

AQUEOUS DYNAMICS AND SURGICAL RESTORATION OF THE NATURAL OUTFLOW SYSTEM

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Glaucoma is a group of diseases characterized by optic nerve damage that can result in vision loss and blindness. The major causative risk factor for primary open-angle glaucoma (POAG) is elevation of intraocular pressure (IOP) caused by dysfunctional aqueous humor drainage. Although it would be helpful for the glaucoma surgeon to know which part of the outflow pathway is "blocked" and then decide which procedure would be the best to remove/restore the blocked site(s), current imaging techniques are not able to provide the necessary information. Also, POAG is not one disease but a group of diseases, and the changes that cause increases in outflow resistance may be located at different sites along the outflow pathway in different patients.

An Overview of the Ocular Outflow Mechanism

The mechanics of aqueous outflow are extremely complex; however, it is important to have at least a basic understanding of how aqueous humor circulation is regulated, in order to facilitate successful management of glaucoma.

IOP is maintained within a normal range by a dynamic balance between aqueous humor production by the ciliary epithelium and drainage through two pathways - the conventional outflow pathway and the uveoscleral pathway. However, the conventional outflow pathway is the major aqueous drainage pathway through which 70–90% of aqueous humor exits¹ and consists of

the trabecular meshwork (consisting of the uveal and corneoscleral meshwork beams and the juxtacanalicular connective tissue [JCT] adjacent to Schlemm's canal), Schlemm's canal (a circular channel comprised of endothelial cells surrounded by connective tissue), the collector channels, and the episcleral veins (Figure 1).

In the healthy eye, aqueous humor drains from the anterior chamber through progressively smaller channels of the trabecular meshwork into the circumferentially-oriented Schlemm's canal. From this canal, circuitous channels, known as collector channels, wind their way toward the surface of the sclera through the intrascleral

venous plexus system, ultimately joining the episcleral vasculature, which drains into the venous system. Flow through this system is driven by a bulk-flow pressure gradient. Active transport is not involved, as neither metabolic poisons nor temperature affects this system to any significant degree.²

Perhaps unsurprisingly, aqueous flow into Schlemm's canal is not evenly distributed throughout the inner wall of Schlemm's canal and scleral venous system. Studies using fluorescent beads show that aqueous outflow is segmental; only a fraction of the trabecular meshwork is actively involved in aqueous humor drainage at any given time, and increased levels of beads are observed in the

