells, the pressure gradient is distributed from the base to the apex of a cell similarly as in lymphatic vessels, but inversely to the distribution in the case of vascular endothelium [42]. In a typical blood vessel, the basement membrane and surrounding tissue provide additional support for endothelial cells, reducing circumferential, and radial stresses acting on cells. In the case of SC cells, the inverted pressure gradient caused by AH flowing into the canal's lumen generates a force that pushes cells away from the basement membrane [43]. However, in contrast to a lymphatic vessel, SC cells are bound by tight junctions, so they maintain the pressure difference between the eyeball and episcleral veins (EPV). Forces related to the pressure drop from the base to the apex of a cell result in cell deformation and the formation of large, dome-shaped diverticula into the canal's lumen, called giant vacuoles [41, 42, 44–47]. Besides tight junctions between endothelial cells, there are extensive links between endothelial cells and cells in the JCM area. These junctions are present when SC cells form protrusions to join with JCM cells, forming parachute-like structures. These junctions, described by Johnstone, play an important role in anchoring the canal's endothelial cells in response to increases in pressure [15, 48]. The size of SC's lumen changes in response to IOP fluctuations [48]. When IOP increases, the TM widens while the canal narrows, and this is

caused by an increase in the number of vacuoles and of the area of the extracellular matrix (ECM), as well as by the fact that both walls of the canal are closer to one another. At high IOP, the probability that the canal's walls will collapse and resistance on drainage outflow pathways will grow increases significantly [48]. When IOP increases to approximately 40 mmHg, the canal collapses, with the exception of segments containing septa [20, 49], which support the walls of SC and prevent occlusion of CCs [20, 48, 49]. In eyes with glaucoma, the lumen of SC is smaller than in healthy eyes [50].

2.5. Microanatomy-giant vacuoles and pores

Giant vacuoles are potential spaces between extracellular matrix (ECM) and the SC's inner wall cells [15]. Giant vacuoles form dynamically and respond to changes in intraocular pressure (IOP) instantaneously [5, 51]. Their quantity and size increase as IOP increases. After enucleation, the IOP drops to zero, and vacuoles disappear within a time of <3 min [52]. The majority of giant vacuoles are found near CCs outlets [52], which suggests that a greater pressure gradient is present at CCs outlets due to the greater aqueous flow [15]. Most probably due to the specific biomechanical microenvironment, endothelial cells are characterized by contractile properties and by an elastic modulus of 1–3 kPa [41], which is slightly greater than in the case of other endothelial cells [42, 47]. SC cells owe their capability of adapting to deformations to the cytoskeleton system fortified with actin microfilaments. Cells of the outer wall have star-shaped F-actin systems that pass through most cells, in contrast to the circumferential F-actin bands observed in endothelial cells of the inner wall [53]. The position of SC cells relative to ECM allows for reception of biomechanical signals from the ECM [37], which affect the expression of cells' genes and adapt them to changes in the rigidity. The rigidity and contractility of SC cells exhibited a strong response to pharmacological stimulation. Medications increasing resistance to drainage increased the rigidity of SC cells, and inversely, medications reducing resistance to drainage reduced the rigidity of these cells [41]. In eyes with glaucoma, endothelial cells are more sensitive and exhibit an amplified response to the increase in the substrate's rigidity that occurs in glaucoma [42]. Stress caused by a rise in IOP can increase cell surfaces by up to 50% and even cause them to thin out [22]. Tight junctions between endothelial cells of the inner wall are very sensitive to increases in IOP and become less complex when IOP is elevated [37]. Endothelial deformation may initiate the formation of pores mediating aqueous transport by loosening intercellular junctions [54–56].

