Fluid Dynamics of a Novel Micro-Fistula Implant for the Surgical Treatment of Glaucoma

Arsham Sheybani,[1] Herbert Reitsamer,[2,3] and Iqbal Ike K. Ahmed[4,5,6]

[1]Department of Ophthalmology and Visual Sciences, Washington University School of Medicine, St. Louis, Missouri, United States
[2]Department of Ophthalmology, University Clinic Salzburg/SALK, Austria
[3]Paracelsus Medical University, Salzburg, Austria
[4]Department of Ophthalmology and Vision Sciences, University of Toronto, Toronto, Ontario, Canada
[5]Credit Valley Eye Care, Mississauga, Ontario, Canada
[6]Trillium Health Partners, Mississauga, Ontario, Canada

Correspondence: Arsham Sheybani, Washington University School of Medicine, 660 South Euclid Avenue, Campus Box 8096, St. Louis, MO 63110, USA; sheybaniar@vision.wustl.edu.

Submitted: February 5, 2015
Accepted: June 10, 2015

Citation: Sheybani A, Reitsamer H, Ahmed IIK. Fluid dynamics of a novel micro-fistula implant for the surgical treatment of glaucoma. *Invest Ophthalmol Vis Sci*. 2015;56:4789–4795. DOI:10.1167/iovs.15-16625

Purpose. The purpose of this study was to describe the fluidics of a novel non-valved glaucoma implant designed to prevent hypotony and compare the fluidics of this device with two commonly used non-valved glaucoma devices.

Methods. The XEN 45 micro-fistula implant was designed to limit hypotony by virtue of its length and width according to the Hagen-Poiseuille equation. Flow testing was performed using a syringe pump and pressure transducer at multiple flow rates. The pressure differentials across the XEN implant, the Ex-Press implant, and 10 mm of silicone tubing from a Baerveldt implant at a physiologic flow rate (2.5 μL/min) were extrapolated.

Results. The XEN 45 achieved a steady-state pressure calculated at 7.56 mm Hg at 2.5 μL/min. At the same flow rate, the Ex-Press device and Baerveldt tubing reached steady-state pressures of 0.09 and 0.01 mm Hg, respectively.

Conclusions. Under flow testing, the XEN micro-fistula implant was able to maintain backpressure above numerical hypotony levels without the use of complex valve systems. This is due to the XEN implant's design, derived from the principles that dictate Newtonian fluids.

Keywords: fluidics, glaucoma surgery, MIGS

Glaucoma is a blinding disease that affects more than 60 million people worldwide.[1] Lowering intraocular pressure (IOP) through use of medication, laser treatments, or incisional surgery can prevent glaucoma progression. The most common glaucoma surgeries (trabeculectomy and tube shunt drainage devices) lower IOP by diverting aqueous humor (AH) from the anterior chamber to the subconjunctival space. These procedures are prone to early (<1 month postoperative) hypotony and hypotony-related complications that can result in severe vision loss in at least 20% of patients.[2] Thus, there is a need to develop approaches to avoid this complication.

Several approaches are currently used in an attempt to avoid postoperative hypotony. These range from modifications to standard surgical techniques to the use of devices to regulate flow of AH. Unfortunately, these approaches are variable and/or require alterations to the surgical procedure that not only limit reproducibility but also do not successfully limit hypotony.

The most common surgical procedure for glaucoma is trabeculectomy. This involves creating a scleral flap over a sclerostomy to regulate flow of AH to the subconjunctival space. The scleral flap is closed with sutures, and suture tension is adjusted until minimal flow is visible at physiologic IOPs. This process does not incorporate metrics that assess flow; the surgeon adjusts the flap suture tension, which ultimately dictates flow.[3] Suture tension is adjusted by direct observation of the seepage of fluid beneath the flap. This subjective assessment of flow, modified by suture tension, is what surgeons rely on to prevent hypotony, although this complication still occurs.

In order to standardize the conduit created beneath the scleral flap in trabeculectomy, the Ex-PRESS (Alcon Laboratories, Inc., Fort Worth, TX, USA) implant is placed at the time of trabeculectomy. Although it reduces the rate of hypotony compared to standard trabeculectomy, flow is still adjusted by suture tension of an overlying scleral flap.[4] As in conventional trabeculectomy described above, the regulation of flow is achieved through a subjective process.

The Ahmed valve (New World Medical, Inc., Rancho Cucamonga, CA, USA) is a glaucoma drainage device composed of silicone tubing attached to a plate housing a valve to limit flow at low pressures. Surgically, the silicone tubing is placed in the anterior chamber, and the plate is secured to the sclera and covered by conjunctiva. This allows AH to flow from the anterior chamber to the subconjunctival space, lowering IOP. Despite the valve, early postoperative hypotony may still occur, often requiring surgeons to leave viscoelastic agents in the anterior chamber.

