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A Cardiovascular Occlusion Method based on the use of a Smart Hydrogel

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***Abstract*—Smart hydrogels for biomedical applications are highly researched materials. However, integrating them into a device for implantation is difficult. This paper investigates an integrated delivery device designed to deliver an electro-responsive hydrogel to a target location inside a blood vessel with the purpose of creating an occlusion. The paper describes the synthesis and characterization of a Pluronic/methacrylic acid sodium salt electro-responsive hydrogel. Application of an electrical bias decelerates the expansion of the hydrogel. An integrated delivery system was manufactured to deliver the hydrogel to the target location in the body. *Ex vivo* and *in vivo* experiments in the carotid artery of sheep were used to validate the concept. The hydrogel was able to completely occlude the blood vessel reducing the blood flow from 245 ml/min to 0 ml/min after implantation. *Ex vivo* experiments showed that the hydrogel was able to withstand physiological blood pressures of > 270 mmHg without dislodgement. The results showed that the electro-responsive hydrogel used in this paper can be used to create a long-term occlusion in a blood vessel without any apparent side effects. The delivery system developed is a promising device for the delivery of electro-responsive hydrogels.**

***Index Terms*— Blood Vessel, Cardiovasular, Delivery Device, Electroactivation, Hydrogel, Occlusion.**

I. Introduction

During the last two decades there have been significant advances in the development of smart hydrogels for biomedical applications [1-3]. Hydrogels are ideal for biomedical applications due to their ability to swell/deswell several thousand times their original volume. Smart hydrogels have the capability of changing their dimensions due to an external stimulus, which can include thermal, magnetic, light, electrical, or pH [4, 5]. However, with the exception of electrical stimulus these methods are less suitable for implantable biomedical applications as they are difficult to integrate into a medical device. Although there have been significant advances in the development of smart hydrogels, integrating them onto an implantable system has been limited [6].

The most commonly used biomedical applications for smart hydrogels are artificial muscles [7] or drug delivery [8], where an applied stimulus causes the hydrogel to expand or deswell which releases a specified volume of drug. Another application which is currently being investigated uses the hydrogel's ability to expand significantly in order to create an occlusion in a blood vessel [9]. Smart hydrogels have previously been used as valves in fluidic devices [10]. Previously, non-stimuli responsive hydrogels have been used to embolize blood vessels in aneurysms. In these cases the hydrogel can be coated on a coil [11] or they can be injected at the site of the aneurysm [12].

There are several medical procedures which require the occlusion of blood vessels including a blood vessel wall bleed, vascular embolization, aneurysms, and prevention of blood from reaching a particular location, such as in cancer therapy[13, 14]. Currently, the treatment for these conditions includes invasive surgical repair or cauterizing the blood vessel [15].

Due to their swelling capacity in aqueous solutions, hydrogels are ideal for creating occlusions in blood vessels because they can be introduced to the vascular system in a compact state and expand significantly in blood. However, once the hydrogel is in contact with the blood it begins to swell immediately, making delivery of the hydrogel to the target location in a timely manner critical. Surgical procedures which involve implantation of a hydrogel can vary in time duration depending on the target location. In the case where an implantation takes several minutes a typical hydrogel could expand and occlude an unwanted blood vessel which has potential to cause fatal side effects. An increased delivery time could be required due to tortousity or stenosis in the blood vessel. Alternatively, a smart hydrogel can be used to reduce the risk of unsuccessful delivery of the hydrogel by decelerating expansion through an applied stimulus.

The stimulus investigated in this paper includes an electrical bias that can be applied to the hydrogel while it is being delivered. Electrical stimuli have previously been shown to actuate electro-responsive hydrogels (ERH) for applications including artificial muscles[16]. ERH applications typically

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include bending of the material in salt solutions. The ERH bends while between two sheet electrodes of opposite potential [17]. Recently it has been shown that an interdigitated (IDT) electrode array can be used to create a uniform cylindrical deswelling [9]. Therefore, the possibility of slowing down the expansion of a cylindrical ERH during implantation is feasible. This paper investigates the use of an ERH to create an occlusion in a blood vessel. However, there are several key challenges which will also need to be addressed including i) the ERH ability to expand and adhere to the blood vessel surface creating an occlusion under normal physiological blood pressures and, ii) the development of a delivery device that can be used for short or long duration implants.

