Aqueous humor exiting through the conventional outflow system must pass from the anterior chamber, across the trabecular meshwork (TM) and inner wall of Schlemm canal (SC), and into the canal itself. From there, aqueous humor flows into the collector channels and the episcleral venous system. Unlike the uveoscleral outflow system, which is pressure insensitive (in humans vs animal models), the rate of conventional outflow is determined by IOP, outflow resistance or facility, the rate of aqueous humor production, and episcleral venous pressure.

In primary open-angle glaucoma, IOP is elevated due to an increase in outflow resistance in the TM—particularly the juxtacanalicular tissue—and the inner wall of SC. Despite the greater resistance in the conventional outflow system, most fluid flow still occurs through this pathway. Even so, the majority of glaucoma therapies do not focus on this site of flow but instead target the rate at which aqueous humor is produced or the uveoscleral outflow system, areas that are not affected in open-angle glaucoma.3

The value of optimizing conventional outflow lies not simply in reducing IOP but also in minimizing fluctuations in IOP. Unlike aqueous suppression, therapy that improves outflow facility results in smaller IOP fluctuations from normal physiologic phenomena such as drinking water. Fortunately, the appropriate selection of glaucoma therapy can modulate conventional outflow.

**MEDICAL THERAPY**

At present, the only commercially available medications that target conventional outflow facility are the miotics (eg, pilocarpine). Their mechanism of action, however, has an indirect effect on the outflow system. These agents stimulate parasympathetic nerves, inducing constriction of the ciliary muscle, which attaches to the scleral spur. Posterior displacement of the scleral spur upon contraction of the ciliary muscle places traction on the TM, increasing aqueous outflow facility without altering the underlying pathology.5,6 Although miotics can significantly reduce IOP, the frequency with which the agents must be administered and their side effects, including accommodative spasm and miosis, have limited the drugs’ current use.

Prostaglandin analogues (latanoprost, travoprost, and bimatoprost) are the most commonly used first-line agents. They appear to decrease IOP primarily by improving flow through the uveoscleral pathway.7 Some studies, however, have suggested that prostaglandins directly affect the TM as well and increase conventional outflow facility, potentially representing another method by which to optimize conventional outflow, although this has not been a consistent finding.8,9 New classes of medication under investigation,
including the rho kinase inhibitors, appear to directly improve conventional outflow facility through their effect on the TM and SC, but these drugs are not yet commercially available in the United States. 

**LASER THERAPY**

Laser trabeculoplasty (LTP), with either an argon or selective laser, directly targets the TM. LTP’s precise mechanism of action remains unclear, but it likely involves the release of inflammatory cytokines, followed by the recruitment of monocytes to the TM. Subsequent remodeling of TM tissue presumably reduces outflow resistance. LTP using other wavelengths of light such as a micropulsed diode laser presumably has a similar mechanism of action.

**TM SURGERY**

Recently, one of the most active areas of research and development in glaucoma therapy has focused on surgical procedures that directly target the TM and SC. Canaloplasty is a modification of nonpenetrating glaucoma surgery. It adds the use of a microcatheter to dilate SC and the threading of a suture circumferentially through the canal. Tensioning the suture presses it against the inner wall of SC and thus stretches the canal and TM. The procedure’s exact mechanism of action is unclear, with no published studies available on the topic. One possibility is that surgery stents open the canal, which can collapse at high pressures and have herniations of the inner wall into the collector channels. Another possibility is that the procedure ruptures the inner wall and juxtanodular tissue of the TM, similar to viscocanalostomy, which is another variation of nonpenetrating glaucoma surgery that involves the injection of viscoelastic into SC at the time of deep sclerectomy. Instead of trying to reduce flow resistance in the TM and inner wall of SC, the Trabectome (NeoMedix Corporation) and the iStent Trabecular Micro-Bypass Stent (Glaukos Corporation) remove or bypass these tissues. Doing so presumably creates a direct path from the anterior chamber to the collector channels.

Specifically, the Trabectome removes a segment of the TM and the inner wall of SC using an ab interno approach. The system consists of a handpiece with an insulated footplate that can be inserted through the TM into SC. An electrocautery generator then ablates the TM and inner wall of SC, while the footplate protects the outer wall from thermal damage. Although the procedure is similar in principle to goniotomy, it differs in that the TM tissue is ablated instead of just incised. This may reduce the likelihood of reapproxima-

"It is to be hoped that research and development will lead to additional therapeutic options for improving outflow facility and reveal the mechanisms of action of trabecular meshwork surgery."

The iStent is a titanium microbypass stent that is approximately 1 mm in length and has an outside diameter of 180 μm. The device fits within SC, while its "snorkel" passes through the TM and into the anterior chamber, providing a direct pathway for aqueous humor to enter the distal outflow system. The FDA approved the device for use in combination with cataract surgery in patients with mild to moderate open-angle glaucoma.

Canaloplasty, the Trabectome, and the iStent achieve a moderate reduction in IOP, typically into the mid- to high teens. These approaches appear to offer a better safety profile than filtering surgery, including a very low risk of hypotony. Moreover, the risk of late-onset endophthalmitis is negligible with the iStent and Trabectome, because there is no filtering bleb.

The complete mechanism of action of TM surgery remains unclear, and there are a number of unanswered questions. First, why is postoperative IOP not closer to episcleral venous pressure, which is around 7 mm Hg in healthy subjects? The iStent and Trabectome would presumably largely bypass or eliminate the resistance in the TM and inner wall of SC. This suggests that outflow resistance downstream of SC may represent a significant proportion of total conventional outflow resistance. In support of this idea, research by Rosenquist et al suggested that resistance distal to SC may account for as much as 50% of total outflow resistance. Second, why do these surgeries fail? Fibrosis of the surgical site is typically absent after failed ab interno trabeculectomy even though decompression of the eye results in blood reflux, demonstrating that the blood-aqueous barrier is open. Whether or not postoperative changes in the distal outflow system occur and result in surgical failure cannot be determined at this time. Finding answers to these questions will likely require the development of techniques for imaging the small-scale structures involved.

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CONCLUSION

Conventional outflow can be modulated with medical, laser, and surgical therapy. It is to be hoped that research and development will lead to additional therapeutic options for improving outflow facility and reveal the mechanisms of action of TM surgery. Improving conventional outflow is critical not only to the reduction of IOP but also to optimizing the quality of IOP control by minimizing fluctuations.

Arthur J. Sit, SM, MD, is a glaucoma specialist and an associate professor of ophthalmology at the Mayo Clinic in Rochester, Minnesota. He has been a consultant to and currently receives research funding from Glaukos Corporation. Dr. Sit may be reached at (507) 284-2878; sit.arthur@mayo.edu.

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