The Baerveldt drainage device (Abbott Medical Optics, Abbott Park, IL, USA) is another glaucoma drainage device, consisting of a silicone tube attached to a plate and implanted in a fashion similar to that used for Ahmed valve. The Baerveldt drain differs from the Ahmed valve in that it requires the silicone tube be tied with an absorbable or releasable suture to prevent hypotony until encapsulation occurs around the plate.

$$\Delta P = (8\mu LQ) / (\pi r^4)$$

ΔP – Pressure loss along the lumen of the tube
μ – dynamic viscosity
L – Length of the tube
Q – volumetric flow rate
r - radius

Figure 1. Hagen-Poiseuille equation.

It does not protect against hypotony, and when the tube fully opens, the fibrous capsule around the plate provides resistance to flow and protection from hypotony. In order to obtain IOP control until the tube opens, surgeons create various numbers of slit incisions in the tubing to allow for flow. Some surgeons place a suture (ripcord) in the lumen to reduce flow in an effort to prevent hypotony. Once the tube opens, hypotony can still occur.[5,6]

Inherent in these approaches is the variability in the procedures and the inability to prevent hypotony in a simple and reproducible manner.[7,8] Not every surgery will be the same if suture tensions are subjectively adjusted; tubes need to be tied or ripcord sutures placed, or viscoelastic agents of various amounts are to be left in the AC. The ideal device would lower intraocular pressure safely in a simple and predictable manner without the need for surgical modifications. Such a device can be designed by using a common physical law applicable to Newtonian fluids (such as AH).

The Hagen-Poiseuille equation allows us to calculate the resistance to flow through a cylindrical tube. Assuming laminar flow of a noncompressible fluid, the outflow resistance and therefore pressure differential increases linearly in relation to the length of the tube and decreases to the fourth power of the lumen radius. A longer, thinner tube will provide more resistance to flow than a shorter and wider tube. Therefore, with a known volumetric flow rate (AH production), we can calculate the pressure differential of a fluid flowing through a cylindrical pipe. We applied these principles to design a cylindrical pipe that provides a set amount of pressure differential across its entire length. This pressure differential is directly related to the amount of resistance in the tube. Therefore, for a given flow rate, we can design a device that theoretically limits hypotony simply due to its dimensions (length and inner lumen radius), without the need for a complex system of valves and regulators. Here, we describe the flow characteristics through the XEN implant and compare the fluid dynamics of this device to two non-valved devices currently used in glaucoma surgery. We discuss why hypotony can still occur with current devices and why several other novel devices with complex mechanisms to avoid hypotony have theoretical disadvantages compared to the XEN implant.

Materials and Methods

Device Composition

The XEN implant is a small hydrophilic tube composed of a porcine gelatin cross-linked with glutaraldehyde. The device has been previously explained in detail, including descriptions of the biomechanical properties and histopathology.[9] There are currently three models of the device, varying by lumen size. The latest implant, the XEN 45, was designed from principles of fluid dynamics to avoid early postoperative hypotony and is discussed below. It causes no foreign body reaction when implanted in animal models[9] and has demonstrated excellent biocompatibility in humans.[10]

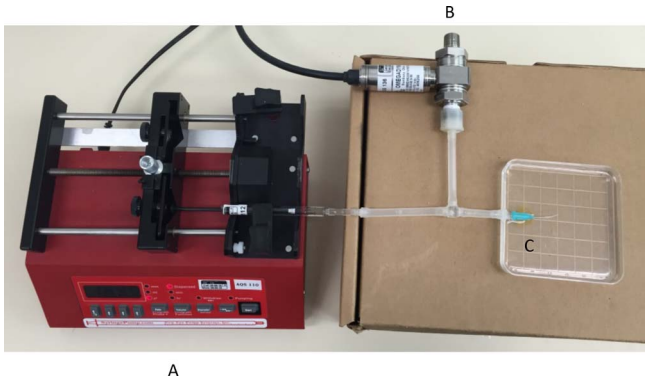

Figure 2. Experimental setup. A syringe pump (**A**) is connected to a differential pressure transducer (**B**) and needle housing (**C**). The differential pressure transducer is connected to a computer that records real-time pressure readings.

Implant Design

The Hagen-Poiseuille equation was used to calculate the required dimensions of a tube that would prevent hypotony at average AH production (Fig. 1). AH production occurs at a rate of 2 to 3 μL/min.[11] In order to prevent hypotony, a device would need to create approximately 5 mm Hg of steady-state pressure at this rate. This pressure can be thought of as the pressure difference between the two ends of a tube. We then calculated the dimensions of a tube required to prevent hypotony with these pressures in mind (erring on the side of less AH production). We set the length of the tube to 6 mm in order to conform to our previous injector systems. Clinically, this length has been ideal to prevent device erosion and ensure that AH is directed posteriorly away from the limbus. At that length, a lumen of 45 μm would provide a steady-state pressure of approximately 6 to 8 mm Hg at 2 to 2.5 μL/min as calculated by the Hagen-Poiseuille equation.