This paper aims to develop a system to deliver a smart hydrogel to the target location with a minimally invasive procedure in order to occlude a blood vessel. This requires integration of various components including: a specifically modified Pluronics ERH, a flexible IDT electrode device to apply the electrical bias, and a manufactured delivery device to deliver the ERH through the blood vessels. Figure 1 shows the application concept that is investigated within this paper. The schematic shows a blood vessel bleed for visual purposes as the concept could be applied to numerous occlusion applications.

This paper deals with design and manufacturing of a delivery device with integrated flexible IDT electrodes that is capable of successfully delivering an ERH to a target location *in vivo*. A proof of concept of the application is demonstrated through in vitro electrical and mechanical characterization of the ERH, followed by a study on the capability of the ERH to occlude a carotid artery in both *ex vivo* and *in vivo* using the integrated delivery device. The development of an integrated delivery device and its operation is described below.

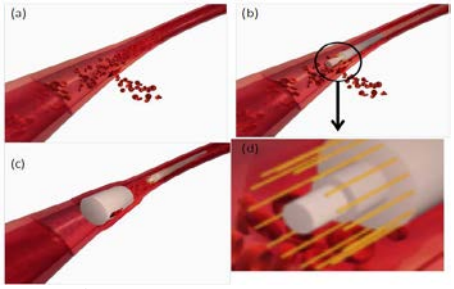


Fig. 1. Schematic of the application and integrated delivery device with interdigitated electrodes to prevent swelling of the hydrogel. (a) application involving a bleeding of a blood vessel (b) delivery of electro-responsive hydrogel where the electrical bias prevents swelling (c) remove electrical bias and release device at the target location allowing hydrogel to passively swell (d) zoomed in image of the electrode configuration with unswollen ERH in the center.

II. MATERIALS AND METHODS

A. Synthesis of Electro-Responsive Hydrogels

The ERH used in this study is a Pluronic/methacrylic acid sodium salt hydrogel (PLMANa). Pluronic F127, an ABA block copolymer, was chosen as a base material because of its known biocompatibility. The ERH was prepared by crosslinking methacrylate endcapped Pluronic F127 (PF127-BMA) with the sodium salt of methacrylic acid, as described previously [18]. Briefly, 1.5 g of PF127-BMA (PL), 2.4 g of hydrolyzed methacrylic acid sodium salt (MANa), and 4.6 g of deionized water (DI) (with resistivity of 18 MΩ cm) were mixed together. A 1 M ammonium persulfate (APS) (Sigma Aldrich A3678) solution (0.75 ml) was added as the initiator, and a 1 M tetramethylethylenediamine (TEMED) (Sigma Aldrich T9281) solution (0.75 ml) as the accelerator. The solution was slowly mixed, covered with a blanket of N_2 gas to avoid oxygen trapping, and then transferred to a mold and refrigerated for 1 hour before being transferred to a water bath at 37°C for 3 hours. The molds consisted of various sized silicone tubes in order to create a cylindrical shape.

After polymerization was completed the samples were removed from the molds and purified in Krebs solution for 3 days to remove any residual material. After purification the samples were air dried to deswell the hydrogels to the appropriate dimensions. The dried hydrogel samples were then used for *in vitro* characterization or they were integrated on the delivery device for *ex vivo* and *in vivo* implantation trials.

B. Swelling Characterization

The rate of swelling and the maximum swelling of the hydrogels are critical for this application. To characterize the ERH, dried hydrogels samples with a diameter of 2.5 mm and lengths of 4 mm were prepared. Samples (n=3) were placed into two different solutions to determine the swelling rate in different ionic concentrated solutions. The samples were submersed in Krebs solution (a blood mimicking solution), and blood plasma for 24 hours. The swelling rate is expected to be similar in blood plasma and Krebs because they both have similar ionic concentrations and previous results have shown that the electroactuation of ERH is similar for both solutions [18]. Swelling was determined by weighing the dried samples (W_d) and the swollen samples (W_s) using the following formula.

$$S = \frac{W_s - W_d}{W_d} * 100\% \quad (1)$$

C. Electroactuation of Hydrogels

Electro-responsivity of the PLMANa material using sheet electrodes for bending tests were previously published [19]. However, to produce radial deswelling, which is required for this application, a 3-D macro-scale interdigitated (IDT) electrode device was developed. The 3-D IDT electrode was used to validate the concept that an electrical bias can decelerate expansion while the hydrogel is being delivered in the body. The IDT electrode configuration creates a uniform electric field, allowing the hydrogel to expand/deswell radially. The IDT electrode device was previously validated [9]. The device consists of 500 µm diameter Pt electrodes that are equally spaced every 45°. The electrodes alternate between cathode and anode, and the hydrogel is situated in the center.

