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Article

Is Ahmed Glaucoma Valve Consistent in Performance?

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Purpose: To investigate the mechanism of action and consistency in flow characteristics of the Ahmed glaucoma valve (AGV) under simulated physiological conditions in-vitro and to evaluate whether resistance during priming has any effect on performance of the device.

Methods: Each newly opened AGV device was connected to a digital manometer and was primed with normal saline. The device was then placed in a saline bath and connected to an open manometer, a digital manometer, and an infusion pump. Saline was infused at a rate of 3 μL/min for 24 hours. Digital manometer readings were recorded at 4 Hz.

Results: Data obtained from 9 devices are presented as medians (ranges). The priming pressure was 1130 (835, 1625) mm Hg. Pressure versus time curves showed two distinct phases; transient and steady phases. The transient phase peak pressure was 24 (13, 45) mm Hg. In the steady phase, opening and closing pressures were 13 (10, 17) and 7 (4, 9) mm Hg, respectively; the valve leaflets briefly opened every 73.9 (51, 76.6) minutes and the fluctuation of pressure (difference between opening and closing pressures) was 6 (3, 9) mm Hg. The Spearman correlation coefficient between priming and opening and priming and closing pressure was $\rho = -0.13$ ($P = 0.72$) and $\rho = -0.36$ ($P = 0.33$), respectively.

Conclusions: The device showed functionality like a valve. The resistance during priming did not affect opening and closing pressures of the AGV. This study showed variable in vitro performance of the AGV.

Translational Relevance: These laboratory findings might, at least partly, explain the variability in the clinical outcome of the device.

Introduction

Implantation of a glaucoma drainage device is a procedure of choice in the management of refractory glaucoma. The two most commonly implanted glaucoma drainage devices are the Ahmed glaucoma valve (AGV) and the Baerveldt implant. The latter carries a higher risk of early postoperative hypotony and related complications.[1–4] The AGV incorporates a unidirectional valve mechanism to prevent postoperative hypotony and a shallow anterior chamber.[5] However, essentially all large studies on outcomes of the AGV include cases of early as well as late hypotony.[1–4,6,7] The introduction of a biomaterial such as the end plate of the AGV facilitates formation of a fibrous capsule around it. The capsule acts as a reservoir until the aqueous is drained. A significantly higher rate of bleb encapsulation and inadequate long-term intraocular pressure (IOP) control has been reported with the AGV than with a nonvalved device.[1–4] The intensity of the fibrous reaction to the implant is reported to vary depending upon a number of factors, such as the properties of the glaucoma drainage device, the individual patient's immune reaction to the implantation, the presence of aqueous in the subconjuctival space, and the factors that are incompletely understood.[8]

The valve mechanism of AGV is a trapezoid chamber containing two thin, silicon elastomer membranes held under tension by insertion of four pegs. The elastic membranes help to regulate fluid

flow by creating resistance to deformation. A fresh valve has a high resistance due to surface adhesion between the membranes. Therefore, the manufacturer recommends priming the device before implantation. Priming is performed by injecting a balanced salt solution through the device tube until a vertical jet of fluid exits from the valve outlet.[5] Priming separates the valve leaflets and initiates fluid outflow. An experiment measured priming pressure in the range of 3000 mm Hg. The magnitude of priming pressure was variable.[9] The effect of the magnitude and variability of the priming pressure on the functionality of the valve is not known.

Previous experiments have tested the AGV after subjecting it to either a gravitational[10–13] and/or a constant flow apparatus.[13–16] These experiments have shown variability in the opening and closing pressures of the device. The variability in performance can potentially affect the clinical outcome of the AGV. The gravitational apparatus has an infinite reservoir at different pressures and represents a steady flow condition. Therefore, this apparatus does not represent the transient in vivo flow dynamics with the limited volume of production of the aqueous humor. A robust constant flow experiment to establish a quality assurance test for glaucoma drainage devices did plot pressure versus time curves but failed to demonstrate whether the AGV acted like a nozzle or a valve.[13] In the case of a nozzle, increasing flow rate increased the pressure in the eye, whereas in case of a valve, the pressure inside the eye was independent of the flow rate.[14] Another experiment suggested a valve mechanism by establishing a flow and valve resistance relationship over a constantly raised flow rate over 15 to 20 minutes but did not establish steady-state condition.[15] These observations indicate a need for a further understanding of the device. This study was designed to critically investigate the mechanism of valve action and the consistency in the flow characteristics of the AGV under simulated physiological conditions in vitro. The study was also designed to evaluate if the magnitude of the resistance offered during priming has any effect on the performance of the device.

