Hydrolytic stability and biocompatibility of injectable hydrogel electrodes for treatment of ventricular arrhythmias

Gabriel J. Rodriguez-Rivera[1], Allison Post[2], Mathews John[2], Skylar Buchan[2], Abbey Nkansah[3], Alberto Maradiaga[3], Megan Wancura[4], Manuel Rausch[3], Mehdi Razavi[2], Elizabeth Cosgriff-Hernandez[3]
[1]McKetta Department of Chemical Engineering, Austin, TX, [2]Texas Heart Institute, Houston, TX,
[3]Department of Biomedical Engineering, Chemistry Department, The University of Texas at Austin, Austin, TX

Statement of Purpose: Ventricular arrhythmias (VA) are the leading cause of sudden cardiac death. A common underlying cause for VA is delayed conduction velocity in scarred myocardium that leads to re-entrant circuits. Our work aims to develop an injectable hydrogel electrode that can be used with a standard pacemaker to increase the stimulation area across the scarred tissue to normalize conduction. We hypothesize that pacing across the scarred area will prevent re-entrant circuits. To this end, we have developed an injectable hydrogel that fills coronary veins and tributaries and converts them into flexible electrodes. Previously, we demonstrated that these ionic hydrogels could be cured in coronary veins and retain conductivity above that of the myocardium after implantation. In this study, we investigated hydrogel biocompatibility and biostability for long-term applications. We also evaluated the mechanical properties and fatigue resistance of the injectable hydrogel.

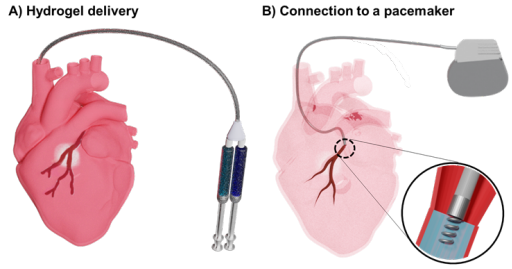

Figure 1: Schematic of the injectable hydrogel system to transform coronary veins into flexible electrodes extensions.

Materials and Methods: The injectable hydrogels were prepared by dissolving poly(ethylene glycol) urethane diacrylamide (PEUDAm), N-acryloyl glycinamide (NAGA), ammonium persulfate (APS), and iron gluconate (IG) in a saline solution. For material characterization, the hydrogel precursors were loaded into double-barrel syringes and injected through a mixing head onto either glass plates to obtain hydrogel slabs or into 3D-printed dog bone molds. Gels were cured for 30 minutes at 37°C prior to testing. Specimens were incubated in PBS at 37°C or 70°C for up to six months and changes in swelling and modulus were monitored as an indication of network degradation. The *in vivo* biostability and biocompatibility of pre-fabricated and *in situ* cured hydrogels were evaluated in a subcutaneous rat model. Gel mechanical properties were assessed using uniaxial extension to determine Young's modulus and ultimate elongation. The fatigue resistance was evaluated after 3000 cycles with a peak strain of 30% at a frequency of 1 Hz, simulating the axial strain of cardiac veins reported in the literature.

Results: PEUDAm hydrogels contain urethane and amide groups resistant to hydrolysis at physiological conditions. There was no change in hydrogel swollen mass and modulus at 37°C or under the accelerated conditions at 70°C after six months. In contrast, a polyethylene glycol diacrylate control, containing esters groups, degraded in less than a week under accelerated conditions. Hydrogel and silicone disc implants elicited comparable, normal wound healing responses after 1, 2, and 4 weeks. The in situ cured hydrogel also elicited a similar wound healing response in the subcutaneous tissue as the pre-fabricated hydrogel discs.

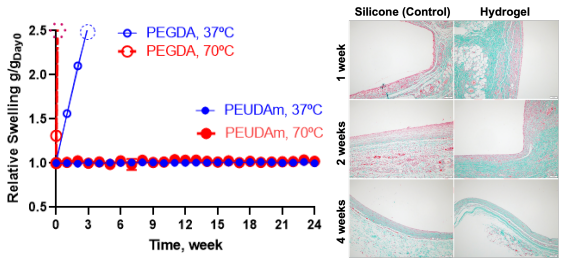

Figure 2: Change in swelling of PEGDA and PEUDAm under hydrolytic conditions (left). Representative microscopic images showing the development and evolution of a thin fibrous cap around the implanted discs and decreased cellularity around the implants (right).

The Young's modulus and ultimate elongation of the hydrogels were 59.1 ± 7.5 kPa and 111 ± 28 %, respectively. There was no change in the maximum stress at the peak strain after 3000 cycles. Furthermore, there was no apparent change in the forces in response to the applied strain during the cyclic testing.

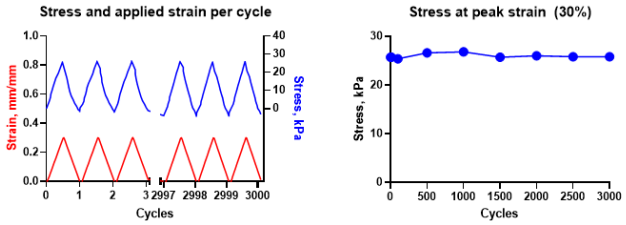

Figure 3: Fatigue Testing. Calculated stress and strain of initial (1-3) and last (2998-3000) cycles. Stress at peak strain vs number of cycles.

Conclusion: This study demonstrated that the injectable PUEDAm hydrogels are resistant to hydrolytic degradation, biocompatible, and mechanically stable for up to 3000 cycles. Future studies will evaluate biostability for up to 6 months using a rat subcutaneous implant model. A setup for assessing fatigue for more extended periods and at a higher frequency is currently under development.