In order to validate the concept in an *in vitro* experiment the hydrogels were purified in DI water following synthesis, in order to reduce the number of ions in the ERH. After purification, the samples were air-dried until deswelling had ceased. Two sets of hydrogels (n=3) were used in the experiment, i) controlled (non-electro biased) and ii) electro-biased sample. The dried hydrogels had a diameter of 3 mm,

due to the size of the macroscale electrodes. After the samples were dried they were placed in the IDT electrode device in a Krebs solution environment. The electrically biased samples were biased using previously reported parameters [20], which consisted of a pulsed DC (monophasic) waveform with 5 V_{pp}, 50% Duty Cycle at 1 kHz. The hydrogels were removed from the experimental setup and weighed periodically throughout the experiment. Swelling was determined based on (1).

D. Fabrication of flexible microelectrodes

Flexible micro-electrodes were required in order to integrate the IDT electrode design into a delivery device. The micro-electrodes were fabricated on a glass substrate for mechanical support as shown in Fig 2a. Polyimide pre-cursor (PI-2611, HD Microsystems) was spin-coated and then imidized in a nitrogen oven at 350ºC resulting in a uniform 5 µm thick polyimide layer [21, 22]. Polyimide was chosen as the flexible substrate because of its biocompatibility and favorable processing properties and low water adsorption. [23, 24]. Following imidization, the surface of the film was micro-roughened to increase adhesion to the subsequently deposited metal layer. A metallization stack consisting of 50 nm titanium (Ti) adhesion layer and a 200 nm gold layer was sputter deposited. Using standard photo-lithography and wet etching techniques, this metal stack was then patterned to form the IDT electrode configuration, the bond pads and the interconnection. On top of this a 100 nm TiW metal layer was deposited. The TiW layer was added as a barrier layer to protect the Au from dissolution at higher voltages (>1 V) in ionic concentrated solution. A 30 nm Pt layer was then deposited using electron beam evaporation and patterned using a lift-off technique. The Pt was used as the electrode material due to its chemical stability under an electrical bias in a salt solution [25]. A second polyimide layer (5 µm thick) was applied and imidized, and acted as an insulation layer between the electrodes. Reactive ion etching was used to etch through the polyimide layer, in order to open up the electrodes, bond pads and to define the shape of the flexible microelectrode device. The devices were mechanically removed from the glass substrate.

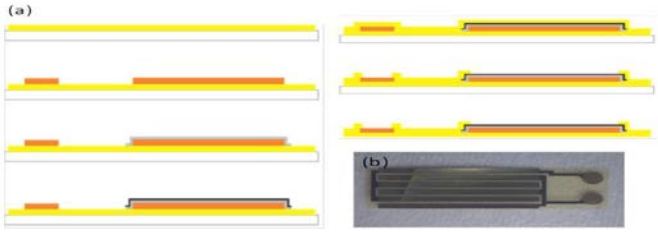


Fig. 2. (a) Schematic of the fabrication process for the micro-electrodes. Top to bottom: glass carrier with first polyimide layer – Ti/Au metallization – additional TiW metallization for the electrodes – Pt metallization for the electrodes – second polyimide layer – opening of electrode and bondpad areas – release from carrier. (b) Picture of flexible micro-fabricated IDT electrodes

Pure Pt electrodes would be the ideal material for the electrodes. However, for reasons such as cost, manufacturability and connectivity, a Pt only metallization is not feasible. Therefore Au was chosen as the core metal, with a thin Pt coating on top. Gold can be easily dissolved under an electrical bias in a chloride-rich electrolyte, so an additional protection layer of TiW was deposited.

The flexible IDT electrode device was fabricated so that it could be attached to the inner wall of a catheter. The IDT design consists of six electrodes that are 800 µm wide with 400 µm pitch and 15 mm in length as shown in Fig. 2b.

E. Delivery Device

The delivery device is a critical component to the system, as the ERH requires an integrated tool for transporting the material to the target location and applying an electrical bias to the material during transportation. The delivery device also must contain a method of holding the ERH during delivery, pushing the ERH out of the catheter, and a method for releasing it after it is swollen.