Methods

This study was carried out at the bioengineering laboratory of a tertiary eye care delivery system. Ethics committee approval was not required for this study. We tested 10 newly opened AGV devices (Model FP7; New World Medical, Rancho Cucamonga, CA). All the devices were of a same batch (lot no. N0415, manufactured in December 2015) and were handled only after covering hands with powder-free gloves. All experiments were conducted at room temperature.

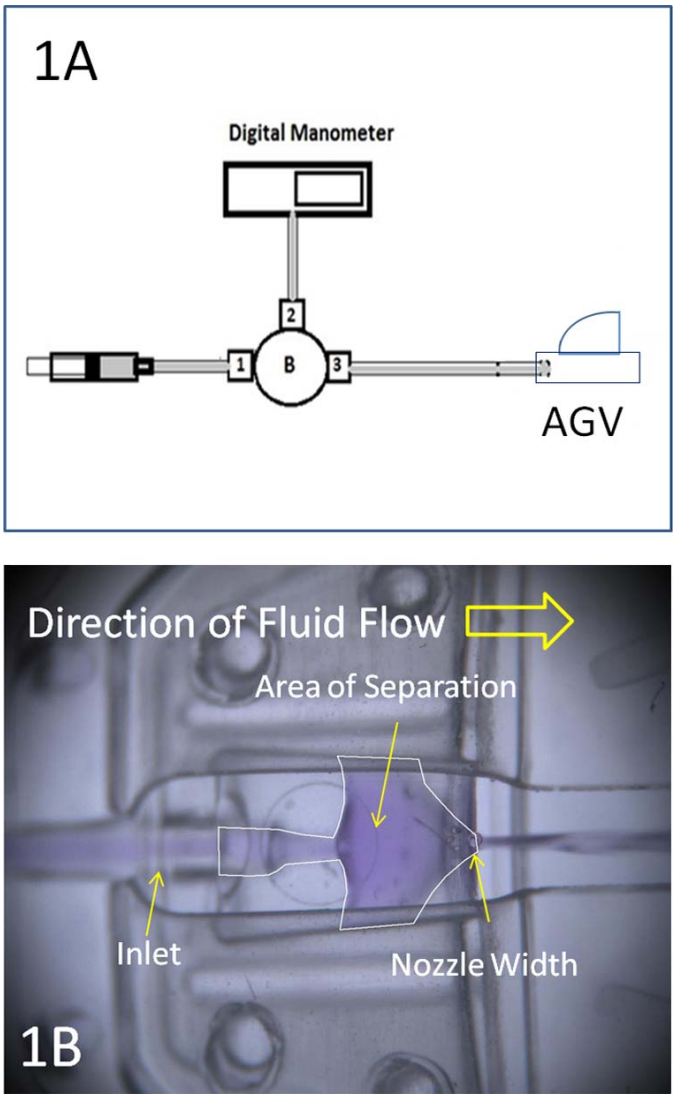


Figure 1. (A) Experimental setup of priming, (B) Area of separation of valve leaflets and nozzle width during priming.

Priming

Each device was connected to a digital manometer and a 5-cc syringe through a 27-gauge cannula (Fig. 1A). Priming was performed using saline colored with trypan blue to increase visibility of fluid flow. The process of priming was captured using a high-speed digital camera connected through an ocular piece of a microscope (Fig. 1B). Data logging at a rate of 4 readings per second was done for manometric

readings (Lutron PM 9100 Manometer; Lutron Electronics, Taipei, Taiwan). The priming pressure was defined as the maximum recorded pressure during the priming process. Priming pressure versus time curve was plotted for each device in MATLAB software (MathWorks, Natick, MA). The site of insertion of the tube into the trapezoid chamber containing leaflets of the valve was marked on the images. The area of separation of the valve leaflets beyond the site of insertion of the tube was calculated using image processing software (ImageJ, Bethesda, MD). The width of outflow through the valve leaflets (nozzle width) was also calculated.

