Published in final edited form as:

Conf Proc IEEE Eng Med Biol Soc. 2010 ; 2010: 5428–5431. doi:10.1109/IEMBS.2010.5626518.

Application of the HeartLander Crawling Robot for Injection of a Thermally Sensitive Anti-Remodeling Agent for Myocardial Infarction Therapy

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Abstract

The injection of a mechanical bulking agent into the left ventricular (LV) wall of the heart has shown promise as a therapy for maladaptive remodeling of the myocardium after myocardial infarct (MI). The HeartLander robotic crawler presented itself as an ideal vehicle for minimally-invasive, highly accurate epicardial injection of such an agent. Use of the optimal bulking agent, a thermosetting hydrogel developed by our group, presents a number of engineering obstacles, including cooling of the miniaturized injection system while the robot is navigating in the warm environment of a living patient. We present herein a demonstration of an integrated miniature cooling and injection system in the HeartLander crawling robot, that is fully biocompatible and capable of multiple injections of a thermosetting hydrogel into dense animal tissue while the entire system is immersed in a 37°C water bath.

I. Introduction

Injection of a locally stiffening material into the left ventricular (LV) myocardial wall has been proposed as a novel therapy to prevent maladaptive LV remodeling due to high wall stresses that develop after myocardial infarction (MI). We have previously used a

biodegradable, thermoresponsive hydrogel based on copolymerization of N-isopropylacrylamide (NIPAAm), acrylic acid (AAc) and hydroxyethyl methacrylate-poly(trimethylene carbonate) (HEMAPTMC) in a mouse model of MI. Upon injection of the liquid into warm tissue, it undergoes reorganization into a semi-rigid gel, providing mechanical bulk to the injected region of myocardium, aiding in prevention of dilatory remodeling of the weakened infarct zone [1].

For a clinical application in humans, a minimally-invasive delivery system is inherently desirable. The principal motivation for development of minimally invasive cardiac surgery (MICS) techniques has been to improve post-surgical recovery times and reduce the complications of surgery inherent in an open approach, such as pain, infection, and wound dehiscence. The subxiphoid approach, utilizing a small abdominal incision, is one such technique that shows much promise, as it avoids thoracotomy entirely, and could spare a human patient general endotracheal anesthesia and lung deflation. Unfortunately, as we have previously shown in a porcine model, approaches to the pericardial space through this route using traditional rigid surgical instrumentation and direct visualization are associated with significant hemodynamic compromise and risk of lethal arrhythmia [2]. As a solution to the risks involved in this approach we propose to utilize the HeartLander crawling robot system to deliver this hydrogel for epicardial injection.

HeartLander (Fig. 1) is a miniature mobile robot designed for minimally invasive cardiac intervention, and has already shown its capability to traverse the entire epicardial surface and to perform accurately-placed epicardial injections on closed-chest beating porcine models *in vivo* [3, 4]. This ability to provide enhanced minimally invasive access to the epicardium makes HeartLander a powerful tool to deliver the hydrogel via a subxiphoid surgical approach.

A major engineering obstacle involved in this approach is cooling the miniaturized injection system required for the working head of the robot, in order to prevent the hydrogel from prematurely setting up in the injection system. Insulation is impractical owing to the small diameter of the injection needle. Peltier effect cooling would require complicated lithography on a cylindrical surface to create the necessary thermocouple junctions. Also, thermocouple cooling would require the delivery of electrical current to the needle itself, within micrometers of the myocardium, potentially creating a risk for arrhythmia.

We hypothesized that a reciprocating needle system, coaxial with a jacket supplying cold, sterile 0.9% saline solution, could be adequately miniaturized to function in HeartLander. In order to meet criteria for success, the system would have to have to meet criteria for: (1) needle diameter ≤ 25 ga to prevent leak back or myocardial injury, (2) sufficient conductive cooling of the imbedded needle to prevent gel setting while the needle is in the injected position (i.e., buried in warm myocardium), (3) sufficient permissible dwell time in the myocardium to inject 0.5 ml of the gel at each site, (4) cooling of the entire length of plumbing for the device, connecting the robot to an external reservoir of gel, approximately one meter from the patient, (5) sufficiently low resistance to flow to permit rapid injection of the viscous gel, (6) the ability to perform repeated injections at multiple sites without needle clogging, (7) physiologic safety and biocompatibility of the cooling method and, lastly (8) no impedance to HeartLander's basic functions of locomotion, turning, navigation, and adherence to the epicardial surface.