We also measured flow rates at various pressures prior to performing these experiments. At 5 mm Hg, the flow rate through this implant was measured at 1.2 μL/min. This is less than that of AH production and therefore theoretically protects against hypotony at average AH production. The Reynolds number through such a tube at 2.5 μL/min of aqueous production is 1.3, meaning that flow is laminar even at this higher rate.

Flow Studies

The experimental setup is shown in Figure 2. It is similar, with slight modifications, to what has been previously described for flow testing of glaucoma implants.[12] A syringe pump (New Era syringe pump model NE-4000; New Era Pump Systems, Inc., Farmingdale, NY, USA) housing a 500-μL syringe was connected to a 23-gauge stainless steel blunt tipped dispensing needle onto which implants would be placed. An Omegadyne differential pressure transducer (model MDWU001V10T3C0-T1A1CE; Omega Co., Stamford, CT, USA) was connected upstream to the devices to be tested. Experiments were conducted in distilled water at 21°C, where the viscosity is 0.9778 centipoise (cP). The viscosity of water at 37°C is 0.6904 cP. Because the viscosity of water is temperature-dependent, all pressure measurements were converted to account for this at physiologic temperature (37°C) by dividing by 1.416 (0.9778/

Investigative Ophthalmology & Visual Science

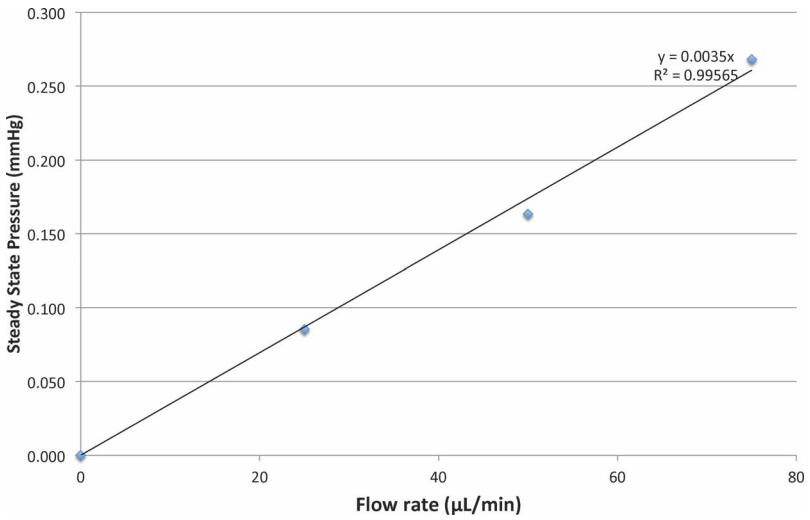

Figure 3. Steady-state pressure at different flow rates of the experimental setup at baseline. *Error bars* are unseen at this scale as the standard deviation is ≤0.001 at each flow rate.

0.6904) where stated. The viscosity of AH at 36°C is only 2% higher than the viscosity of water at the same temperature (Vass C, et al. *IOVS* 2004;45:ARVO E-Abstract 5030). This was not corrected because the difference is negligible. Once the syringe pump reached the desired flow rate (25 µL/min, 50 µL/min, and 74 µL/min), it was left to equilibrate until a steady-state pressure (there was no change in pressure over 5 minutes) was measured. The steady-state pressures at various flow rates were measured. Linear regression was used to extrapolate steady-state pressure at physiologic flow rates (2.5 µL/min) through the Ex-Press and Baerveldt devices. There was such little resistance to flow (essentially 0 mm Hg) when steady-state pressures were measured at physiologic flow rates that measuring steady-state pressure at higher flow rates was performed so that pressures could be detected for these two devices. Because pressures at these flow rates are linearly related, linear regression is a valid method for obtaining these results. The XEN implant measurements occurred at actual near-physiologic flow rates (1, 2, 5, and 10 µL/min) becauase measured pressures were above 0 mm Hg.

Initial steady-state pressure of the experimental setup was measured without a device on the needle. This value was then subtracted from the steady-state pressure measured for each device for every flow rate, and these adjusted values were reported in this study. Dye was placed in the distilled water solution, and flow was observed using a microscope to ensure that the system did not leak when devices were tested.

