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Development and validation of a test facility for pivotal characterization of glaucoma drainage devices

Abstract: Implant devices for micro invasive glaucoma surgery (MIGS) are gaining increasing acceptance in clinical ophthalmic use. The implant requirements are defined in international standards, such as ANSI Z80.27-2014 and the 2015 Guidance for Industry and Food and Drug Administration Staff “Premarket Studies of Implantable Minimally Invasive Glaucoma Surgical (MIGS) Devices”. The exact fluid-mechanical characterization represents a crucial part of the development and approval of innovative implant devices for MIGS. The current work describes the development and preliminary validation of a versatile test facility for pivotal characterization of glaucoma drainage devices. The test setup enables a pressurization of test specimens by means of two water columns. For measurement of pressure and volume flow, a pressure transducer and a total of three liquid flow meters were implemented into the test setup. Validation was conducted by experimental pressure-flow characterization of standardized tubes and a comparison to theoretical results according to Hagen Poiseuille's law for stationary laminar flow of a Newtonian fluid in a tube with a circular cross section. Ultrapure water at $(35 \pm 2)^\circ\text{C}$ was used for the analyses. The developed test setup potentially enables pressure-flow characterization of test specimens in a wide flow range of $0 \mu\text{l min}^{-1} \leq Q \leq 5.000 \mu\text{l min}^{-1}$. The preliminary test facility validation showed a good agreement of measured and theoretical volume flow characteristics as a function of the pressure difference, in the currently investigated flow range of $Q < 80 \mu\text{l min}^{-1}$. The developed test facility is suitable for pivotal *in vitro* characterization of

glaucoma drainage devices. Future investigations will focus on the final validation of the whole flow range and on the use of the test facility for fluid-mechanical characterization of self-developed prototypes of glaucoma microstents as well as commercially available glaucoma drainage devices.

Keywords: glaucoma drainage devices, microstent, MIGS, intraocular pressure, microfluidics

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1 Introduction

Glaucoma is a widespread disease characterized by progressive optic neuropathy, accompanied by structural damage to the optic nerve and loss of visual field [1]. For lowering of intraocular pressure (IOP) as the major risk factor implant devices, especially for MIGS, are increasingly used in clinical ophthalmology [2].

For development and approval of innovative implant devices for MIGS pressure-flow characterization plays an important role. Therefore, we developed a test setup simulating physiological pressure and volume flow conditions inside the eye (Fig. 1 and Fig. 2).

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The test setup has already been described in previous work and represents one of a few described technical solutions for the measurement task, known from the international literature [3-5]. The physiological aqueous humour flow rate inside the eye ranges between $1.78 \mu\text{l min}^{-1}$ to $4.26 \mu\text{l min}^{-1}$ [6]. Nevertheless, under physiological pressure conditions volume flow through most glaucoma drainage devices (GDD) extends this narrow range by almost two orders of magnitude [7]. Therefore, an *in vitro* test setup for fluid-mechanical characterization of GDD must cover a large volume flow range.

Our previously described test setup was capable of online measuring the volume flow Q as a function of the pressure difference $\Delta p = p_1 - p_2$, but was limited to a flow range of $0 \mu\text{l min}^{-1}$ to $40 \mu\text{l min}^{-1}$. For larger volume flows, a time-consuming discrete volume flow measurement was required by weighing the mass of water that flowed per unit of time.

The current work describes the extension of the test setup with regard to expanding the volume flow range. Based on this, preliminary validation of the test setup was conducted. The test setup expansion was carried out considering relevant international standards, such as ANSI Z80.27-2014 and the 2015 Guidance for Industry and Food and Drug Administration Staff “Premarket Studies of Implantable Minimally Invasive Glaucoma Surgical (MIGS) Devices”.

2 Materials and methods

The test setup enables a pressurization of test specimens by means of two water columns in a range of $0 \text{ mmHg} \leq \Delta p \leq 40 \text{ mmHg}$ (Fig. 2, Fig. 3). An additional

water column extension allows for pressurization up to 100 mmHg . For measurement of pressure difference Δp and volume flow Q , a pressure transducer (DMP 331, BD SENSORS GmbH, Germany) and a total of three liquid flow meters (SLI-0430, SLI-1000 and SLI-2000, Sensirion AG, Staefa, Switzerland) were implemented into the test setup. Ultrapure water at a physiological temperature of $(35 \pm 2) ^\circ\text{C}$ was used as test medium. The temperature is regulated using a heating element and a temperature sensor in the medium. Additionally, the whole test setup is encased by a climate chamber (SI60D, Bibby Scientific Limited, UK). Automated regulation of water columns was implemented using a pump and various magnetic valves. For visual observation of GDD valve mechanisms a camera system (VRmFC-22/C-PRO camera, VRmagic GmbH, Germany) and a microscopic lens (VZM 600i zoom lens, Edmund Optics, USA) were implemented. In-house developed control electronics and software enable the wireless definition of measurement programs and data acquisition.