Pores are structures in the inner wall with sizes ranging from 0.6 to 3 μm [25, 43, 57], and they are responsible for 10% of the resistance to aqueous drainage [37]. They may be found in the walls of giant vacuoles, but they may also be unrelated to them [21]. They form the main pathway of aqueous flow through the inner wall of SC. Two pore types have been identified and characterized: type I pores (transcellular) and type B pores (paracellular) [25]. They differ in their locations, filtration ability, and formation mechanisms [43]. B pores are larger, but they are outnumbered 3–4 to 1 by I pores. Type B pores form as a result of local loosening and widening of intercellular junctions [43]. Braakman et al. [26] presented a segmentation of the aqueous drainage stream, and type B pores account for the majority of aqueous flow. Type I pores may form as a result of a combination of deformations of the cellular membrane at the

base and apex of an endothelial cell, which may occur under the influence of the aqueous filtration stream, and caveolae, vesicles, and minipores [43, 58]. Pores in Schlemm's canal are most frequently formed from minipores 60 nm in size, covered by a diaphragm containing PLVAP (plasmalemma vesicle-associated protein) [43, 58]. Molecular pore formation processes are not well known, but PLVAP is most probably involved in them, considering that pore formation is significantly impaired in mice with PLVAP deficiency [58, 59]. Pore density in the interior wall fluctuates between 1000 and 2000/mm² [55, 60]. When IOP is elevated, the number of pores in the inner wall increases [25, 51, 55]. Giant vacuoles and pores are unique features of the endothelium of SC's inner wall and of the endothelium of the arachnoid villi in the central nervous system [42, 61, 62]. Scanning electron micrograph of the inner wall of Schlemm's canal can visualize the giant vacuoles and pores at the base of a bulging structure (**Figure 1**) [56].

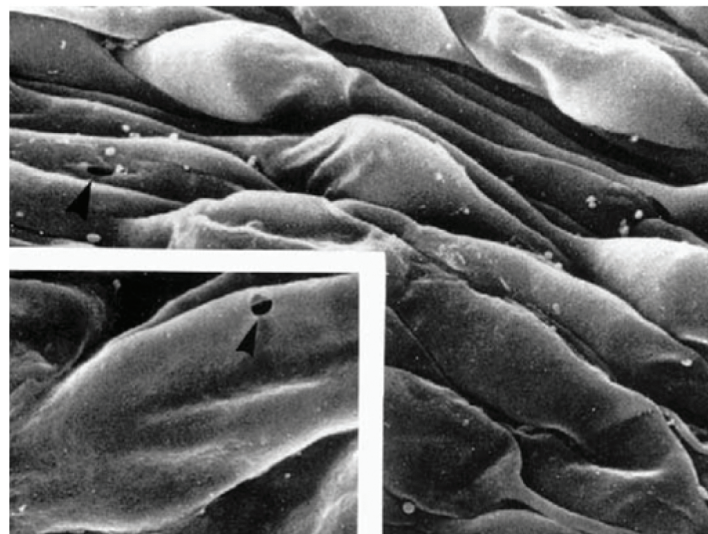


Figure 1. Scanning electron micrograph of the giant vacuoles and pores of the inner wall of Schlemm's canal. A pore (arrow) is observed at the base of a bulging structure (modified from Allingham et al. [56]).

The formation of giant vacuoles is directed in one direction, providing a preferential aqueous drainage pathway through the endothelium by means of a one-way valve mechanism. In the case of a pressure increase in episcleral veins and in SC that exceeds IOP, the number of vacuoles and pores decreases, preventing blood reflux from SC into the anterior chamber [42, 63, 64]. Certain medications, such as glucocorticosteroids or sphingosine-1-phosphate (S1P), which induce polymerization of the cytoskeleton's proteins [65, 66], may inhibit the formation and reduce the density of vacuoles, increasing resistance to drainage [67, 68]. Eyes with glaucoma exhibit reduced pore density, which emphasizes the critical role of the inner wall in maintaining homeostasis of AH. The aqueous flow resistance is considerably increased by the hydrodynamic interaction between pores and their basal substrate- subendothelial (basement membrane of SC cells and extracellular matrix of JCT) [69]. In particular, flow is concentrated near every pore, forming funnels that flow through the region of extracellular matrix closest to a given pore, which significantly reduces the effective area available for flow through these

regions [42]. The goal of glaucoma therapy oriented toward SC may be to increase pore density, and thus drainage, leading to reduction in IOP [55].