The basic concept of the device is to contain a holder, which can hold the dried hydrogel prior to expansion, a catheter to protect the hydrogel during delivery, a flexible IDT electrodes inside the catheter, a mechanical pusher to extend the hydrogel out of the catheter, a conical balloon at the proximal end of the ERH to temporarily block the blood flow, and a method to release the holder. Figure 3 shows the schematic design and the manufactured device (Aran Research and Development, Israel). The delivery device consists of a 9 FR sheath that is pre-inserted into the target location and a 7 FR catheter containing the holder, the IDT flexible electrodes, and the ERH. The holder is a stainless steel wire of 0.9mm which partially penetrates the ERH. The ERH can be molded to contain a 0.9mm hole in the middle. A through-hole guide wire was not used because a hole extending through the entire length of the ERH would prevent a full occlusion by allowing residual blood flow through the ERH. Figure 3d shows the dried hydrogel mounted on the holder. The flexible IDT electrodes were bonded to the inside of the catheter using UV curable biocompatible non-conducting epoxy (Loctite 3341). The IDT electrodes are connected to electrical wires that extend back to the handle where they can be connected to a signal generator as shown in Fig. 3c. Figure 3e shows a micrograph of the tip of the catheter with ERH and IDT electrodes. The balloon can be used to prevent blood flow when the flow is going in the direction of the insertion, this helps prevent the risk of the hydrogel being released prematurely from the holder. However, in cases where the blood flow is against the insertion such a balloon is not necessary. The handle contains ports for the catheter, sheath and balloon; it also contains a mechanical pusher that extends the ERH from the catheter and into the environment. Figure 3d shows the extended ERH before it is loaded into the catheter and Fig. 3e shows the tip of the hydrogel as it is pushed out of the catheter.

The operational procedure for the delivery of the hydrogel begins with inserting the sheath to the desired location. Next, the dried hydrogel is mounted on the holder and retracted into the catheter which is then inserted into the device through the handle. The electrical bias can then be applied via a signal generator if the procedure is likely to take several minutes. The electrical bias is required to prevent swelling, because the ERH starts to swell when it comes into contact with fluid, and if the ERH swells while inside the catheter the pusher will not be able to deploy the ERH out of the catheter without the risk of damaging the ERH. Once the tip of the catheter is at the target location the hydrogel is extended out of the catheter, the

balloon is inflated, the electrical bias is switched off, and expansion is started. The holder remains in place until the ERH expands to the blood vessel wall, which can be assessed by using a light push/pull movement, then the holder is retracted into the catheter and the delivery device is removed, leaving behind the hydrogel to occlude the blood vessel. The occlusion of the blood vessel can also be monitored via angiography or fluoroscopy.

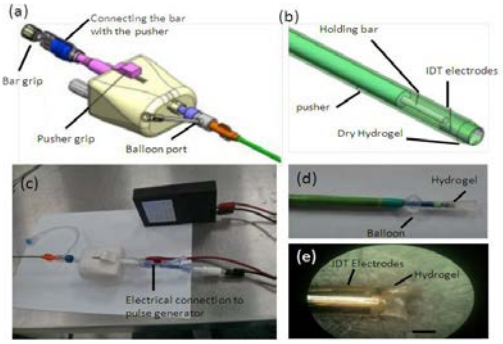


Fig. 3. Schematics and images of the ERH delivery device a) schematic of the handle for the delivery device which contains a pusher and rotator, an electrical connection for the electrodes, a saline/dye supply port and balloon inflation port. B) Schematic of the distal end of the delivery device containing the dry hydrogel, flexible IDT electrodes, holding bar, and pusher. C) Photo of the manufactured delivery device handle with electrical connection. D) Photo of hydrogel on the delivery device before it is loaded and the inflated balloon. E) Micrograph of the IDT electrode and hydrogel as it is being pushed out of the sheath. Scale bar is 2mm.

F. Ex Vivo Concept Testing

Prior to *in vivo* testing the authors performed *ex vivo* occlusion experiments to determine if the ERH could create an occlusion in an extracted carotid artery. The carotid artery of a sheep was mounted in a custom built circulatory system with Krebs solution being pumped through it. The carotid artery was placed in a tissue bath with Krebs solution to minimize the effect of altering the mechanical elasticity due to air. The circulatory system allowed the researchers to increase the pressure and monitor the maximum pressure needed to move the ERH after it was swollen.