Figure 3: Technical implementation of test setup for pressure-flow characterization of GDD in the laboratory of the Institute for ImplantTechnology and Biomaterials e.V., Rostock-Warnemünde, Germany: water column 1 representing the anterior chamber of the eye (a), liquid flow meter set (b), water column 2, including pressure and temperature sensor, representing Tenon's space (c), test chamber including microstent (d), climate chamber (e) and camera system for visual observation of GDD (f).

Preliminary validation was conducted by experimental pressure-flow characterization of glass capillaries (minicaps CE 0,5 µl, Hirschmann Laborgeräte GmbH & Co. KG, Germany) with an inner diameter of 0.14 mm and a length of 31.80 mm. Comparison of the experiments to theoretical results was conducted considering Hagen Poiseuille's law for stationary laminar flow of a Newtonian fluid in a tube with a circular cross section.

The current preliminary validation includes a pressurization and depressurization of glass capillaries in a physiological pressure range of $0 \text{ mmHg} \leq \Delta p \leq 21 \text{ mmHg}$ in increments of 1 mmHg. A total of $n = 5$ measurements were recorded using the SLI-0430, the SLI-1000 and the SLI-2000 volumetric flow sensor, respectively.

3 Results

The developed test setup enables pressure-flow characterization of test specimens in a physiological pressure range of $0 \text{ mmHg} \leq \Delta p \leq 21 \text{ mmHg}$. An exemplary plot of the volume flow as a function of the pressure difference using the SLI-0430 sensor is shown in Fig. 4.

Figure 4: Exemplary plot of the measured volume flow through a glass capillary (inner diameter 0.14 mm, length 31.80 mm) as a function of the pressure difference using the SLI-0430 sensor during pressurization and depressurization ($n = 5$) compared with the theoretical curve according to Hagen Poiseuille's law. Flow medium ultrapure water at $(35 \pm 2)^\circ\text{C}$.

No pronounced hysteresis was found between pressurization and depressurization. The test facility validation showed good agreement of measured and theoretical volume flow characteristics as a function of the pressure difference,

characterized by an average deviation between experiment and theory of 5%. The corresponding results using the SLI-1000 and SLI-2000 sensors show average deviations between experiment and theory of 15% and 33%, respectively. It should be noted that these sensors are designed for a significantly larger volume flow and therefore operate in the lower measuring range (SLI-1000) or even below the minimum measuring range (SLI-2000), within the current study.

The temperature control of the test setup enables constant test conditions. In this regard, a constant temperature of $(36.34 \pm 0.20)^\circ\text{C}$ was achieved during the measurements. As a fundamental advantage, the fast measuring time of approximately 30 min for the current measuring regime has to be noted.

4 Discussion

The developed test setup is suitable for pivotal *in vitro* characterization of glaucoma drainage devices. Test conditions defined in the governing standard ANSI Z80.27-2014, for example the relevant pressure range and the test temperature of $(35 \pm 2)^\circ\text{C}$, were technically implemented [6]. The in-house developed software allows for a flexible definition of measurement programs as required within the governing standard. Therefore, measurement results are suitable for the calculation of the GDD flow resistance under physiological conditions, for the determination of valve opening and closing pressures in an aqueous environment or for the investigation of leakages [6].

Currently, implant devices for MIGS are gaining increasing acceptance in clinical ophthalmic use. These devices, such as iStent, iStent inject or iStent SUPRA (Glaukos Inc., Laguna Hills, CA, USA), MINiject (iSTAR Medical SA, Wavre, Belgium), XEN Gel Stent (Allergan plc, Dublin, Ireland) or preserflo MicroShunt (Santen Inc., Miami, FL, USA), have a small lumen to counteract ocular hypotension [2]. Therefore, under physiological pressure conditions low volume flow is expected. While the liquid flow meter SLI-0430 represents the measuring device of choice for such low volume flows in a physiological range, the liquid flow meters SLI-1000 and SLI-2000 potentially enable a significant extension of the measuring range. These sensors will be helpful in future investigations of large lumen GDD, such as Molteno 3 (Molteno Ophthalmic Ltd., Dunedin, New Zealand) or Ahmed FP7 (New World Medical Inc., Rancho Cucamonga, CA, USA).

After the current preliminary validation of our test setup an extension of the validation for the whole volume flow

range of $0 \mu\text{l min}^{-1} \leq Q \leq 5.000 \mu\text{l min}^{-1}$ is planned. Consequently, future investigations will focus on the use of the test facility for fluid-mechanical characterization of self-developed prototypes of glaucoma microstents as well as for benchmark testing of commercially available devices.

Author Statement

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