AN IMPLANTABLE HYDROGEL CHECK VALVE FOR HYDROCEPHALUS TREATMENT—DEVELOPMENT AND IN VITRO MEASUREMENTS

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ABSTRACT

Permanently stable cerebrospinal fluid (CSF) draining devices are needed for treating hydrocephalus, a debilitating brain disorder. Currently implemented shunts are unreliable as long term implants primarily due to their largely protracted form. The proposed hydrogel valve attempts to generate greater permanency as a chronic implant by forming a direct CSF channel across the physiologically blocked natural valve formations, the arachnoid granulations (AG), and restoring near-natural CSF draining operations. In this way, all CSF draining operations are confined within the cranium. The valve relies on innate hydrogel swelling phenomenon to strengthen reverse flow sealing at idle and negative pressures. *In vitro* measurements in emulated CSF solutions display operation spanning targeted range of normal healthy draining (cracking pressure, $P_T \sim 1 - 110$ mmH₂O and outflow hydraulic resistance, $R_h \sim 24 - 152$ mmH₂O/mL/min), with negligible reverse flow leakage. Overtime tests demonstrate the valve's operational reproducibility and *in situ* feasibility, substantiating its potential for use as a permanent implant.

INTRODUCTION

Hydrocephalus is a chronic brain disorder caused by the inability to drain cerebrospinal fluid (CSF) sufficiently, causing CSF to excessively accumulate within brain ventricles, and leading to fatal increases in intracranial pressures (ICP) [1]-[3]. The disorder may cause abnormal enlargement of the head, convulsions, mental disabilities, and even death. Arachnoid granulations (AGs) serve as a one-way conduit for draining CSF from the interior subarachnoid space (SAS) of the brain to the sinus, immediately exterior (Figure 1), and are in many cases, blocked, in hydrocephalus. Standard treatments to safely lower and maintain ICP in hydrocephalus involve implantation of a large valve (shunt) into the brain to transport CSF through an intracranial tube (catheter) to outside of the skull and to a distal organ. However, more than half of these shunts fail within the first two years requiring additional invasive surgeries [1]. Failure mechanisms are frequently attributed to the shunts' physically obtrusive and lengthy form making them vulnerable to external forces and/or siphoning effects (overdrainage caused by negative pressures created by tube height) [1]. Further, the intracranial catheter element may predispose the brain to risk of infection.

The valve of this work intends to rebuild a CSF channel by directly bypassing the blocked physiological CSF valves or AGs (Figure 1) and utilizes innate hydrogel swelling phenomena to strengthen sealing against leakage. By physically confining drainage channels within the skull, complications caused by the physical bulk of currently implemented shunts – infections, externally induced obstructions, siphoning, trauma, etc. – may be alleviated. This artificial CSF draining valve is intended to be embedded through the meninges and in place of blocked AGs to channel CSF from the SAS to the sinus to restore draining operations of normal healthy AGs. The valve must not only replicate fluid flow behavior of actual ventricular CSF draining without reverse flow leakage, but also be permanently stable in operation over the lifetime of the patient.

To restore CSF draining, the valve must essentially function

as a check valve, that is, a one-way channel. In addition, when the valve is open, its hydrodynamic behavior should emulate healthy physiological draining. That is, the cracking pressure (P_T), flow rate (Q_O), and fluidic resistance (R_h) should be in range of normal CSF draining. In summary, the check valves target 3 basic features: 1) infinite diodicity or only flow in the positive direction ($Q_O \geq 0$), 2) zero flow when the pressure difference across the valve, ΔP , is less than the cracking pressure, P_T , ($Q_O = 0$ when $\Delta P < P_T$), 3) a designated non-zero or zero P_T . Such valves have been miniaturized by means of microelectromechanical system (MEMS) technology and are commonly in the form of a cantilever, membrane, duckbill flap, and/or spring-loaded ball [4]-[6]. Despite their enormous progress and development, most MEMS-based valves fall short in one or more of the abovementioned basic operational elements and especially so in avoiding finite leakage ($Q_O < 0$) that occurs due to inadequate sealing mechanisms at idle ($\Delta P \sim 0$) and/or negative pressures ($\Delta P < 0$). In addition, fabrication of MEMS valves usually requires a high degree of complexity to cope with leakage issues.