2.6. Distribution of aqueous humor

AH in Schlemm's canal is not distributed uniformly through the canal's inner wall, but rather appears preferentially at certain locations. Drainage of AH most frequently occurs near CCs [70]. Twice as many giant vacuoles are present near collectors, which suggests that aqueous flow through the inner wall is dependent on the value of pressure [52]. Studies involving the application of fluorescent markers have also demonstrated an elevated level of markers in the pigmented part of TM adhering to CCs, suggesting that the preferred drainage outflow pathways are present near collectors [70]. Histological research on human eyes has proven that, between the 25th and 30th year of life, CCs are randomly distributed around the eye, with preferential dislocation in the inferior nasal quadrant [1, 71]. This has been confirmed by three-dimensional micro-CT tests [72]. There is high diversity in the size of CCs outlets, with values ranging between 5–50 μm and up to 70 μm depending on the type of test [1, 71, 72]. From the CCs, AH flows through a winding system of venous plexuses, from the deep scleral plexus, through the limbal plexus, to the intrascleral plexus, which ultimately leads to the episcleral veins [6].

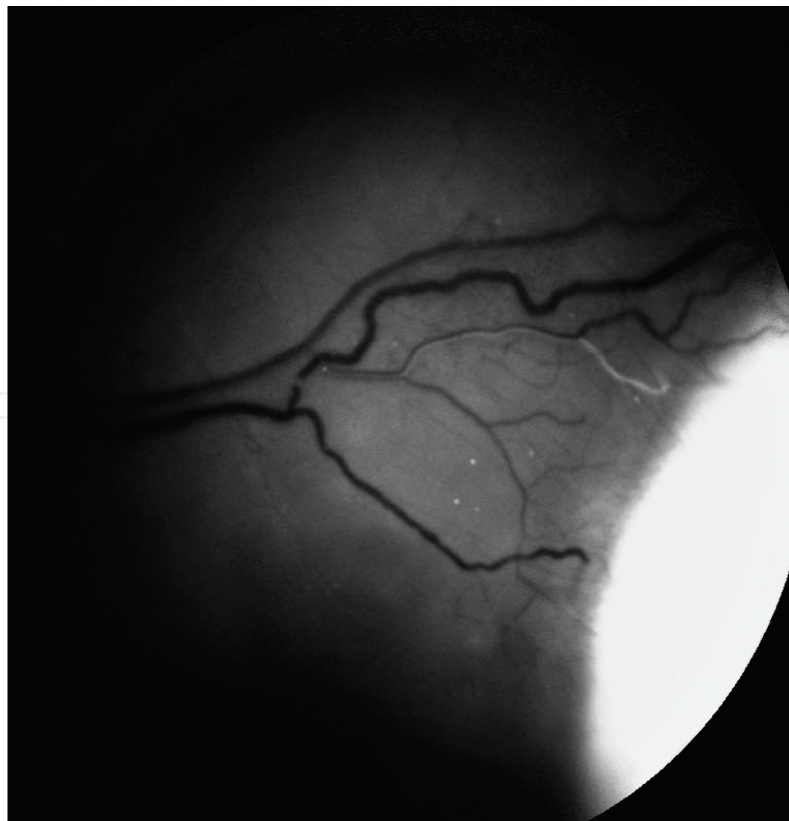


Figure 2. Aqueous veins.

