

New Concepts in Our Understanding of Glaucoma

How dynamic pulsatile mechanisms determine aqueous outflow.

BY MURRAY JOHNSTONE, MD

The traditional glaucoma model is predicated on evidence from microsurgical studies that date to the middle of the last century.¹ The model became entrenched in the literature but does not conform to findings from a later, more complete body of evidence by the same author and his colleagues.²⁻⁵ The midcentury studies led to the following series of premises based on indirect evidence and assumptions:

- Seventy-five percent of the resistance to aqueous outflow is located in the trabecular meshwork (TM)
- The site of resistance is in a geometrically stable juxtacanalicular space
- Extracellular matrix in the juxtacanalicular space, acting as a passive filter, controls the flow of aqueous humor
- Aqueous humor flow itself is passive
- The TM does not move in vivo

Grant, who performed the studies from which these initial premises were developed,¹ eventually published studies along with colleagues that challenged his earlier conclusions.²⁻⁵ The later research suggested that

- Approximately 25% of resistance can be attributed to the TM, about 25% to the distal outflow pathways, and approximately 50% to apposition between the walls of Schlemm canal (SC)^{2,3}
- The juxtacanalicular space cannot act as a stable passive filter. First, it does not have enough extracellular matrix material to do so. Second, it enlarges up to 300% as the IOP rises within a physiologic

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range. Third, biomechanical studies have demonstrated that SC inner-wall endothelium is the primary tissue layer undergoing deformation in response to an increase in pressure^{4,5}

- The TM's distension into SC causes the canal's walls to become appositional at nearly physiologic pressures, creating resistance by preventing aqueous access to collector channels^{4,5}
- Pulsatile aqueous flow from SC into the aqueous veins provides direct evidence that aqueous flow is not passive but rather the result of dynamic phenomena⁶ (Figure 1)
- Pulse-dependent motion of the TM accounts for aqueous outflow, as shown by recent phase-sensitive optical coherence tomography (PhS-OCT) studies (Figure 2) in ex vivo primate eyes⁷ and in human eyes⁸