Figure 1: Obstructed CSF flow in hydrocephalus and methods to introduce alternative CSF draining channels (existing shunt treatment approach and hydrogel, HG, valve of this work).

The valve presented here is simple in design (only 3 materials: the silicon valve seat, a parylene coating, and the moveable hydrogel membrane) and fabrication (3 basic steps and no release-related processes and no photoresist). Early work demonstrated the feasibility of the hydrogel valve and its capacity in restoring CSF draining operations [7]. On the other hand, these initial studies addressed little on the following issues: weak operational-reproducibility and long-term durability—aspects critical for permanent medical implants. The use of photoresist in fabrication of the valve was found to compromise its operational stability and functionality. Additionally, the hydrogel membrane experienced large stress causing unpredictable buckling upon hydration. The valve demonstrated here resolves these challenges by eliminating the sacrificial photoresist along with all release-related procedures, and by implementing a stress-relief spiral flexure. Basic benchtop hydrodynamic experiments in emulated

CSF solutions demonstrate targeted behavior in range of normal CSF draining. *In situ* feasibility and practical applicability is further substantiated by measurements of its overtime performance in semi-accelerated conditions emulating amplified pulsatile CSF drainage behavior.

MATERIALS AND METHODS

Basic Operation

The valve entails deflection of a simple circular hydrogel diaphragm anchored by spiral flexures to a silicon substrate (Figure 2). In the closed state, when $\Delta P < P_T$, the hydrogel diaphragm closes the inlet orifice to prevent flow ($Q_O = 0$). The liquid induced swelling behavior of the hydrogel provides a pre-induced sealing force between the hydrogel diaphragm and silicon seat and orifice, effectively establishing a threshold for valve opening (ie. P_T). In the open state, when $\Delta P \geq P_T$, the spiral flexures bend upwards, allowing fluid to flow out through the silicon inlet via. When open, steady state Q_O is primarily governed by the size of the inlet orifice, which acts as a fixed linear hydraulic resistance. The spiral flexure design relieves in-plane stresses caused by the lateral expansion of the hydrated hydrogel and maximizes out-of-plane axial swelling to strengthen sealing.

Figure 2: Basic operation of hydrogel membrane valve.

Design

The valve consists of a center circular hydrogel diaphragm hinged to three spiral flexure supports anchored to the silicon substrate and is designed to provide linear flow operation as well as minimal reverse flow leakage. During positive pressure differentials, venous drainage is linear as may be denoted by its outflow resistance, R_h , which ranges from 81.5 – 136 mmH₂O/mL/min as observed in healthy individuals [3]. Design parameters of the valve are listed in Table 1. Membrane deflection is not linearly related to pressure, yet the linear operation may be conceived by rendering flow dependency on the fixed geometries of the valve (ie. the inlet orifice), rather than the pressure-varying displacement of the diaphragm.

Flow rate (Q_O) through the valve may be modeled by a linear expression, $Q_O = \Delta P/R_h$, where R_h is hydraulic resistance. For a deformable membrane valve, R_h may be modeled as a summation of series resistors: the fixed inlet orifice resistance (R_{inlet}), the variable displacement resistance formed by membrane deflection (R_w), and the resistance of the channels formed by the exposed area between flexures (perforations). The latter perforation area is much larger than the area of the former two and may be disregarded in these approximations. The resistance of the circular inlet is [8],

$$R_i = \frac{8\mu L_i}{\pi r_i^4} \quad (1)$$

where μ is dynamic viscosity of the fluid ($\mu(\text{water}) \approx 1.002 \text{ mPa}\cdot\text{s}$ at 20°C and $\approx 0.68 \text{ mPa}\cdot\text{s}$ at 38 °C, and $\mu(\text{CSF}) \sim 0.72 \text{ mPa}\cdot\text{s}$ at 38 °C), r_i is the radius of the silicon inlet orifice, and L_i is the length of the orifice or substrate thickness (500 μm). The variable displacement resistance may be approximated to a rectangular orifice,