Dried ERH of 3.9 mm diameter (n=3) were used in this experiment due to the size of the arteries. The hydrogels were held in place with a catheter until they were fully swollen then the catheter was removed. Pressure in the circulatory system was increased until movement of the ERH was visually seen. This experiment was used to validate the capability of the ERH to occlude the blood vessel, and to show that the ERH could withstand physiological blood pressures. If the ERH could not withstand blood pressure, the hydrogel would become dislodged and could create an emboli.

G. In Vivo Testing

In vivo testing of the occlusion capabilities of the ERH was performed in an adult sheep. The hydrogel samples were sterilized using ethylene oxide. All procedures were carried out with the approval of the ethical committee for animal experiments at KU Leuven, Belgium. The sheep (n=4) were sedated with an intramuscular injection of ketamine (15 mg/kg). Anesthesia was induced with isoflurane 5% (Isoba, Scherin-Plough, Brussels), and the animal was intubated with an oral-gastric tube. Anesthesia was maintained with isoflurane (2-4%). Arterial lines were inserted in the ears, while heart rate, blood pressure, CO_2 and blood O_2 were monitored. The hydrogel was implanted in the right carotid artery and pressure measurements were monitored distal and proximal to the hydrogel to validate occlusion using an intra-arterial catheter. A Doppler flow device was used to measure the blood flow. The surgical procedure took approximately 3 hours from initial incision to skin closure.

Once the hydrogel had expanded to the blood vessel wall the delivery device was removed. Angiography was used (every ten minutes) following the procedure to visually validate the occlusion of the blood vessel. The sheep were monitored for side effects and sacrificed after 4 weeks in order to retrieve the ERH to investigate any signs of deterioration.

III. RESULTS AND DISCUSSION

A. Characterization of Electro-Responsive Hydrogel

The PLMANa hydrogel swelling rates in Krebs solution and blood plasma are shown in Fig 4. The results show that the average swelling rate was similar for both solutions, which is expected since Krebs solution has a similar ionic concentration as blood plasma. The hydrogel samples had a swelling rate of 258% and 279% within 30 minutes for Krebs and blood plasma respectively. After 24 hours the samples in Krebs solution swelled 1540% on average compared to 1450% for blood plasma. The maximum swelling results show no significant difference between the two set of samples $p>0.1$. The results confirm that Krebs solution can be used as an alternative to blood plasma for in vitro testing, and that the PLMANa hydrogels swell significantly in physiological fluid. The swelling rate in whole blood is expected to be slightly slower due to the presence of proteins and other molecules. Free swelling hydrogels swell in all dimensions. However, in a blood vessel the hydrogel will begin to swell radially until it contacts the vessel wall and then it will begin to expand lengthwise until it reaches equilibrium. A higher final swelling value is desired as it allows the hydrogel to be smaller during insertion, but it would have the disadvantage of having reduced mechanical properties.

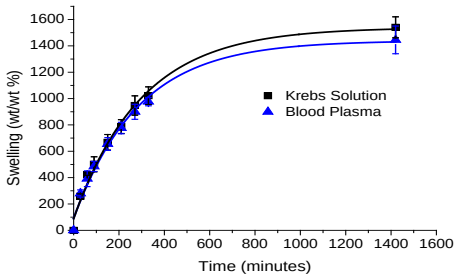


Fig. 4. Average swelling results versus time PLMANa in Krebs solution and Blood plasma. Error bars represent the standard deviation, and the line is a fitted model.

The results for the *in vitro* electro-actuation experiment using the macro-scale IDT electrodes, were used to validate the deceleration of the hydrogel's swelling due to an electrical bias is shown in figure 5. The results show that the electrically biased hydrogels did not expand as quickly as the non-biased hydrogels. A t-test showed that there was a significant difference between the two samples $p<0.01$. Swelling of a

polyelectrolyte hydrogel is governed by the osmotic pressure of the counter ions. The added salt ions from Krebs or blood plasma decelerate the process compared to pure water. Swelling stops when the chemical potential of ions inside the ERH and bulk solution are equal. The electrical bias causes the hydrogel to swell even slower, interfering with the diffusion of the ions until equilibrium is reached. Both sets of samples expand which was expected as the hydrogel still absorbs the fluid from the Krebs solution. The results also show that the difference in the expansion increases with time. The expansion rate of the ERH decreases as the hydrogels expand. This is related to the depth of the electric field. The dried samples were 3 mm in diameter where as the IDT electrodes have a configuration diameter of approximately 6 mm. The depth of the electric-field from the IDT in this case was previously shown to be shallow [9]. As the hydrogel expands it becomes closer to the electrodes thus increasing the impact of the applied electrical bias. Based on these results an ideal IDT electrode would expand/shrink with the hydrogel, however this is difficult to achieve.