2.7. Aqueous veins

Aqueous humor moves through the TM into SC, issuing forth from its lumen into CCs, aqueous veins (AVs) (**Figure 2**) and the system of episcleral veins (EPV) (**Figure 3**), ocular veins, and into the general circulation [21, 73]. AVs have lumens that are directly connected to CCs, and because of this, they are directly connected to the episcleral veins draining blood into the general circulation, bypassing the deep scleral and intrascleral venous plexuses [74, 75]. AVs containing initially clean AH are joined to episcleral veins filled with blood, which is why transition zones can be identified on the surface of the conjunctiva as large vessels with a transparent, central lumen bounded by dark blood from all sides. Linear stratification into AH and blood occurs due to the differences in these fluids' viscosity and density [76]. The composition of blood and aqueous in transition zones changes as IOP changes. Direct observation of these changes is a reliable indicator for assessment of the effectiveness of topical and surgical therapy oriented toward IOP reduction in glaucoma [77]. AVs differ in their position, size, and anatomical configuration. In a slit lamp test, 2–3 AVs are usually visible, and sporadically, up to 6 AVs may be seen [78, 79]. AVs are nonuniformly distributed and are present in the greatest number in the inferior nasal quadrants [78, 80]. Their size varies from 20 to 100 μm , 50 μm on average [78, 81, 82]. Histologically, AVs cannot be distinguished from conjunctival and EPV [80].

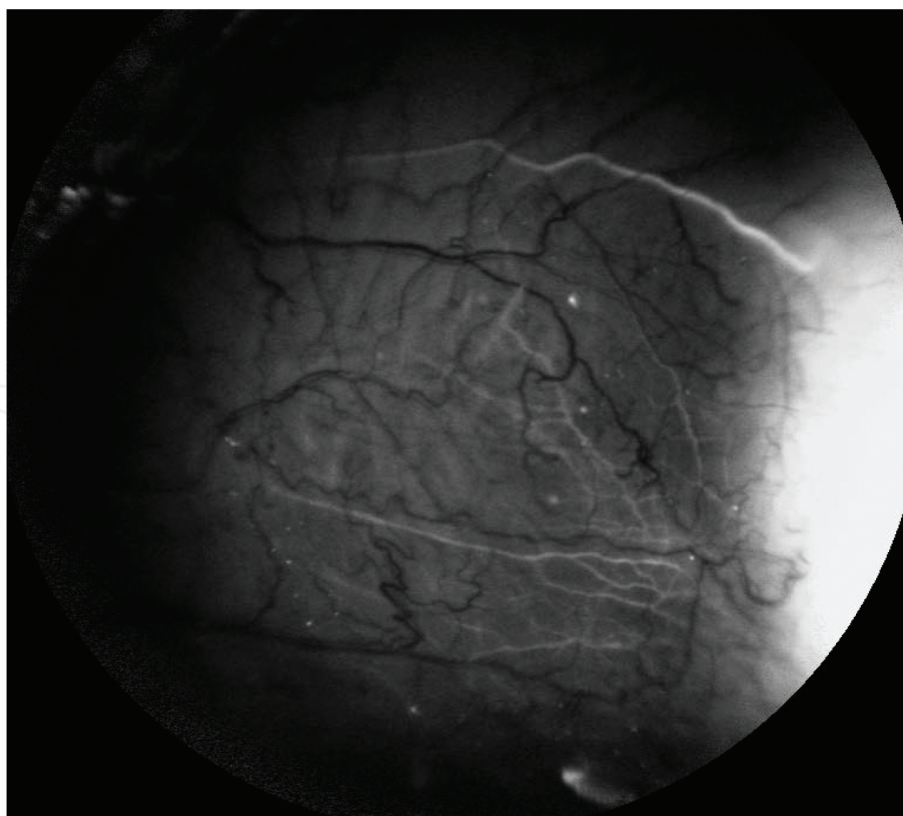


Figure 3. Episcleral veins.