$$R_w(h_o) \approx \frac{12\mu L_o}{w_o h_o^3 (1 - 0.630 h_o/w_o)} \quad (2)$$

where L_o is the channel length formed by the outer edge of the hydrogel center diaphragm and the outer edge of the silicon inlet orifice along the longitudinal axis of the substrate ($L_o = r_o - r_i$), w_o is the channel width or cylindrical circumference formed by the silicon orifice ($w_o = 2\pi r_i$), and h_o is channel height formed by the deflection of the membrane ($h_o \approx w$). Upon increasing ΔP , and hence w , outflow resistance will further become determined by the fixed size and resistance of the inlet orifice (R_i), rather than by the variable membrane gap, and the valve will obtain the desired linear drainage characteristics.

The maximum deflection of the spiral flexures as a function of ΔP may be estimated by [9],

$$w = \frac{3\Delta P \pi r_i^2 L_f^3}{E W_f t^3} \quad (3)$$

where L_f and W_f are the length and width of the flexure beam, respectively, and E is Young's modulus ($\sim 10 - 150 \text{ kPa}$ for liquid infused HEMA-based hydrogels). By ensuring that $R_i > R_w$, drainage will be further dictated by static R_i , rather than the nonlinear $R_w(h_o)$, and thereby foster targeted linear flow behavior. To ensure that the majority of draining operations are within the linear range, it is informative to estimate the ΔP at which Q_O responds nearly linearly. This minimum ΔP_{min} may be estimated by first equating $R_i = R_w(h_o)$ to find minimum deflection w_{min} ,

$$w_{min} \approx \left(\frac{3L_o r_i^3}{4L_i} \right)^{1/3} \quad (4)$$

The w_{min} expression may be substituted into (3) to find ΔP_{min} , which based on design criteria (Table 1), is in the range of $\Delta P_{min} \approx 4 - 25 \text{ mmH}_2\text{O}$, which is considerably smaller than actual ventricular ΔP that may reach up to 500 mmH₂O, as well as standard designated shunt cracking pressures of $P_T \approx 10 - 230 \text{ mmH}_2\text{O}$. As ΔP_{min} represents the lower range of ΔP during which outflow behavior is determined by diaphragm deflection rather than static geometries, the low estimated ΔP_{min} indicates that nonlinear behavior only occurs for a small window of operation.

Table 1: Design parameters for valve

Design Variable	Symbol	Value
Hydrogel diaphragm flexure		
Young's modulus	E	10 – 150 kPa
thickness	t	200 – 500 μm
flexure length	L_f	1400 – 2000 μm
flexure width	W_f	100 – 200 μm
center diaphragm radius	r_o	500 – 600 μm
Silicon inlet orifice		
radius	r_i	200 – 400 μm
length	L_i	500 – 750 μm

In the valve's closed state, when the differential pressure between SAS and draining region is less than the cracking pressure ($\Delta P < P_T$), the strength of the reverse leakage seal and the cracking pressure are related to valve geometry and hydrogel material properties. Hydrogel volumetric swelling ratio is given by [10],

$$\left(\frac{V}{V_0} \right)^{-2/3} \approx \frac{k}{\zeta Z} \quad (5)$$

where V and V_0 are swollen and dry gel volumes, respectively, k is gel elasticity, ζ is degree of gel ionization, and Z is potential ions per dry gel volume. P_T may be estimated by rearranging (3) to solve for pressure (P) as a function of hydrogel expansion.

However, such a crude approximation negates radial expansion that will decrease P_T . Instead, the diaphragm is made sufficiently thick relative its diameter in an attempt to offset vertical displacements caused by lateral swelling-induced stresses concentrated at the anchors.