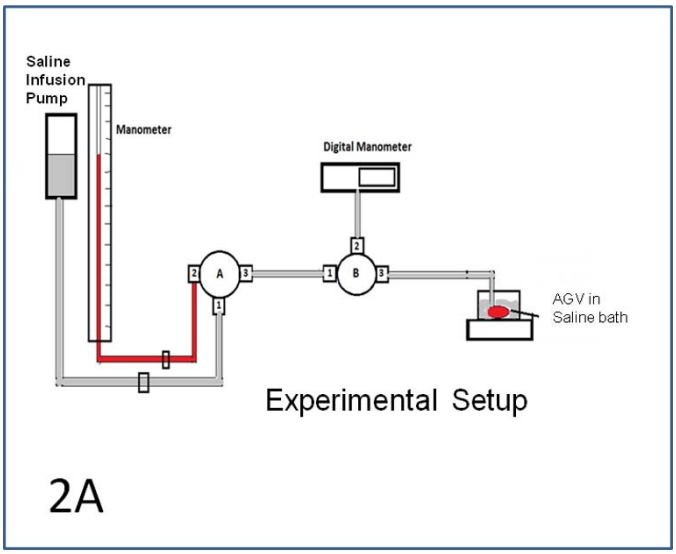
Flow characterization

Following priming, each AGV device was placed in a saline bath and was connected to an open manometer, a digital manometer, and an automated infusion pump (Fig. 2A). The depth of immersion was kept at 3 cm for all the devices. The system was primed to remove any air bubbles. Saline was infused into the system at the rate of 3 μL/min for 24 hours. This flow rate was maintained for the system to model the eye's rate of production of aqueous humour. Digital manometer readings were recorded at 4 Hz by using computerized data logging. The pressure curves were plotted against time in MATLAB software (MathWorks). The transient phase opening pressure of AGV was defined as the peak pressure before attaining the steady phase (see below). Opening and closing pressure was defined as the maximum and minimum pressure, respectively, in the steady phase. Fluctuation of pressure was the difference between opening and closing pressures. All the pressure readings were corrected for the depth of immersion.

After 24 hours of data logging, each AGV device was disconnected from the experimental apparatus and was reexamined under the microscope after injecting colored saline through a 5-cc syringe. This process was also captured by using the microscope-mounted camera (Fig. 2B). Thereby, the area of separation of the valve leaflets beyond the site of insertion of the tube as well as the diameter of the nozzle after attaining the steady phase were calculated from the captured images. Supplementary Movie S1 shows injection of colored saline into the AGV during priming as well as after flow characterization.

Statistical Analysis

Shapiro–Wilk test was used to check the normality distribution of the data. The data were described as medians (first, third quartiles) for uniformity. The spread of data was also reported as appropriate. The data obtained from the digital manometer were filtered through Fourier transformations. Subsequently, pressures versus time curves were plotted. The percent increase in the area of separation of valve leaflets at the end of 24 hours of flow characterization was calculated by comparing the calculated area of separation of valve leaflets at the end of priming and that at the end of the experiment. The percent increase in nozzle width at the end of 24 hours of flow characterization was similarly calculated. Nonparametric Spearman rank correlation coefficients were calculated between priming pressure, peak pressure



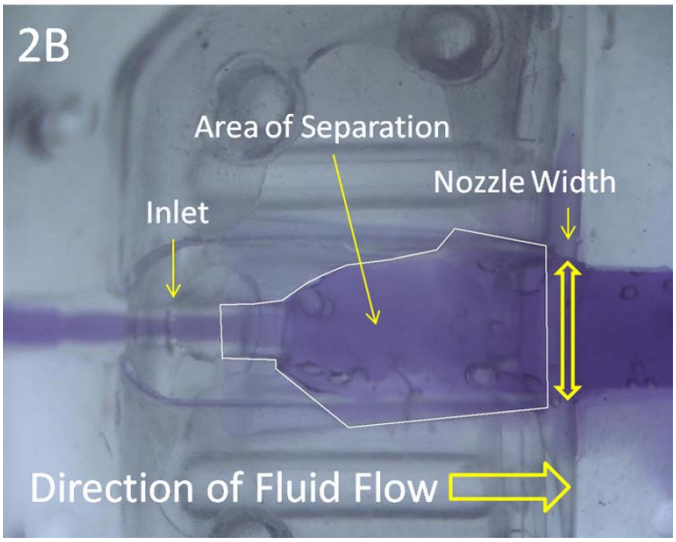


Figure 2. (A) Experimental setup of flow characterization, (B) Area of separation of valve leaflets and nozzle width subsequent to flow characterization.