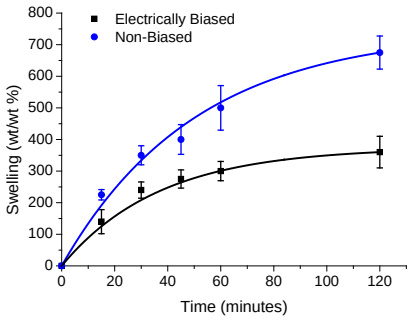


Fig. 5. Average swelling results versus time for electrically biased samples compared to non-biased (control) samples, the line is a fitted model, and error bars represent the standard deviation.

Previous results demonstrated that an electrical bias does not significantly affect the swelling equilibrium level, as the ERH swells normally, once the biased is removed [9].The overall results from the *in vitro* electro-actuation experiment validate the concept that an IDT electrode configuration can slow down expansion of the hydrogel. Therefore, an IDT electrode configuration integrated into a delivery system could be used for operations that require longer insertion times. Another electrode configuration option includes using a peripheral electrode with a center core electrode (guide wire). However, the disadvantage to using a center core electrode is that a hole needs to be created in the hydrogel which prolongs the swelling rate to cause a full occlusion.

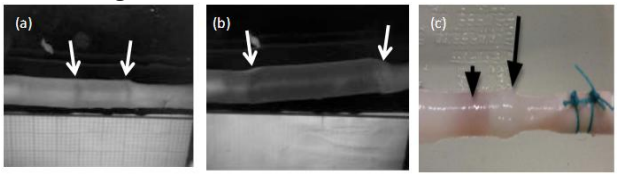


Fig. 6. Images of the hydrogel swelling in an *ex vivo* carotid artery. (a) 12 minutes post implant, (b) 30 hours post implant (c) imaging showing bulging properties of the hydrogel. Arrows show location of the hydrogel and balloon of delivery device (big arrow).

The flexible IDT electrodes were validated for single use only, because the TiW layer developed micro-cracks when bent, which lead to the dissolution of the Au layer during an applied electrical bias due to its exposure to chloride ions in Krebs solution. There are methods to resolve this issue in the future, for instance: i) an all Pt IDT electrode or ii) to electroplate a thick Pt layer after the flexible material has been bent. As mentioned in section II, the first option is expensive and difficult to fabricate since thick Pt is difficult to pattern. The latter option would protect the gold layer from dissolution by coating it with a crack-free Pt layer.

B. Ex Vivo Results

The image in Fig.6 shows swelling of the ERH at various time intervals. The results show that the ERH was able to occlude the *ex vivo* carotid artery of a sheep. In addition, a bulge in the artery is visually noticeable. The bulge helps to prevent the hydrogel from moving. Once the hydrogel swelling force cannot overcome the elastic properties of the blood vessel the hydrogel starts to expand laterally instead of radially, which can be seen from the expansion in length from Fig. 6a to Fig. 6b.

TABLE I
Characteristics of Swollen Hydrogels in *Ex Vivo* Carotid Arteries

	Diameter of Carotid Artery (mm)	Length of Hydrogel fully Swollen (mm)	Diameter of Hydrogel fully Swollen (mm)	Volume Expansion (%)	Maximum Pressure (mmHg)
Gel 1	7.35	20.5	7.94	1003	220
Gel 2	7.45	22.8	7.64	978	240
Gel 3	6.47	29.3	7.25	906	>270

Table I shows the results from the ex vivo test for the three hydrogel samples. The carotid artery had an initial diameter of 7.1 ± 0.5 mm. The fully swollen hydrogels had a diameter of 7.6 ± 0.3, which shows that there was an average bulge increase of approximately 0.5 mm. This amount of bulge is not significant to cause long-term permanent damage to the blood vessel. The overall volume expansion of the hydrogel was 962 ± 50%. The average maximum pressure that the ERH were able to withstand before being dislodged was 243 ±25 mmHg, which is higher than normal physiological blood pressure. However, the maximum pressure that the ERH could withstand is believed to be highly dependent on the length of the fully swollen hydrogel. Therefore, a longer material should be more difficult to dislodge. This is to be expected as the force required to dislodge the material is related to both the friction and the contact force which is dependent on the contact length.