The Ex-Press P-50 was placed on the end of 10 mm of silicone tubing (300-µm internal diameter) in order to provide a water-tight seal directing flow only through the Ex-Press. The Baerveldt tubing was removed from the plate, and 10 mm of tubing was attached to the needle. Flow testing was also performed with a single 5-0 monofilament nylon suture as well as with a single 4-0 silk suture spanning the entire lumen of the tubing to simulate the surgical modification instituted by some surgeons. The XEN implant was directly attached to the end of an implant fixation block. The implant fixation block is a stainless steel block with a Luer fitting on one end and a small-diameter hole on the other end and with a passage connecting the two. The diameter of the hole is based on the outside diameter of the implant used and is selected to be approximately 10 µm smaller than that of the implant. When the implant hydrates, it swells to form a very light press-fit with the hole, thus forming a watertight seal.

Statistical Analysis

Linear regression was computed using Excel (Microsoft Co., Redmond, WA, USA). R^2 values and regression formulas are displayed in each graph. Experiments were repeated three times. Data are reported as averages of three experiments with standard deviations. Standard deviation was not reported for calculated values obtained from the linear regression plots.

Results

Baseline flow of the experimental setup is shown in Figure 3, with only the 23-gauge needle. Even at 75 µL/min, the steady-state pressures, or pressure differential across the system, were 0.268 ± 0.002 mm Hg and 0.085 ± 0.001 mm Hg at 25 µL/min, respectively. Graphs and results represent actual values at 21°C.

Linear regression of steady-state pressures for the Ex-Press device and Baerveldt tube are shown (Fig. 4). At 2.5 µL/min of flow, the Ex-Press had a steady-state pressure of 0.13 mm Hg, whereas the Baerveldt tube had a steady-state pressure of 0.02 mm Hg. Figure 5 shows pressure plots for the 5-0 monofilament and 4-0 silk suture inside the lumen of the Baerveldt tube. The single 4-0 silk suture inside the lumen reached a steady-state pressure at 2.5 µL/min of 1.16 mm Hg compared to 0.3 mm Hg with the 5-0 suture.

The XEN implant steady-state pressure is shown (Fig. 6). At 2 µL/min, the XEN 45 implant reached a steady-state pressure of 8.9 mm Hg or 6.28 mm Hg at 37°C. At 2.5 µL/min, the device had a calculated steady-state pressure of 10.98 mm Hg. Adjusting for the viscosity of water at physiologic temperature (37°C), this equals a pressure differential of 7.56 mm Hg. By comparison, at 37°C, the Ex-Press and Baerveldt devices had pressure differentials of 0.09 and 0.01 mm Hg, respectively.

Discussion

Glaucoma filtering surgery is not standardized, and attempts to control flow in a reproducible manner still result in early postoperative hypotony, with potentially blinding complications. In this study, we tested a novel glaucoma implant and its ability to achieve a steady-state pressure above hypotony levels at physiologic AH production rates.

Investigative Ophthalmology & Visual Science

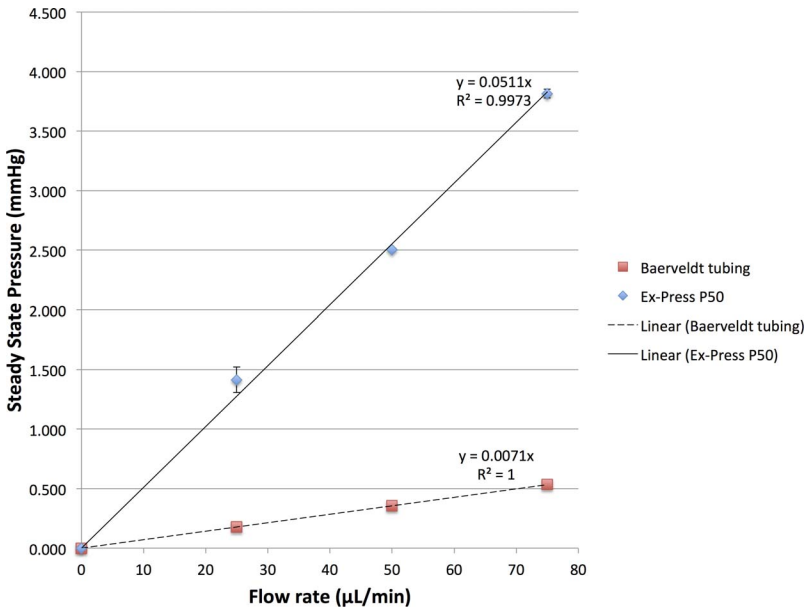

Figure 4. Linear regression of steady-state pressures for the Ex-Press device and Baerveldt tubing. *Error bars* show standard deviation. For the Baerveldt tubing, *error bars* are unseen at this scale as the standard deviation is ≤0.001 at each flow rate.