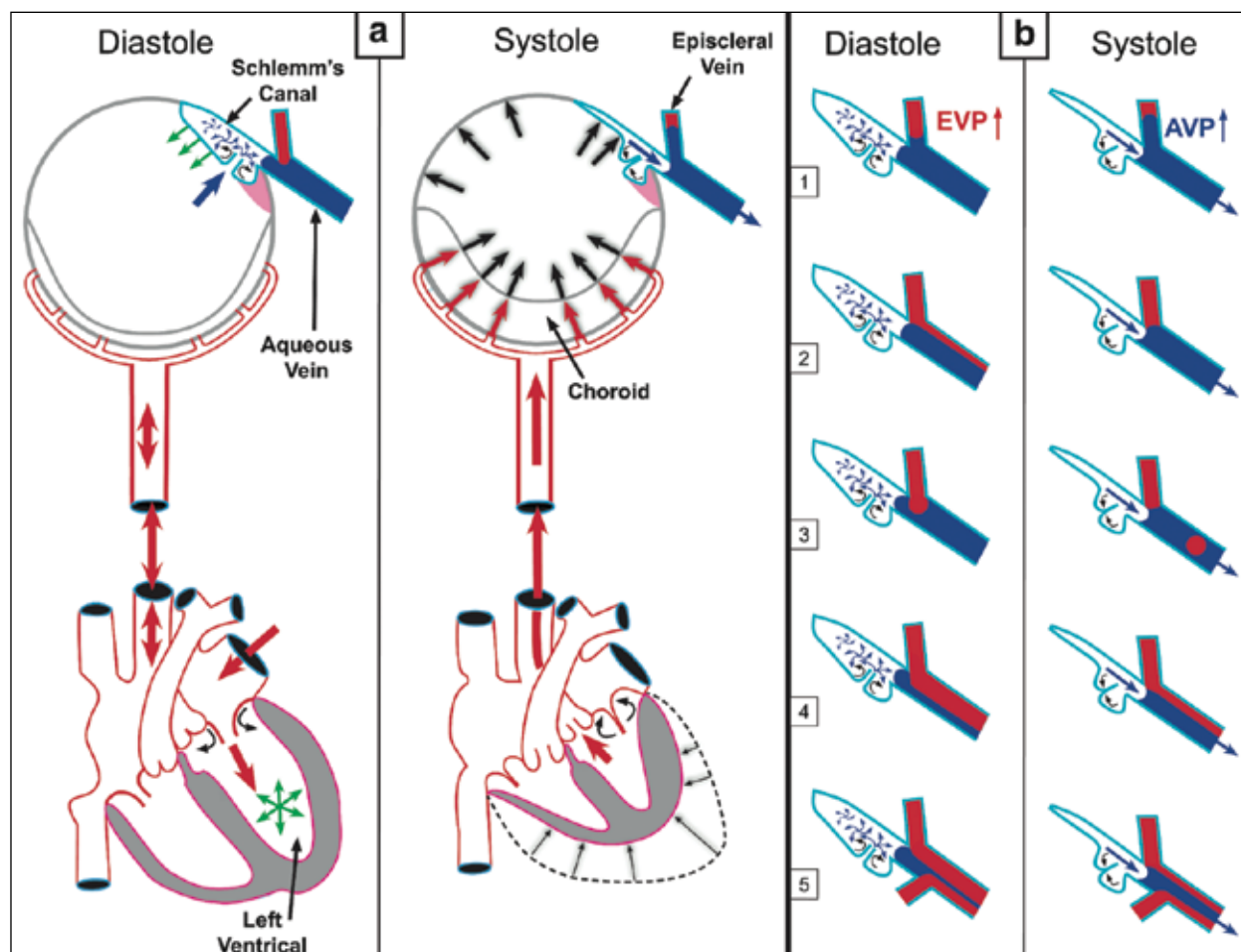


Figure 1. Cardiac source of pulsatile flow. Systole-induced choroidal vasculature expansion (red arrows). Transient IOP increase (large black arrows). Aqueous pulse wave distends the TM, forcing it outward into SC. One-way channels into SC prevent backflow (small curved arrows). Distention of the TM into SC reduces SC volume. SC pressure increases. Small black arrow denotes aqueous discharge from SC. Aqueous pulse wave then enters the aqueous vein (panel A, systole). Blood enters the left ventricle (green circle of arrows). Double red arrows indicate absence of a pressure wave in diastole. TM moves inward during diastole (green arrows). Aqueous enters SC (large blue arrow) (panel A, diastole). During diastole, episcleral venous pressure (EVP) is slightly higher than aqueous vein pressure (AVP), resulting in an increase in EVP. The relative increase in EVP causes episcleral vein blood to move toward (B 1) or into (B 2-5), the aqueous mixing vein. The next systole causes a transient increase in AVP. The oscillations result in pulsatile flow manifestations in the aqueous veins. The AVP increase causes transient movement of a standing aqueous wave into a tributary episcleral vein (B 1), transient elimination of a lamina of blood (B 2), a bolus of blood swept into the increased aqueous stream (B 3), an oscillating increase in the diameter of the aqueous component of a persistent lamina (B 4) or a trilaminar (B 5) aqueous flow wave (panel B). Reproduced with permission from Johnstone M, Jamil A, Martin E. Aqueous veins and open angle glaucoma. In: Schacknow PN, Samples JR. *The Glaucoma Book*. Heidelberg, Germany: Springer; 2010:68.