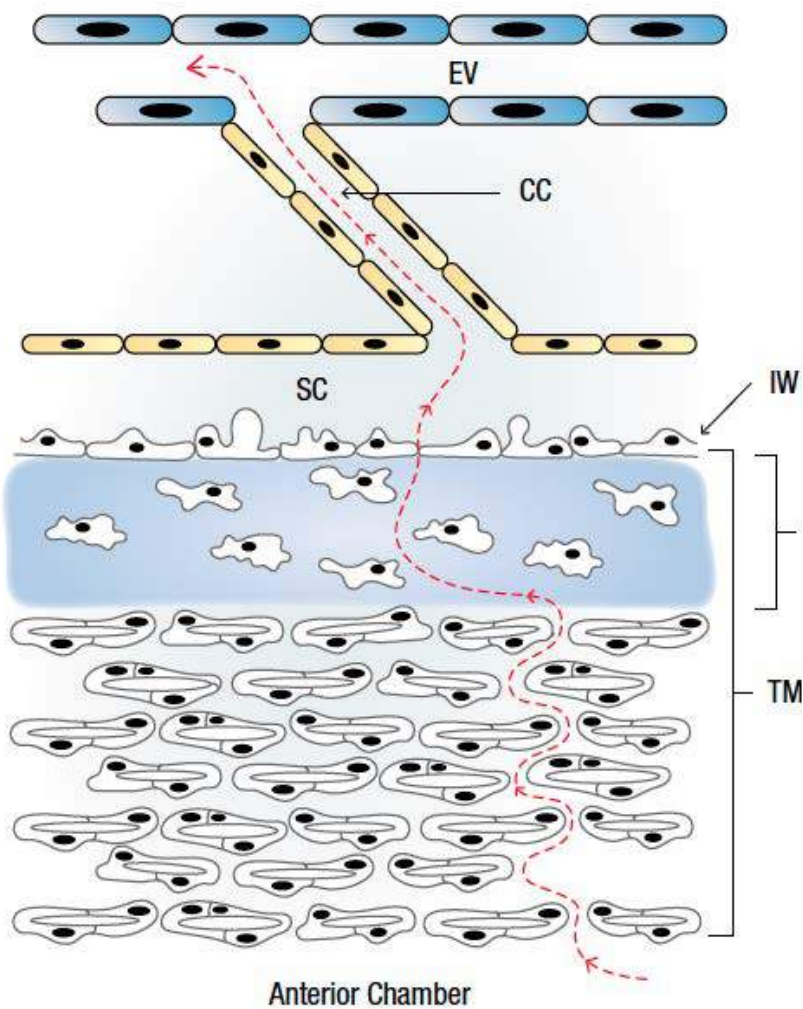


Figure 1: Schematic illustrating the major components of the conventional outflow pathway. Aqueous humor (red dashed line) flows through the initial portion of the trabecular meshwork (TM), juxtacanalicular connective tissue (JCT) region, inner wall of Schlemm canal (IW), Schlemm canal (SC), collector channel (CC), and finally reaches the episcleral vein (EV). Multiple TM cells encase the trabecular beams (tan) within the TM. The JCT is composed of sparse cells and substantial ECM.

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pigmented trabecular meshwork adjacent to collector channel ostia, which join Schlemm's canal. This suggests that preferential flow pathways are present near the entrances or ostia of these collector channels.² However, not all of the collector channel ostia are involved in active flow at a given time.³

Sites of Outflow Resistance

As noted previously, one of the challenges in glaucoma treatment is that the location of increased aqueous outflow

resistance in eyes with POAG is unclear, especially because it remains uncertain as to the source(s) and location(s) of the resistance in the normal eye. While there is general consensus that the resistance of the normal eye resides within the JCT and/or inner wall of Schlemm's canal, or some dynamic combination of both, this does not mean that the additional resistance found in the eye with POAG is the result of higher resistance in the same location(s).

Some of the changes that occur in POAG eyes have been identified, such as increasing extracellular matrix in the JCT⁵⁻⁷ decrease in number of pores of the inner wall of Schlemm's canal^{8,9} a shorter scleral spur, which is associated with a higher percentage of Schlemm's canal collapse¹⁰, collapse of Schlemm's canal and herniation of trabecular meshwork into the collector channel ostia blocking outflow¹¹. However, we cannot identify the location(s) of increased outflow resistance in each individual patient.

Experimental evidence suggests that in the trabecular meshwork, the majority of outflow resistance is generated in the inner wall endothelium of Schlemm's canal and its underlying matrix in the JCT in normal monkey eyes.^{5,6} Yet, their contribution to total outflow resistance remains unknown.^{7,8} However, following complete trabeculotomy, Rosenquist et al⁹ reported that 49% of outflow resistance is eliminated at a perfusion pressure of 7 mmHg (corresponding to the normal IOP in enucleated human eyes with no episcleral venous pressure), while Grant¹⁰ reported 71% of outflow resistance was eliminated at a perfusion pressure at 25 mmHg. Schuman et al¹¹ reported that 35% of outflow resistance was eliminated after a 1 o'clock hour ablation of the tissue from the outer wall of Schlemm's canal (and distal by using the excimer laser at a perfusion pressure at 10 mmHg). These studies suggest that one-third to half of the outflow resistance lies distal to the inner wall of Schlemm's canal at normal pressure^{9,11} and that a portion of outflow resistance is related to pressure-dependent changes in the outflow pathway.⁸ Schlemm's canal becomes narrower or collapsed with elevated IOP, which is associated with decreases in outflow facility and effective filtration area.^{12,13} Blockages of collector

channel ostia have also been reported, both clinically and histologically.^{1,14} Such structural changes would contribute to increased distal outflow resistance.

Restoration of the Natural Outflow System

Clearly, if a glaucoma surgeon were to remove the site(s) where increased outflow resistance resides, IOP would fall. However, if it is not possible to identify the site(s) of increased outflow resistance in a specific POAG eye, it is difficult to determine which parts of the outflow system are more relevant than others in terms of lowering IOP. Consequently, it is important to address all aspects of the ocular outflow system:

1. TRABECULAR MESHWORK

Recent research by Kaufman's group has shown that the trabecular meshwork is not a passive filter as previously thought but an active and complex organization of component tissues that maintain IOP in a steady state.¹⁵

The portion of the trabecular meshwork with active flow that leads directly into Schlemm's canal appears to be the more darkly pigmented section on gonioscopic view where the flow of aqueous and the phagocytosed pigment are greater. Poor identification of the correct area may be one of the reasons for the lack of success in some of the MIGS procedures, where a stent has to be positioned in the trabecular meshwork under gonioscopy. Opening a pathway through the meshwork, either by removing tissue or punching a hole and inserting a stent, encourages flow of aqueous into Schlemm's canal. Disruption of the inner wall of the endothelium by visco-canalostomy has been shown to permit communication between the lumen of the canal and the juxta-canalicular space^{20,21}. Stretching the tissue layers

“Increases in outflow resistance in patients with POAG may be located at different sites along the outflow pathway.”