The total flow rate of AH (at steady-state IOP) out of the anterior chamber of the eye is equal to the total aqueous production rate (at that same instance) in the eye. Therefore the IOP is a function of the total outflow resistance of all outflow channels combined. When an implant, in the form of a cylindrical tube, is added as an outflow channel to the eye, then the Hagen-Poiseuille law can be applied to calculate the resistance to flow through such a tube. This holds true under the assumption that all outflow occurs preferentially through this implanted tube. This assumption is essentially correct when the resistance through the tube is significantly less than the cumulative resistance of the other outflow channels.

The XEN 45 micro-fistula implant was designed by applying the Hagen-Poiseuille equation. This law provides the pressure differential across a tube with constant dimensions for a noncompressible Newtonian fluid under laminar flow (like AH at physiologic flow rates). The pressure differential across a tube is proportional to the resistance to flow. Resistance to flow is directly proportional to the length and inversely proportional to the radius of the tube to the fourth power. Thus, a longer, thinner tube provides a larger pressure differential, or more resistance to flow.

By knowing the volumetric flow rate and dynamic viscosity of a fluid, one can design the dimensions of a tube in order to achieve an ideal pressure differential (resistance to flow) across the tube. This pressure differential is equivalent to the pressure required to propel fluid across the tube at a set flow rate. This is the same as the steady-state pressure that we measured in

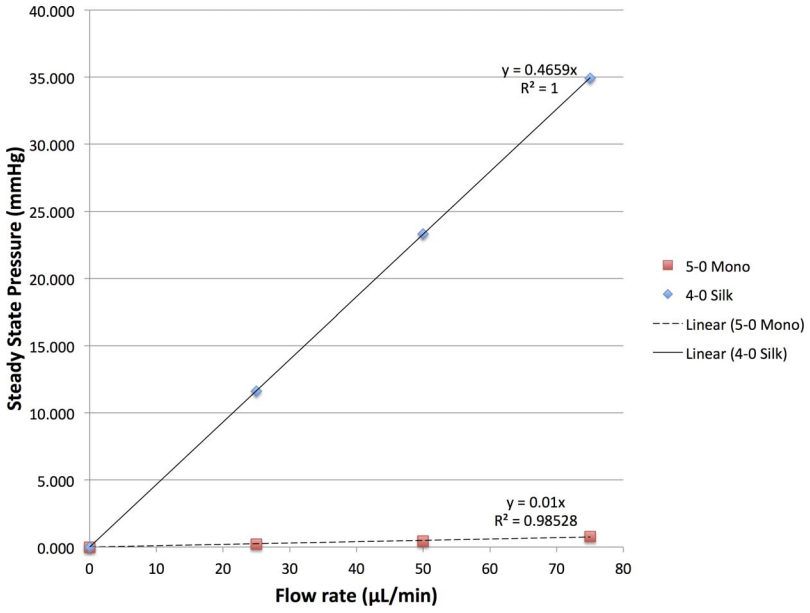

Figure 5. Steady-state pressure at various flow rates through a Baerveldt tube with 5-0 monofilament and 4-0 silk suture in the lumen. *Error bars* are unseen at this scale as the standard deviation is ≤0.001 at each flow rate.

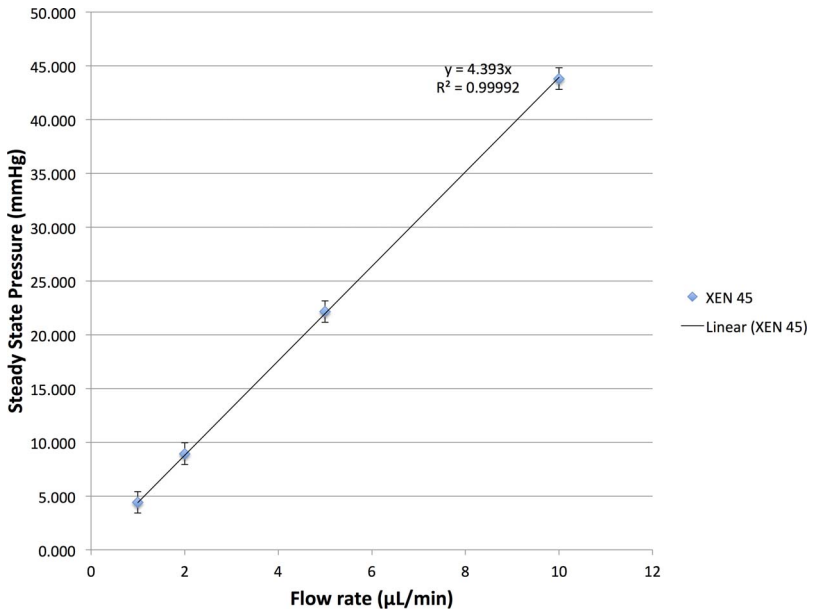

Figure 6. Steady-state pressure at various flow rates for the XEN 45 implant. *Error bars* show standard deviation.

our study. This steady-state pressure can be thought of as the tube's backpressure or resistance to flow when placed in the anterior chamber. In other words, it is the pressure at which the anterior chamber is held when flow occurs through the tube. To avoid hypotony, resistance to flow should be calculated at physiologic flow rates equivalent to AH production rates assuming there is no flow through conventional or alternative pathways (trabecular meshwork or uveoscleral flow). One can make this assumption when flow rate through a tube is greater than the cumulative flow rate through physiologic pathways.