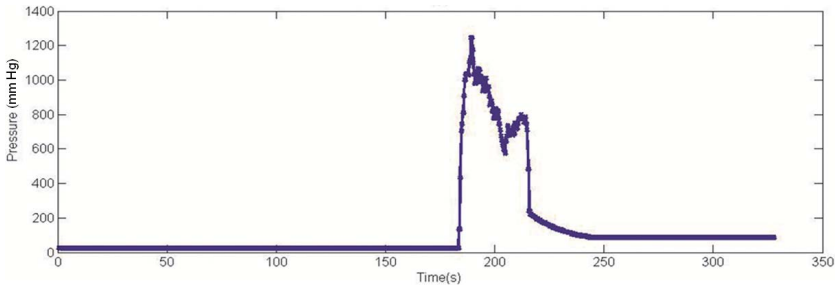


Figure 3. Pressure versus time curve during priming of AGV number 3.

and duration of the transient phase, opening and closing pressures, and percent increase in area of separation of valve leaflets as well as nozzle width. Statistical analyses were performed using the statistical software Stata 12.1 (StataCorp, College Station, TX).

Results

A total of 10 new AGV devices (FP7 model; New World Medical) were tested. Data obtained from one device (AGV number eight) were discarded due to incomplete recording that was accidental. Thus, data obtained from the remaining nine devices were analyzed. All the variables except the area of separation of valve leaflets during priming, the duration between opening and closing cycles of valve leaflets, and the width of nozzle postflow characterization were normally distributed.

The median priming pressure was 1130 (1030, 1145) mm Hg. The priming pressure ranged between 835 to 1625 mm Hg. Figure 3 shows priming pressure versus time curve. The curve shows a sharp upshot and rapid fall of priming pressure. Figure 1B shows the area of separation of valve leaflets and the width of nozzle of fluid outflow during priming. The median area of separation of leaflets of AGV during priming was 1.79 (1.48, 1.92) mm^2. Similarly, the median width of the nozzle during priming was 0.16 (0.13, 0.24) mm.

Pressure versus time curves showed two distinct phases in seven devices (Fig. 4). The first phase in which the pressure fluctuated in larger and irregular cycles was named transient phase. The subsequent phase of equilibrium in which the pressure cycles were smaller and regular was termed stable phase. No transient phase was noted in the flow properties of two devices (AGV numbers four and nine), and they directly exhibited the stable phase. The median duration of the transient phase was 3.74 (3.05, 7.59) hours and ranged between 3.05 to 12.56 hours in seven devices. The median number of pressure spikes was 1 (1, 2) per AGV device in the transient phase. The median value of the peak pressure attained in the transient phase indicated by the letter A in Figure 4

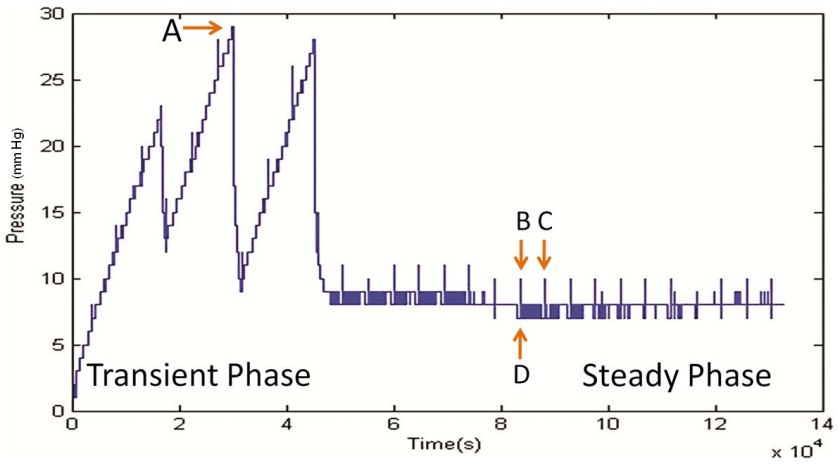


Figure 4. Pressure versus time curve during flow characterization of AGV number 1. *A* Peak pressure in the transient phase, *B* and *C* opening pressure, and *D* closing pressure.