“Experimental evidence suggests that in the trabecular meshwork, the majority of outflow resistance is generated in the inner wall endothelium of Schlemm's canal and its underlying JCT. Approximately one-third to half of the outflow resistance lies distal to the inner wall of Schlemm's canal at normal pressure.”

“One of the challenges of glaucoma treatment is that the location of increased aqueous outflow resistance and how this resistance is generated is unclear.”

of the trabecular meshwork, as is hypothesized during the Canaloplasty procedure²² may also encourage the aqueous outflow.

2. SCHLEMM'S CANAL

It is hypothesized that aqueous passes through the endothelial lining of Schlemm's canal from the JCT via giant vacuoles and pores, which are fewer in number in glaucomatous eyes and may explain the increase in outflow resistance. Increasing IOP leads to progressive collapse of the canal, which as it collapses, decreases active flow area¹³. Consequently, outflow resistance and IOP increase even further. The reduction in the size of Schlemm's canal may account for nearly half of the decrease in outflow facility observed in POAG eyes.¹²

Dilating Schlemm's canal with viscoelastic material and holding it open with a suture/stent as described in Canaloplasty may remove the resistance to flow by increasing the size of Schlemm's canal.²²

3. COLLECTOR CHANNELS

The collector channels which connect to the aqueous veins and the distal part of the outflow pathways originate in the outer wall of Schlemm's canal. Collector channels are not evenly distributed around Schlemm's canal circumferentially and outflow is segmental, being higher in areas close to the large collector channels as shown by accumulation of pigment in these areas.

Manufacturers of MIGS stents, e.g. iStent, Hydrus, recommend positioning the stent(s) close to a patent collector channel to increase the possibility of surgical success.

We have shown in both bovine eyes¹³ and in human eyes¹⁶ that an increase in pressure causes the TM to herniate into the ostia of the collector channels, blocking the passage of aqueous. We have shown that these changes are reversible in normal eyes when the pressure is lowered back to normal level but some of these herniations may become permanent in the eyes with POAG. Cannulating the whole of

Schlemm's canal, as in Canaloplasty, and injecting viscoelastic material may "pop" open these herniations and enable 360° access to collector channel ostia for the egressing aqueous.

4. EPISCLERAL VENOUS SYSTEM

The pressure in the episcleral venous system – known as EVP – is very variable from one patient to another. An ARVO 2014 poster from Kazemi and colleagues at the Mayo Clinic showed that EVP can vary from 3 mmHg to 14 mmHg, and it would seem that if the pressure gradient differential is low and resistance is also located distally in the episcleral venous system, restorative outflow surgery has less chance of being effective than if the pressure gradient differential is high.¹⁷

The next major step to be taken in research is to understand and locate, in vivo, the blocked sites along the aqueous outflow pathway in

glaucomatous patients and to be able to address all of the sites of increased outflow resistance. In the meantime, one of options that glaucoma surgeons can choose in lowering IOP in glaucoma patients is canaloplasty, which is specifically designed to address sites of blockage and restore natural aqueous outflow distal to the inner wall of Schlemm's canal.

Future Directions

As noted previously, an imaging technique that can visualize the blocked sites along the aqueous outflow pathway in vivo could further aid the treatment of glaucoma. Kagemann and colleagues at the University of Pittsburgh School of Medicine have used spectral-domain optical coherence tomographic systems for the purpose of visualizing the aqueous outflow system in three dimensions in healthy subjects. They

found that outflow pathways from Schlemm's canal to the superficial vasculature can be identified and tracked using this method.¹⁸ In my own laboratory, we have developed a novel fluorophore-guided method of studying the structure and function of the aqueous outflow system. This unique method uses the effective filtration area as a new parameter in examining the structural changes responsible for the reduced outflow in glaucomatous eyes.

The ability to identify site(s) of outflow resistance in patients with glaucoma will be very important, and we are on our way towards achieving this. However, in the absence of this information, canaloplasty is one of the choices currently available for glaucoma specialists to provide their patients with a comprehensive glaucoma treatment designed to restore the eye's natural outflow system. ●

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