In vivo, AH is produced at 2 to 3 µL/min. Statistical hypotony has been defined as an IOP of <6.5 mm Hg, but this definition may not hold clinical significance.[13] To be consistent with prospective clinical trials, an undesirably low IOP is defined as ≤5 mm Hg.[2] The XEN 45 implant was designed to prevent hypotony at a range of 2 to 2.5 µL/min, erring on the side of lower AH production rates and assuming no subconjunctival resistance once fibrosis occurs. Essentially, the implant was designed to prevent hypotony under the most conservative conditions: low AH production with no subconjunctival resistance. The XEN implant, as measured by our experiments, provides 6.28 to 7.85 mm Hg of backpressure, thus theoretically protecting against hypotony. Data from clinical trials with this device in humans confirm our results as there have been no hypotony-related complications with the XEN 45 implant (data not yet published).

Protection from early postoperative hypotony does not mean that low IOP's cannot be achieved. An in vivo study in rabbits explored the effect of subconjunctival resistance on IOP in both valved and non-valved devices. Holding pressures for the devices were measured after flow through the system had been stopped. After 15 minutes of a stable IOP (range: 2.0–7.1 mm Hg), the conjunctiva around the device was disrupted, eliminating any resistance the conjunctiva provided. The IOP in both the valved and non-valved devices fell rapidly to 0 mm Hg once the conjunctiva was disrupted.[14] This demonstrates that once the bleb has matured and subconjunctival fibrosis has occurred, the resultant IOP will ultimately be limited by subconjunctival resistance. In other words, the device no longer limits the flow at steady-state pressures since the resistance in the subconjunctival space is significantly higher. In addition, higher bleb resistance may decrease flow through the implant so by Poiseuille's law the implant would then provide less resistance to flow through its lumen. Thus, in theory, although the XEN implant would not be able to achieve an IOP of <5 mm Hg; if there is no subconjunctival resistance, IOP's approximately 6 mm Hg is theoretically possible. The purpose of the XEN implant is to prevent hypotony before subconjunctival fibrosis has occurred, but this does not equate to higher long-term pressures than in devices with less resistance to flow. Subconjunctival resistance will ultimately limit the IOP in subconjunctival filtering surgery.

Clinically, the Ex-Press device, when placed without a scleral flap, results in hypotony.[15] Our flow studies showed that the device does not provide enough resistance to flow. This explains why the device should be placed under a scleral flap similar that in trabeculectomy surgery. The surgical variability to flow is then dictated by the surgeon's subjective analysis of flow beneath the flap intraoperatively. In fact, computational modeling of glaucoma surgery comparing trabeculectomy to Ex-Press shunt surgery found that the IOP difference was <1 mm Hg (higher with Ex-Press), confirming that the implant intrinsically does not provide significant outflow resistance.[16]

The Ex-Press device has a beveled opening that tapers to a 50-µm inner lumen.[17] In reality, the opening is approximately 200 µm in inner diameter. Not only does this provide almost no resistance to flow, as our data show, but the design of the device makes it amenable to occult occlusion. Theoretically, even a 100-µm particle could pass through the outer lumen, obstructing the inner lumen and not be visible clinically.

The tubing used in Baerveldt implants also provides such little resistance to flow that hypotony can still occur.[2] Even with modifications to the procedure with sutures in the lumen of the tube, there is no significant outflow resistance. Instead, the device relies on the resistance to outflow provided by the fibrotic reaction that occurs postoperatively.[18,19] During the early postoperative course, inadequately tying the tube closed could result in hypotony.

The tubing for the Ahmed valve is the same silicone tubing used on the Baerveldt shunt. However, the valve theoretically should prevent hypotony despite virtually no outflow resistance provided by the tube. As tested, the Ahmed valve has a

lower pressure differential at lower flow rates and a greater pressure differential at higher flow rates. This relationship is nonlinear, so in theory this device should work well to protect against hypotony at low flow rates (low AH production) while decreasing IOP more effectively at higher flow rates (high AH production).[20] However, if the valve mechanism fails, there is no protection against hypotony in the early postoperative period.