Table. Spearman Correlations

Parameter	Priming Pressure	Peak Pressure in Transient Phase	Duration of Transient Phase	Opening Pressure	Closing Pressure	% Increase in Area of Separation of Valve Leaflets	% Increase in Nozzle Width
Priming pressure	1.00						
Peak pressure in transient phase	0.15 ($P = 0.69$)	1.00					
Duration of transient phase	0.10 ($P = 0.78$)	0.89* ($P < 0.01$)	1.00				
Opening pressure	−0.13 ($P = 0.72$)	−0.23 ($P = 0.55$)	−0.57 ($P = 0.10$)	1.00			
Closing pressure	−0.36 ($P = 0.33$)	−0.18 ($P = 0.63$)	−0.05 ($P = 0.88$)	0.28 ($P = 0.45$)	1.00		
% Increase in area of separation of valve leaflets	−0.33 ($P = 0.38$)	0.30 ($P = 0.43$)	0.27 ($P = 0.47$)	−0.16 ($P = 0.67$)	−0.07 ($P = 0.85$)	1.00	
% Increase in nozzle width	−0.15 ($P = 0.70$)	−0.36 ($P = 0.32$)	−0.25 ($P = 0.50$)	0.12 ($P = 0.74$)	0.03 ($P = 0.92$)	−0.36 ($P = 0.33$)	1.00

* Indicates significant value.

was 24 (20, 29) mm Hg and ranged between 13 and 45 mm Hg.

The steady phase opening pressure indicated by letters B and C in Figure 4 was 13 (10, 14) mm Hg and ranged between 10 to 17 mm Hg. Similarly, the steady phase closing pressure indicated by letter D in Figure 4 was 7 (7, 7) mm Hg and ranged between 4 to 9 mm Hg. The median duration between opening and closing cycles of the valve leaflets in the steady phase was 73.99 (58.68, 76.07) minutes and ranged between 51.05 to 76.67 minutes.

The median area of separation of leaflets of AGV after attaining the steady phase was 3.36 (2.97, 3.48) mm^2 and showed a percentage increase of 87.7 (51.83, 104.54) from the corresponding area of separation during the priming. Similarly, the width of the nozzle after attaining the steady phase was 1.23 (1.2, 1.37) mm and showed a median percentage increase of 448 (315.62, 706.66) from the corresponding width during priming (Figs. 1B, 2B).

The fluctuation of pressure in the steady phase was 6 (3, 8) mm Hg and ranged between 3 to 9 mm Hg.

The Spearman correlation coefficient between priming and opening ($\rho = -0.13$) as well as closing pressure ($\rho = -0.36$) was statistically insignificant ($P =$ 0.72 and 0.33, respectively). Peak pressure in the transient phase was significantly correlated with duration of the same phase ($\rho = 0.89$, $P < 0.01$). There was no significant correlation in any other data pair (Table).

Discussion

This study was designed to investigate the in vitro performance of the AGV under simulated physiological conditions. We collected the data at a high frequency and ran the experiment for an adequate duration. The implants tested in our study, being engineered and belonging to the same batch of production, should have had identical operating characteristics. Nevertheless, our experiment exhibits variability in the flow characteristics of the sample AGV.

Priming of the device is necessary for several reasons. The fluid follows the path of least resistance and breaks the adhesion between the two leaflets of the valve. The step ensures proper opening of the valve and can identify manufacturing defects. Our study explored the relationship between priming

pressure and functionality of the valve to deny any influence of the variability in the former on the latter. This information should be assuring to a glaucoma surgeon. The discrepancy in the level of the priming pressure observed between our study and a previous study[9] could be primarily attributed to the different principles of recording the priming pressure.