2.8. Aqueous humor drainage

IOP is the primary factor affecting AH drainage. Drainage through the conventional outflow pathway is directly proportional to the IOP value within the range of physiological values [83, 84]. Drainage facility is the measure of how easily AH leaves the eye, and it is the inverse of resistance to drainage [20, 85]. In healthy human eyes, drainage facility has a value of $0.40 \mu\text{l}/\text{min}/\text{mmHg}$ at an IOP of 10 mmHg [86]. The main point of resistance to AH drainage is located at the JCM level in juxtacanalicular connective tissues, in the inner wall of SC, and its basement membrane [21, 69]. Elevated IOP in glaucoma is caused by an increase in aqueous outflow resistance on its drainage outflow pathways, not by an increase in aqueous production [87]. AH flow, defined as the movement of AH from the posterior chamber of the eye through the pupil into the anterior chamber, is lower than aqueous production because it does not include the AH that leaves the posterior chamber via other pathways [85]. The value of AH flow through the anterior chamber is not dependent on sex [88]. AH flow amounts to $2.4 \pm 0.6 \mu\text{l}/\text{min}$ and decreases with age by 2% per decade [88], which may result in a reduction of up to 30% [89]. It has also been observed that flow is halved during the night ($1.13\text{--}1.6 \mu\text{l}/\text{min}$) as compared to the day ($3.0\text{--}3.1 \mu\text{l}/\text{min}$) [89, 90]. In studies with fluorescein, it was observed that flow value is also significantly lower in eyes with pseudoexfoliation syndrome than in physiologically correct eyes [88].

2.9. Effective filtration areas

Based on observations of the distribution of pigment and perfusion markers, it was determined that, circumferentially, drainage of AH in healthy eyes is nonuniform and segmented [91–94]. At any given time, only some AH drainage pathways are actively involved in aqueous percolation. These active areas are called effective filtration area (EFA) [50, 80, 95]. EFA is a valuable method for measuring resistance to flow and the effects of IOP changes. Segmented drainage has been described in mice [96], pigs [97], cows [91, 93], monkeys [94], and humans [70, 97, 98]. Higher marker concentration was present in the TM neighboring the outlets of CCs, and in humans, more pigment was also observed at this location, suggesting that EFA locations can be determined by using pigment distribution as a marker [80]. A sudden increase in IOP in cow eyes caused a significant reduction in EFA [91, 93]. When IOP increased suddenly, the marker was present in a greater concentration near CC outlets. When IOP was correct, the drainage patterns were more uniform, and when IOP was elevated, drainage became more segmented [91]. EFA reduction is linked to reduction in drainage facility and is reversed when pressure is reduced from high to normal level [99]. EFA reduction was also observed in an animal model, in eyes with glaucoma and chronic IOP elevation that had undergone laser therapy [100]. In this study, reduction in the marker level was determined in regions of the TM that had undergone laser therapy. It was stated that active drainage shifted from areas that had undergone laser therapy to areas not affected by therapy. In a study, where a marker was applied, significant EFA reduction was observed in eyes with glaucoma in comparison with healthy eyes [101]. In addition, the inversely proportional dependence between EFA and IOP has been documented on an animal model in the eyes of a mouse with ocular hypertension [96].

2.10. Pulsating flow

Drainage of AH is a complex process. Besides the traditional approach, according to which the AH moves passively in a combined stream through TM into SC, downward along the pressure gradient determined by the heart [102], a significant effect of the active process driven by means of a mechanical pump is also assumed [77]. Pulsating flow occurs as a result of oscillating compressive force caused by transitional IOP increases occurring during the cardiac cycle, blinking, and eye movements. These transitional IOP spikes cause microscopic deformations of the flexible structural elements of drainage outflow pathways. During contraction, the canal's endothelial cells move to the outside, forcing AH flow to the outlets of CCs and AVs. When the value of IOP drops, flexible elements move back to their original configuration, which leads to a relative reduction in pressure in SC inducing AH flow into the SC's lumen [11, 102, 103]. The theory that pulsating flow drives AH drainage is reflected in the dynamic equilibrium between AH and blood in AVs [104]. During contraction, the pulse wave causes flow of AH through AVs, resulting in visible widening of the aqueous layer in their lumens [78]. Eyes with glaucoma exhibit reduced pulsating flow in comparison with healthy eyes [105, 106]. In healthy eyes, the TM is susceptible to deformation under the influence of naturally occurring, dynamic changes in pressure and volume of AH flow from the anterior chamber to SC. Reduction in pulsating flow in glaucoma may be caused by changes in the TM's elasticity [75].

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