Fabrication

Hydrogel valve fabrication entails standard micromachining and photolithography processes on a Si <100> wafer and involves three basic steps. The fabrication process is shown in Figure 3. First, 150 nm SiO₂ is PECVD coated on the Si substrate. This oxide layer serves to strengthen adhesion to subsequent hydrogel. A conformal 100 nm film of parylene-C is deposited atop this oxide layer and then patterned using O₂ plasma at 150 – 200 W to create a negative pattern for the hydrogel anchors. The parylene layer provides low surface binding energy to moveable parts of the hydrogel diaphragm. Second, hydrogel is deposited and patterned following substrate adhesion promotion and demarcating hydrogel thickness by fixing 200 – 500 μ m thick rubber spacers at wafer perimeters. The hydrogel is synthesized using a chemical composition of the monomer, 2-hydroxyethyl methacrylate (HEMA), crosslinker, ethylene glycol dimethacrylate (EGDA), and photoinitiator, 2,2-dimethoxy-2-phenylacetophenone (DMPA), at a volumetric ratio of 1.0/0.04/0.1. Hydrogel curing and patterning is performed by UV exposure through a mask and developed in isopropyl alcohol and water. Finally, the third step is to form the inlet orifice by deep reactive ion etching (DRIE) the backside of the Si substrate. Residing topside exposed oxide and parylene films are etched using buffered hydrofluoric acid and O₂ plasma, respectively. Fabricated valves are shown in Figure 4.

Figure 3. Cross-sectional fabrication process (left) and topside view (right). (i) 0.5–2.0 μ m parylene (Py) negative-anchor films deposited on Si and patterned by RIE. (ii) Hydrogel (HG) solution is poured and patterned by UV. (iii.a) Backside inlet formed by DRIE of Si and RIE of Py and (iii.b) then hydrated to swell HG.

Figure 4. Photograph of fabricated valve.

RESULTS

Experimental Setup

Benchtop testing of the hydrogel valve were performed in a simulated CSF solution (phosphate buffered saline, PBS, or artificial CSF, aCSF) replicating the ionic consistency (pH $\sim$ 7.4) and viscosity of its physiological counterpart, containing 10% blood to exemplify situations of infarction of blood-containing particles. Temperature was maintained at $\sim$ 38 – 40 $^{\circ}$ C by a constant temperature water bath, to replicate the warmer implant brain environment. The inlet pressure, P_i , outlet pressure, P_o , and ΔP across the valve was measured by amplifying and converting voltage output from a differential pressure transducer (PX26-001DV, Omega) with 1% accuracy, and linearity from $-700 < P < 700$ mmH₂O with $\sim$ 1 mmH₂O resolution. Q_o was measured by recording the differential pressure across a fixed fluidic resistance: a 35 cm long rigid pipe having an inner diameter of 0.5 mm. The resistor was calibrated directly using a syringe pump input and displayed linearity from $-700 < Q_o < 700$ μ L/min with $\sim$ 2 μ L/min resolution. All amplified voltage data were fed to a data acquisition card (DAQ) for computer monitoring. The complete setup encompassing the three sets of measurements is shown in Figure 5.

Figure 5. Experimental setup for valve characterization and concurrent parallel testing of multiple valves in hydrodynamic environment for overtime testing.

Basic Hydrodynamic Measurements

Basic hydrodynamic measurements to obtain pressure-flow curves involved inputting flow or pressure and measuring the resulting pressure or flow, respectively. The flow source input was provided by a syringe pump and the pressure source input by a high volume water column. It was found that the type of source did not affect results considerably (Figure 6), and therefore the syringe pump was used for the majority of testing. Figure 6(a) shows multiple measurement sets of pressure-flow data for a valve with $t \sim 300$ μ m, $L_f = 1.45$ mm, $W_f = 200$ μ m, $r_o = 550$ μ m, and $r_i = 250$ μ m. Measurements were initially performed in water and in a 10% aqueous microparticle (diameter $\sim 20 - 53$ μ m) suspension at ~ 23 $^{\circ}$ C. Measurements of the valve introduced in the emulated CSF with 10% blood at $\sim 38 - 40$ $^{\circ}$ C shifts operation to a lower R_h as expected based on the lower viscosity of the heated *in vitro* fluid. Figure 6(b) displays evaluated range of R_h and P_T for a larger valve with $t \sim 250$ μ m, $L_f = 2$ mm, $W_f = 200$ μ m, $r_o = 600$ μ m, and $r_i = 250$ μ m in water at ~ 23 $^{\circ}$ C, in a 10% microparticle aqueous suspension at ~ 23 $^{\circ}$ C, and in emulated CSF with 10% blood at $\sim 38 - 40$ $^{\circ}$ C.