EXPLAINING THE REGULATION OF AQUEOUS OUTFLOW

In the dynamic model of glaucoma,⁹ pulse-dependent choroidal expansion causes the ocular pulse to create continuously oscillating, pulsatile waves that impinge on the TM (Figure 1). Ex vivo histologic^{4,9} and PhS-OCT evidence^{7,8} indicates that the TM moves outward in response to systolic

pulse-induced increases in IOP. Outward movement of the TM increases pressure in SC, narrowing its lumen and forcing fluid into collector channels and the aqueous veins during systole.⁶ In the subsequent diastolic interval, the IOP drops, and the TM can recoil toward the anterior chamber. The TM's movement reduces pressure in SC, permitting the entrance of aqueous from the anterior chamber.

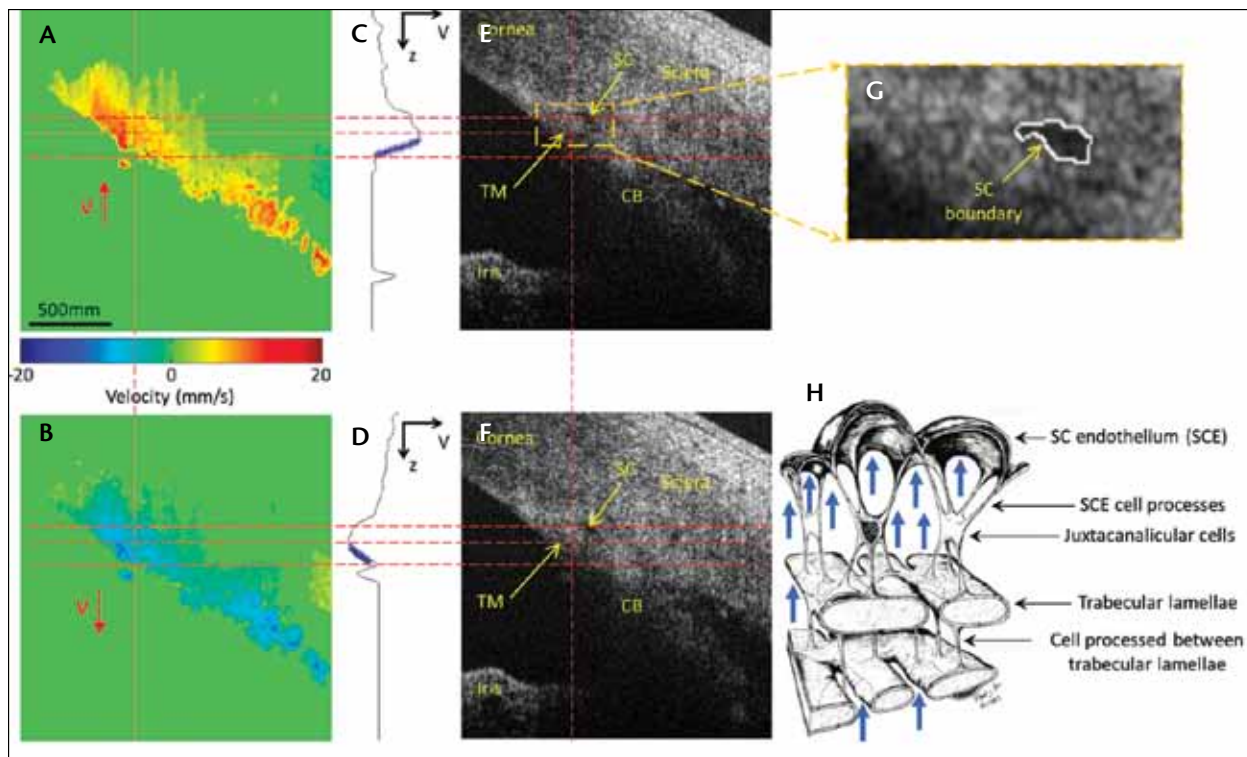


Figure 2. Ex vivo pulse-induced TM movement and SC deformation in a nonhuman primate eye at 8-mm Hg mean IOP. Representative cross-sectional images of tissue velocity in the corneoscleral limbus. Red corresponds to TM movement into SC during systole (A). Blue corresponds to TM movement away from SC during diastole (B). Depth-dependent velocity profiles along the vertical dashed lines in Figure 2A and B, respectively (C and D). Corresponding optical coherence tomography microstructural images from Figure 2A and B (E and F). Enlarged view of the area marked by the dashed yellow square in Figure 2E (G). The closed white curve in Figure 2G depicts the boundary of SC. Schematic of the SC endothelial attachment to the underlying trabecular lamellae (H). The bold arrows in Figure 2H indicate tissue responses to deforming forces induced by IOP transients. The horizontal lines are used to mark approximately the position of the TM, facilitating comparison between figures. Reproduced with permission from Li et al.⁷

Aqueous from the juxtacanalicular space flows to SC via the distal end of funnel-shaped collector vessels that arise from SC endothelium, attain a cylindrical or tubular shape, and attach to the canal's external wall. Suspended within SC, the aqueous collector vessels are subjected to oscillating changes in the pressure gradient similar to what occurs in all other vessels in the circulatory loops that return fluid to the heart. Both above and below the heart, oscillatory cardiac-induced changes in tissue pressure control such fluid movement toward the heart. The readily observable central retinal vein is often cited as a classic example of the behavior.

WHAT GOES WRONG IN GLAUCOMA?

In glaucomatous eyes, multiple abnormalities of the dynamic processes are present,¹⁰ including a progressive decrease in the elasticity and compliance of the TM that reduces the motion necessary to maintain vigorous pulsatile flow. Associated progressive apposition between the

