Outflow Resistance

Implications for canal-based surgery.

BY ARTHUR J. SIT, SM, MD

Welcome to Glaucoma Today’s second installment of “Bench to Bedside: How Laboratory Studies May Better Explain Why Procedures Work and Why They Fail.” The essence of this series is to explain the “why” of the clinical quandaries we glaucoma specialists often face. This group of articles tackles why canal-based surgery does not lower IOP to episcleral venous pressure (EVP). One would think it should, but on average, it does not. Basic laboratory experiments may improve our understanding.

We asked three basic and clinician scientists critical questions about outflow to bridge the gap in this clinical puzzle from bench to bedside. In the first installment, Murray Johnstone, MD, analyzed past and recent research on outflow resistance and discussed how high-resolution optical coherence tomography and optical microscope platforms permit the real-time observation of collector channel motion. (See Dr. Johnstone’s article in the January/February issue of GT, and watch his video on the opening and closing of collector channels.) In this second installment, Arthur J. Sit, SM, MD, provides his answers to four questions about outflow. Stay tuned for a response from Haiyan Gong, MD, PhD, in the next appearance of “Bench to Bedside.”

—Ronald L. Fellman, MD, and Davinder S. Grover, MD, MPH, section editors

The classic outflow experiment by Rosenquist et al1 found greater downstream resistance to aqueous outflow than Grant’s classic study.2 Why? Does this article at least partially explain IOP control after canal-based surgery?

The differences in protocols between the study by Rosenquist et al1 and the original study by Grant2 provide clues to the mechanism of action and results of canal-based surgery. As discussed by Rosenquist et al, the perfusion pressures used by Grant in his original experiments were not physiologic, given that the EVP in cadaver eyes is essentially zero. In this situation, the pressure drop from the anterior chamber to the episcleral veins is much larger than if the EVP were at a physiologic level. This abnormal pressure difference can create sources of outflow resistance that would not be present with lower perfusion pressures. In particular, Schlemm canal typically has very low flow resistance (at least over short segments), but a collapsed canal can have very significant resistance. In addition, herniations of the inner wall into the collector channels at high perfusion pressure can further increase resistance by reducing the perfusion area of the trabecular meshwork (TM) and the inner wall of Schlemm canal that aqueous humor crosses.3 Not only would a complete trabeculotomy relieve the resistance of the inner wall and juxtacanalicular tissue, but it would also address the abnormal resistance caused by the high pressure gradient, resulting in a greater overall reduction of resistance.

When these results are applied to modern canal-based surgeries, it becomes clear that there can be multiple mechanisms of action. First, surgeries that bypass the TM in a small area but do not alter Schlemm canal are likely to reduce outflow resistance, but they may have limited efficacy at high IOPs unless positioned directly adjacent to a collector channel. In contrast, surgeries that alter Schlemm canal but do not change its inner wall and the TM may be helpful in reducing canal collapse or herniations, but these procedures will not alter TM resistance. Surgeries that perform both tasks may have the best potential efficacy, at least in the short term. Long-term efficacy, however, may be determined by mechanisms not present in the cadaver models of Rosenquist et al and Grant.
“Outflow facility is simply the mathematical inverse of outflow resistance.”

The question of why these surgeries do not produce lower long-term IOPs comparable to those achieved in cadaver models is still a mystery, particularly because EVP is likely lower than 10 mm Hg. This value is based on older studies that estimated the pressure required to partially collapse an episcleral vein.\(^4\) Ideal tube laws as well as experimental evidence in monkeys indicate that the external pressure that just begins to collapse a vein is the one closest to true EVP. My colleagues and I have found that EVP is more typically around 7 mm Hg in healthy human eyes.\(^5,6\) Some experimental animal models that measure EVP by direct cannulation report higher EVP,\(^7\) but it is possible that the process of cannulating vessels alters the EVP or that different species have different EVPs due to variations in habitual body position compared with humans.

If distal outflow resistance is higher than initially anticipated, is most of the resistance coming from deep in the sclera, or is it more superficial?

This really is the key question. Our current knowledge of the distal outflow system and episcleral venous plexus is poor. Anatomical structures can be discerned by the use of latex or neoprene casting, but this tells us little about the functional anatomy of the distal outflow system. Many of the vessels, particularly in the episcleral venous plexus, have smooth muscle and can contract to reduce vessel diameter, significantly increasing outflow resistance. In the episcleral venous system, arteriovenous anastomoses exist that can alter the back pressure characteristics of the system by changing the degree of connectivity with the arterial system. Imaging in living subjects will be required to fully explain the complexities of the distal outflow system.

What is outflow facility, and how is it measured? What is the correlation between outflow facility and outflow resistance?

Outflow facility is simply the mathematical inverse of outflow resistance. The best way to measure it is with a two-level constant pressure perfusion system, in which the eye is perfused at two different pressures and resistance is calculated as the ratio of the flow rate difference divided by the pressure difference. This invasive technique is not suitable for routine use in humans. Outflow facility in humans must therefore be measured by tonography or fluorophotometry. Both of these techniques involve numerous assumptions but generally produce the same mean outflow facility.

In your opinion, why is circumferential flow in Schlemm canal limited, and does this influence canal-based surgery?

Circumferential flow in Schlemm canal can be limited for two reasons. First, discontinuities or areas of narrowing can create regions of high resistance to circumferential flow. Although human eyes tend to have roughly contiguous canals, there can still be variations in diameter. Second, there may be segments of the distal outflow system (e.g., associated with certain collector channels) that are low resistance. Fluid would preferentially flow out of these channels instead of continuing circumferential flow. The implication for canal-based surgery is that treating more of Schlemm canal will result in a lower IOP, at least in the short term. Rosenquist et al demonstrated that larger trabeculotomies in cadaver eyes resulted in lower outflow resistance when perfused at physiologic pressures.\(^1\) The factors that determine long-term outcomes still need to be clarified.

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