Table 2: Measured specifications for hydrogel valves

	Targeted	Measured
ΔP	-200 – 600 mmH ₂ O	-800 – 300 mmH ₂ O
Q_o	0.1 – 3.0 mL/min	0.01 – 1.0 mL/min
P_T	10 – 230 mmH ₂ O	1 – 110 mmH ₂ O
R_h	81.5 – 136 mmH ₂ O/mL/min	24 – 152 mmH ₂ O/mL/min

Figure 6: Basic hydrodynamic measurements. (a) Plot of Q_O vs. ΔP for the hydrogel valve with $t \sim 300 \mu\text{m}$ and $L_f = 1.45 \text{ mm}$ in water at $\sim 23^\circ\text{C}$ and in emulated CSF with 10% blood at $\sim 38 - 40^\circ\text{C}$. Measurements in water are shown for both pressure and flow source inputs. (b) Evaluated range of R_h and P_t for another hydrogel valve with $t \sim 250 \mu\text{m}$ and $L_f = 2 \text{ mm}$, in water at $\sim 23^\circ\text{C}$, 10% microparticle aqueous suspension at $\sim 23^\circ\text{C}$, and in emulated CSF with 10% blood at $\sim 38 - 40^\circ\text{C}$.

Overtime Measurements

The overtime study involved parallel concurrent operation of multiple hydrogel valve devices subjected to pulsatile flow over several weeks in the emulated CSF solution consisting of 10% blood and at $\sim 38 - 40^\circ\text{C}$. A peristaltic pump was used to crudely emulate largely amplified and accelerated forms of physiological pressure waves possessing $\Delta P \sim 300 - 800 \text{ mmH}_2\text{O}$ and frequency of 1 – 4 Hz. Weekly pressure-flow response measurements for the valve with $t \sim 300 \mu\text{m}$ and $L_f = 1.45$ are shown in Figure 7(a). The collected data was also analyzed to determine R_h and P_t to quantify relative variation in overtime performance (Figure 7(b)). The deviations seen in R_h and P_t overtime are negligible relative to the variation observed for operation in water prior to prolonged operation under semi-accelerated conditions.

CONCLUSION

The miniature hydrogel valve presented here has been shown to operate with targeted hydrodynamic specifications ($R_h \sim 24 - 152 \text{ mmH}_2\text{O/mL/min}$) in range of actual physiological CSF draining and the desired self-sealing properties to possess negligible leakage. Overtime measurements in amplified pulsatile conditions demonstrate the valve's ability to sustain operationally reproducible draining operations and the potential implant-relevant longevity qualities. The valve is simple in both design and fabrication, and only comprises two or three materials, silicon, hydrogel, and parylene (removable), all of which are biocompatible. These results serve to strengthen the valve's useful application in treating hydrocephalus in a safer and more robust manner than current shunts. Future work to evaluate its ability to drain CSF in real brains will entail *in vivo* testing in animals.

Figure 7: Overtime measurements during continuous operation under semi-accelerated conditions in emulated CSF (10% blood) at $\sim 38 - 40^\circ\text{C}$: (a) Q_O vs. ΔP for the valve with $t \sim 300 \mu\text{m}$ and $L_f = 1.45 \text{ mm}$. (b) R_h and P_t for the valve during overtime operation and in the initial water environment at $\sim 23^\circ\text{C}$.

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