walls of SC also occurs. Stiffening of the TM and apposition between SC's walls produce clinical manifestations. As glaucoma worsens, pulsatile flow initially slows and eventually stops.^{6,10} In eyes with abnormal pressure control, diurnal changes in IOP are preceded by alterations in the vigor of pulsatile flow. Glaucoma drugs such as adrenergics, miotics, and prostaglandin analogues induce an increase in pulsatile flow that precedes the drop in IOP.

In healthy eyes, the occlusion of distal episcleral veins increases pulsations in the more proximal aqueous veins, with a pulsatile aqueous wave even entering regional episcleral veins (called the *aqueous influx phenomenon*). In contrast, in glaucomatous eyes, blood refluxes into the aqueous veins from tributary episcleral veins to enter the aqueous vein emissaries communicating with SC (called the *blood influx phenomenon*). Blood reflux into SC may be caused during gonioscopy by a goniolens-induced increase in EVP or by aqueous aspiration. In normal sub-

jects, the pressure gradient reversal causes the TM to move rapidly away from the SC external wall, creating a large SC lumen into which blood quickly flows. In early glaucoma, TM movement slows and, as the disease progresses, eventually stops. The progressive reduction in TM motion is initially recognizable by a decrease in the rate at which SC filling occurs and, in later states of glaucoma, by a complete absence of SC blood entry.¹⁰

HOW CAN DYNAMIC CONCEPTS IMPROVE GLAUCOMA MANAGEMENT?

Slit-lamp examination of aqueous veins^{6,10} and gonioscopic examination of SC blood reflux¹⁰ can make use of what researchers know about TM movement and abnormal pulsatile flow in glaucoma. Matthias Grieshaber, MD,¹¹ used this information to evaluate the prognosis of canaloplasty, Ronald Fellman, MD,¹² to assess the effectiveness of ab interno trabeculectomy, and Ike Ahmed, MD (written communication, April 2013), to determine the best site at which to place a microinvasive glaucoma surgical device.

Investigators can now use PhS-OCT technology to analyze the properties of the TM that allow it to move normally.^{7,8} This tool offers the possibility of an office-based, non-contact, noninvasive, quantitative procedure to determine the TM's ability to maintain tightly controlled IOP homeostasis, perhaps a better surrogate than the occasional IOP

measurements that clinicians currently use. Characterization by PhS-OCT scans may help to predict the need to initiate or escalate therapy in addition to providing office-based guidance to determine the relative benefits of medical, laser, or surgical interventions. ■

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