Fig.7. Angiography of occluded carotid artery 1 hour after delivery of hydrogel, the black arrow shows location of the hydrogel.

C. In Vivo Results

Results from the *in vivo* testing of the occluded carotid artery of sheep are shown in Fig. 7 and Table II. All four ERH

successfully occluded the carotid artery as shown in the angiography in Fig. 7. The average flow in the carotid artery before implantation of the hydrogel was 245 ± 7 ml/min, while after implantation the flow was 0 ml/min in all four sheep. The flow rate remained 0 ml/min throughout the duration of the experiment. There was a slight pressure drop over the hydrogel due to collateral flow.

TABLE II
In Vivo Results

Sheep	Flow before Implant (ml/min)	Flow after Implant (ml/min)	Angiography
1	235	0	Occluded
2	250	0	Occluded
3	250	0	Occluded
4	243	0	Occluded

The animals did not show any visual side effects in behavior due to the occlusion of the carotid artery, and no changes were seen on the CT scans. After the sheep were sacrificed the ERH implants were explanted to investigate the integrity of the implants and vessels. Figure 8 shows the explanted hydrogel. Visually, the ERH was intact and showed no signs of deterioration or cracking. The ERH did not adhere to the wall of the carotid artery. The swollen ERH had a diameter of 7.4 ± 1.1 mm and they had an initial diameter of 3 mm. The ERH also swelled lengthwise once the hydrogel was in contact with the vessel wall.



Fig. 8. Explanted carotid artery with occluded hydrogel. Black arrows show the location of the hydrogel. The thick black arrow shows a thrombus at the proximal site.

IV. CONCLUSION

This paper demonstrates the successful synthesis of an ERH and its ability to occlude a carotid artery both *ex vivo* and *in vivo*. The in vitro mechanical and electrical characterization of the ERH validates the concept of using an electrical bias to decelerate the expansion of the material. Removal of the electrical bias allowed the ERH to passively swell, which provided precise control over the timing of the ERH swelling. *Ex vivo* results of the carotid arteries showed that the ERH could withstand physiological blood pressures of >270 mmHg while maintaining an occlusion. *In vivo* experiments validated that the ERH could be delivered to the carotid artery and it created an occlusion, which prevented blood flow.

The delivery device that was developed allows for a minimal invasive implantation of an ERH to a blood vessel to create an occlusion. The delivery device had an integrated electrical connection that could be powered using a signal generator connected to the IDT electrode. The electrical bias applied to the ERH could be used to decelerate the expansion of the ERH in long duration surgical procedures.

Future work in this area will include optimization of the ERH material to increase the expansion rate and optimization of the electrode configuration and electrical bias parameters. In addition a complete biocompatibility experiment of the hydrogels and their interaction with the physiological environment will be conducted, along with long-term studies to determine the ERH stability.

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REFERENCES

[1] J. Burdick, and G. Prestwich, "Hyaluronic acid hydrogels for biomedical applications," *Advanced Materials*, vol. 23, no. 12, pp. H41-H56, 2011.

[2] A. Guiseppi-Elie, "Electroconductive hydrogels: Synthesis, Characterization and biomedical applications," *Biomaterials*, vol. 31, pp. 2701-2716, 2010.

[3] A. Hoffman, "Hydrogels for Biomedical Applications," *Advanced Drug Delivery Reviews*, vol. 54, no. 1, pp. 3-12, 2002.

[4] C. Alarcon, S. Pennadam, and C. Alexander, "Stimuli responsive polymers for biomedical applications," *Chemical Society Reviews*, vol. 34, no. 3, pp. 276-285, 2004.

[5] H. Meng, and J. Hu, "A brief review of stimulus-active polymers responsive to thermal, light, magnetic, electric, and water/solvent stimuli," *Journal of Intelligent Material Systems and Structures*, vol. 21, no. 9, pp. 859-885, 2010.

[6] H. Schwerdt, R. Bristol, and J. Chae, "Miniaturized Passive Hydrogel Check Valve for Hydrocephalus Treatment," *IEEE Transactions on Biomedical Engineering*, vol. 61, no. 3, pp. 814-820, 2014.

[7] M. Bassil, J. Davenas, and M. El Tahchi, "Electrochemical properties and actuation mechanisms of polyacrylamide hydrogel for artificial muscle application," *Sensors and Actuators B: Chemical*, vol. 134, no. 2, pp. 496-501, 2008.