Opening pressures for the Ahmed valve are high, requiring the device to be primed with an average pressure of approximately 3000 mm Hg.[21] Thus, inadequate priming prior to surgical implantation can lead to device failure. Although the valve is designed to close at pressures less than 8 mm Hg, according to the manufacturer, the valve mechanism can malfunction (where the IOP is <8 mm Hg) in up to 50% of these devices when tested under simulated conditions.[22] It is important to note that clinical studies do not support early clinical hypotony rates of 50% because an IOP of <8 mm Hg does not necessarily result in clinical hypotony. However, aside from low AH production and leakage around the tube, valve failure may partially explain why hypotony is still seen with the device. Studies show that the Ahmed device acts to restrict flow rather than behaving like a true valve that opens and closes at certain pressures.[23] Furthermore, intraoperative testing of opening and closing pressures was predictive of low postoperative IOP with the device, suggesting variability in the valve mechanism.[24] In addition, other valved devices do not open and close as described by manufacturers and do not necessarily limit hypotony as closing pressures have been measured at <5 mm Hg.[25]

There are several novel devices with adjustable valve mechanisms in published reports.[26–28] In principle, having control of the pressure postoperatively seems ideal. Unfortunately, these devices incorporate complex mechanisms for outflow resistance compared to a valveless system. The valve of a device can fail, leading to elevated IOPs.[29] Focal tube constriction to regulate flow, as proposed by these devices, yields unpredictable pressure regulation, a finding that holds theoretically true according to the Hagen-Poiseuille equation.[30] In these devices, very small changes in inner diameter over such a short length can have very significant changes in outflow resistance. In addition, several of these devices[26,27] use magnetic components, and we suspect that patients with these devices would not be able to undergo magnetic resonance imaging (MRI). Adjustable devices will also ultimately be limited by fibrosis, so the utility of the adjustable valve would be short-lived. This is why the Baerveldt tube (providing only 0.01 mm Hg of outflow resistance) does not universally result in late postoperative hypotony after the tube has opened when fibrosis around the device has occurred.

A perceived limitation of the study is the differing flow rates that were used to test the Ex-Press and Baerveldt devices in comparison to the XEN implant. However, as measured flow at these rates is linear in relation to pressure, linear regression is a valid method of reporting these results. The coefficient of determination of our experiments shows an excellent goodness of fit. The pressure through the Ex-Press and Baerveldt was almost 0 mm Hg at physiologic flow rates so was virtually undetectable by our very sensitive pressure transducer. Extrapolation of pressures from higher flow rates as we report here is valid.

Glaucoma surgery should be reproducible with minimal intraoperative or postoperative complications.[23] This may be achieved with the use of devices. The device should not involve significant intraoperative adjustments that add to the variability and complexity of the early postoperative course. It should also contain a simple mechanism protecting against hypotony to reduce the probability of device failure.[31] Current devices used in glaucoma filtering surgery and several novel devices do not meet these goals. Then XEN 45 implant provides outflow resistance that should protect against hypotony at physiologic flow rates without the need for complex valve systems and intraoperative manipulations.

Acknowledgments

Supported by AqueSys, Inc.

Disclosure: **A. Sheybani**, AqueSys (F, R); **H. Reitsamer**, None; **I.I.K. Ahmed**, AqueSys (F, C, R)