We demonstrated two distinct phases in the flow characterization of the AGV. Previous experiments using the gravitational flow apparatus have reported high variability in opening[11,12] and closing[10–13] pressures. However, the equilibrium points chosen by them are likely to have fallen within the transient phase. Our observation of higher variability in the transient phase principally matches with their inference. Previous experiments using the constant flow apparatus did plot pressure versus time curves.[13–16] But, they could not differentiate between the transient and the steady phase due to insufficient frequency of data collection[13–16] and/or inadequate duration of the experiment.[15,16] Porter et al.[13] described a steady increase in pressure before a valved device opened. This phenomenon corresponds to the opening of the AGV in the transient phase in our experiment. A comparison of our data obtained during priming and after flow characterization suggests that the valve experiences a gradual opening of the leaflets and widening of the nozzle in the transient phase. After experiencing variable height of pressure as well as duration of the transient phase, the devices attained a relatively narrow range of opening and closing pressures in the stable phase. The variability in the transient phase is a probable reason of poor correlation between the parameters obtained during the transient and the stable phase in our study.

Our experiment demonstrated the cyclic opening and closing of the valve mechanism. We did also demonstrate that the valve opens and closes about every hour under physiological flow rate in an in vitro condition. Alteration in flow rate might alter the frequency of the valve operation but is unlikely to alter the opening and closing pressures. Francis et al.[15] did negate the effect of increasing rates of inflow on the pressure curve of the AGV. The periodic cycles of opening and closing of the valve leaflets are indicative of pressure fluctuation in the system to the magnitude of the difference between the opening and closing pressures. The pressure fluctuation was as high as 9 mm Hg during an approximately 1-hour cycle in our study. The higher level of pressure fluctuation is a cause of concern. Fluctuation of IOP is considered to be a risk factor for progression of glaucoma.[17,18]

The postproduction sterilization process could be one of the possible sources of variability in the performance of the device.[19] Sterilization can result in adhesion between the valve leaflets. The adhered leaflets offer more resistance and take longer to separate. Our observation of a high correlation between duration and peak pressure of the transient phase is indicative of adhesion between the valve leaflets. The process of sterilization may also alter the mechanical properties of the leaflets.[19] In a previous experiment on modeled leaflets of the AGV, the variability in the resistance at different flow rates was attributed to the flexibility of the leaflet material.[20] However, other factors such as area of the valve leaflet and tension acting upon valve leaflets may also affect the valve action. Further exploration of these parameters might offer further insights into the performance of the device.

In a quarter device, the steady phase opening pressure crossed the low teen range. The AGV works on the principle of differential pressure that refers to the drop of pressure in a tubing system. Differential pressure can be determined by subtracting the outlet pressure from the inlet pressure. Because the AGV was submerged in a saline bath, its outlet pressure can be considered as nil. On the other hand, the bleb resistance in an in vivo condition will determine the outlet pressure. Therefore, a higher outlet or bleb pressure can reduce the IOP-lowering effect of the AGV. Besides, a device with a higher opening pressure (e.g., in higher teens in in vitro conditions) is likely to end up at an inadequate IOP control in the long term, with the addition of tissue resistance to the dynamics of the flow. Prata et al.[14] have shown higher pressures in vivo than in vitro due to tissue-induced resistance around the glaucoma drainage device.

The FP7 and FP8 models differ in the surface area of the base plate, but the dimensions of the tube as well as the valve assembly are identical in them. Therefore, we do not expect any difference in terms of priming, opening, and closing pressures between the models.

Our study has limitations. Our sample size might not represent the entire population of the AGV. We did not follow any recommended sampling technique for quality testing. However, we could not do an a priori calculation of sample size due to lack of information such as batch size. In general, the approved engineered products were identical and the sample size for quality control, especially when the

testing process is destructive, was limited.[21] The normal distribution of most of the functional parameters of the device might indicate adequate representation of the device. Our results cannot be directly applied to in vivo situations. Nevertheless, our study contributes to the understanding of the functionality of the AGV. The effect of the variability in the flow characteristics of the AGV on the clinical outcomes of the device is an area of further research.

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Supplementary Material

Supplementary Movie S1. Injection of colored saline into the AGV during priming and after flow characterization.