[8] S. Murdan, "Electro-responsive drug delivery from hydrogels," *Journal of controlled release*, vol. 92, no. 1, pp. 1-17, 2003.

[9] N. Jackson, N. Cordero, and F. Stam, "3-D Interdigitated Electrodes for Uniform Stimulation of Electro-responsive Hydrogels for Biomedical Applications," *Journal of Polymer Science Part B: Polymer Physics*, vol. 51, pp. 1523-1529, 2013.

[10] D. Eddington, and D. Beebe, "Flow control with hydrogels," *Advanced Drug Delivery Reviews*, vol. 56, no. 2, pp. 199-210, 2004.

[11] D. Kallmes, and N. Fujiwara, "New expandable hydrogel-platinum coil hybrid device for aneurysm embolization," *American Journal of Neuroradiology*, vol. 23, no. 9, pp. 1580-1588, 2002.

[12] H. Bearat, M. Preul, and B. Vernon, "Cytrotoxicity, in vitro models and preliminary in vivo study of dual physical and chemical gels for endovascular embolization of cerebral aneurysms," *Journal of Biomedical Materials Research Part A*, vol. 101, no. 9, pp. 2515-2525, 2013.

[13] P. Carmeliet, and R. Jain, "Angiogenesis in cancer and other diseases," *Nature*, vol. 407, pp. 249-257, 2000.

[14] P. White, S. Lewis, H. Nahser *et al.*, "HydroCoil Endovascular Aneurysm Occlusion and Packing Study," *American Journal of Neuroradiology*, vol. 29, pp. 217-223, 2008.

[15] D. Palanker, A. Vankov, Y. Freyvert *et al.*, "Pulsed electrical stimualtion for control of vasculature: temporary vasoconstriction and permanent thrombosis," *Bioelectromagnetics*, vol. 29, pp. 100-107, 2008.

[16] E. Moschou, M. Madou, L. Bachas *et al.*, "Voltage-switchable artificial muscles actuating at near neutral pH," *Sensors and Actuators B: Chemical*, vol. 115, no. 1, pp. 379-383, 2006.

[17] P. Glazer, M. van Erp, A. Embrechts *et al.*, "Role of pH gradients in the actuation of electro-responsive polyelectrolyte gels," *Soft Matter*, vol. 8, no. 16, pp. 4421-4426, 2012.
[18] P. Glazer, P. Verbrugghe, K. Adesanya *et al.*, "Electro-actuation of biocompatible Pluronic/methacrylic acid hydrogel in blood plasma and in blood mimicking buffers," *RCS Advances*, vol. 4, no. 4, pp. 1890-1894, 2013.
[19] L. Engel, O. Berkh, K. Adesanya *et al.*, "Electromechanical response and the role of applied current," *Sensors and Actuators B: Chemical*, vol. 191, pp. 640-658, 2014.
[20] N. Jackson, and F. Stam, "Optimization of Electrode Activation Parameters for Electro-Responsive Hydrogels for Biomedical Applications," *Journal of Applied Polymer Science*, Submitted.
[21] N. Jackson, and J. Muthuswamy, "Flexible chip-scale package and interconnect for implantable MEMS movable microelectrodes for the brain," *Journal of Microelectromechanical Systems*, vol. 18, no. 2, pp. 396-404, 2009.
[22] T. Stieglitz, M. Schuettler, and J. Meyer, "Micromachined polyimide-based devices for flexible neural interfaces," *Biomedical Microdevices*, vol. 2, no. 4, pp. 283-294, 2000.
[23] A. Mercanzini, P. Colin, J. Bensadoun *et al.*, "In vivo Electrical Impedance Spectroscopy of Tissue Reaction to Microelectrode Arrays," *IEEE Transactions on Biomedical Engineering*, vol. 56, no. 7, pp. 1909-1918, 2009.
[24] T. Stieglitz, "Development of a micromachined epiretinal vision prosthesis," *Journal of Neural Engineering*, vol. 6, no. 6, pp. 065005, 2009.
[25] N. Lago, K. Yoshida, K. Koch *et al.*, "Assessment of biocompatiblity of chronically implanted polyimide and platinum intrafascicular electrodes," *IEEE Transactions on Biomedical Engineering*, vol. 54, no. 2, pp. 281-290, 2007.



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