References

1. Tham Y-C, Li X, Wong TY, Quigley HA, Aung T, Cheng C-Y. Global prevalence of glaucoma and projections of glaucoma burden through 2040: a systematic review and meta-analysis. *Ophthalmology*. 2014;121:2081–2090.
2. Gedde SJ, Herndon LW, Brandt JD, Budenz DL, Feuer WJ, Schiffman JC. Postoperative complications in the Tube Versus Trabeculectomy (TVT) study during five years of follow-up. *Am J Ophthalmol*. 2012;153:804–814.
3. Birchall W, Bedggood A. Do scleral flap dimensions influence reliability of intraocular pressure control in experimental trabeculectomy? *Eye (Lond)*. 2007;21:402–407.
4. Netland PA, Sarkisian SR, Moster MR. et al. Randomized, prospective, comparative trial of EX-PRESS glaucoma filtration device versus trabeculectomy. (XVT Study). *Am J Ophthalmol*. 2014;157:433–440.
5. Christakis PG, Tsai JC, Kalenak JW, et al. The Ahmed versus Baerveldt study: three-year treatment outcomes. *Ophthalmology*. 2013;120:2232–2240.
6. Barton K, Feuer WJ, Budenz DL, et al. Three-year treatment outcomes in the Ahmed Baerveldt comparison study. *Ophthalmology*. 2014;121:1547–1557.
7. Lim KS, Wells AP, Khaw PT, Frcophth F. Needle perforations of Molteno tubes. *J Glaucoma*. 2002;11:434–438.
8. Breckenridge RR, Bartholomew LR, Crosson CE, Kent AR. Outflow resistance of the Baerveldt glaucoma drainage implant and modifications for early postoperative intraocular pressure control. *J Glaucoma*. 2004;13:396–399.
9. Lewis RA. Ab interno approach to the subconjunctival space using a collagen glaucoma stent. *J Cataract Refract Surg*. 2014;40:1301–1306.
10. Sheybani A, Lenzhofer M, Hohensinn M, Reitsamer H, Ahmed IIK. Combined phacoemulsification with a novel ab-interno gel stent for the surgical treatment of open angle glaucoma: a pilot study. *J Cataract Refract Surg*. 2015. In press.
11. McLaren JW. Measurement of aqueous humor flow. *Exp Eye Res*. 2009;88:641–647.
12. Eisenberg DL, Koo EY, Hafner G, Schuman JS. In vitro flow properties of glaucoma implant devices. *Ophthalmic Surg Lasers*. 1999;30;662–667.
13. Ritch R, Shields M, Krupin T. *The Glaucomas: Clinical Science*. 2nd ed. St. Louis: Mosby; 1996.
14. Prata JA, Mérmoud A, LaBree L, Minckler DS. In vitro and in vivo flow characteristics of glaucoma drainage implants. *Ophthalmology*. 1995;102:894–904.
15. Dahan E, Carmichael TR. Implantation of a miniature glaucoma device under a scleral flap. *J Glaucoma*. 2005;14:98–102.
16. Villamarin A, Roy S, Hasballa R, Vardoulis O, Reymond P, Stergiopulos N. 3D simulation of the aqueous flow in the human eye. *Med Eng Phys*. 2012;34:1462–1470.
17. Estermann S, Yuttitham K, Chen J, Lee O-T, Stamper RL. Comparative in vitro flow study of 3 different Ex-PRESS

miniature glaucoma device models. *J Glaucoma*. 2013;22: 209–214.

18. Dohlman CH, Grosskreutz CL, Chen TC, et al. Shunts to divert aqueous humor to distant epithelialized cavities after keratoprosthesis surgery. *J Glaucoma*. 2010;19:111–115.
19. Gedde SJ, Schiffman JC, Feuer WJ, Herndon LW, Brandt JD, Budenz DL. Treatment outcomes in the Tube Versus Trabeculectomy (TVT) study after five years of follow-up. *Am J Ophthalmol*. 2012;153:789–803.
20. Pan T. Thin-film coupled fluid-solid analysis of flow through the Ahmed glaucoma drainage device. *J Biomech Eng*. 2005; 127:776.
21. Cheng J, Abolhasani M, Beltran-Agullo L, Moss EB, Buys YM, Trope GE. Priming the Ahmed glaucoma valve: pressure required and effect of overpriming. *J Glaucoma*. 2015;24:34–35.
22. Moss EB, Trope GE. Assessment of closing pressure in silicone Ahmed FP7 glaucoma valves. *J Glaucoma*. 2008;17:489–493.
23. Kara E. Kutlar I. CFD analysis of the Ahmed glaucoma valve and design of an alternative device. *Comput Methods Biomech Biomed Engin*. 2010;13:655–662.
24. Bochmann F, Kipfer A, Tarantino J, Kaufmann C, Bachmann L, Thiel M. Intraoperative testing of opening and closing pressure predicts risk of low intraocular pressure after Ahmed glaucoma valve implantation. *Eye*. 2014;28:1184–1189.
25. Porter JM, Krawczyk CH, Carey RF. In vitro flow testing of glaucoma drainage devices. *Ophthalmology*. 1997;104:1701–1707.
26. Villamarin A, Roy S, Bigler S, Stergiopulos N. A new adjustable glaucoma drainage device. *Invest Ophthalmol Vis Sci*. 2014; 55:1848–1852.
27. Paschalis EI, Chodosh J, Sperling R, Salvador-Culla B, Dohlman C. A novel implantable glaucoma valve using ferrofluid. *PLoS One*. 2013;8:e67404.
28. Moon S, Im S, An J, et al. Selectively bonded polymeric glaucoma drainage device for reliable regulation of intraocular pressure. *Biomed. Microdevices*. 2012;14:325–335.
29. Feldman RM, el-Harazi SM, Villanueva G. Valve membrane adhesion as a cause of Ahmed glaucoma valve failure. *J Glaucoma*. 1997;6:10–12.
30. Rietveld E, van der Veen AJ. Postoperative pressure regulation in glaucoma shunt surgery. *J Glaucoma*. 2004;13:216–220.
31. Ophthalmol BJ. Experimental flow studies in glaucoma drainage device development. *Br J Ophthalmol*. 2001;85: 1231–1236.

Investigative Ophthalmology & Visual Science