We report herein the successful construction of such a system, fully integrated into the HeartLander robot. We demonstrate the ability for the system to inject multiple sites in animal tissue *ex vivo*, with the entire apparatus immersed in 37°C water. We further

demonstrate a wide safety margin in the system's thermal profile and the full functionality of the modified HeartLander robot's locomotion system.

II. Methods

A. HeartLander Crawling Robot

The design and construction of the HeartLander crawling robot are described in detail elsewhere [3]. Briefly, as shown in Fig. 2, the HeartLander system consists of a working head (A), comprising two crawling feet (B, C) and the operating end of any attached surgical instrumentation, in this case the injection needle (D). This head is the portion of the assembly that is introduced into the patient's body, through the subxiphoid incision, and which crawls on the surface of the heart. An umbilicus consisting of several linear channels, connects this head to the drive apparatus and operator ends of any surgical equipment fed through the 1-2 mm diameter operating channel. The motive and steering forces are transmitted via two nitinol wires (E) and a tube (F) supply vacuum for adhesion of the foot to the cardiac surface. Two vacuum chambers (G) alternately adhere and release in order to allow the two feet to move separately in an "inch worm" fashion to provide forward or backward locomotion. Steering is accomplished by bending the trajectory of the front foot by varying the tension in the two nitinol drive wires. Navigation in the pericardial space is accomplished using CT image guidance and a magnetic tracking coil system, referenced to external fiducials on the chest wall.

B. Thermosetting Hydrogel

The synthesis and properties of the thermosetting hydrogel are described in detail elsewhere [1]. Briefly, the gel is an aqueous solution of a copolymer of N-isopropylacrylamide (NIPAAm), acrylic acid (AAc) and hydroxyethyl methacrylate-poly(trimethylene carbonate) (HEMAPTMC). Upon reaching temperatures greater than approximately 24°C, the polymer undergoes a phase transition in which it expels water from its matrix and leaves solution as a dense, elastic gel with excellent mechanical properties for flexibly reinforcing myocardial muscle tissue. The material is both biocompatible and biodegradable at a very slow rate, allowing it to be absorbed and removed from the injection site as the healing process occurs over the course of weeks to months.

C. Injection and Cooling System

The working channel of HeartLander was re-engineered to accommodate a 22 ga thin-walled channel of standard stainless steel hypodermic tubing, leading up the umbilicus and terminating in a female Luer connector attached to the injection syringe containing the liquid hydrogel. This syringe is moved reciprocally by hand, with respect to the guide tube of the working channel in order to accomplish needle insert and withdrawal at the tissue target under the front foot. This guide channel consists of 16ga thin wall PTFE tubing, running freely through a port in the rear foot and rigidly affixed to the front foot, opening into a curved channel machined in the acrylic body of the front foot, making a 90° circular bend downward to guide the needle into the tissue. In order to negotiate this bend, the needle tip (the most distal 30 cm, approximately) of the hydrogel channel is machined into 25ga nitinol tubing, itself silver-soldered into the 22ga hydrogel delivery channel, which is also the mechanical linkage for the actions of injection and withdrawal.

The PTFE guide channel terminates at the proximal (external, or operator) end in a female Luer connector, which itself attaches to a three-way 90° Luer adapter. The needle-tube assembly passes coaxially through this channel and thus through the straight arm of the three-way adapter to exit through a rubber septum which acts a leak-proof bearing surface for the reciprocating action of the injection tubing-syringe assembly. The orthogonal port of

the three-way adaptor is connected to a pressurized reservoir of 0.9% sterile saline solution (itself immersed in an ice-water bath) via standard IV tubing with an inline flow regulator valve. Thus, cold saline solution flows through the guide tubing and exits the front foot of HeartLander via the same channel as the needle tip. This saline effluent stream drains onto the surface of the myocardium, and out of the pericardial incision.

D. Tissue Model *Ex Vivo*

As a proof of concept and an initial trial of ruggedness, we simulated conditions of myocardial injection within our living swine model using warmed chicken (*Gallus gallus domesticus*) pectoralis muscle tissue *ex vivo* submerged in a 37°C water bath. In various trials, HeartLander was applied and moved manually over the surface of the muscle sample. Injections were made in 0.25-0.5 ml aliquots and were inspected visually by incision through the injection site, 5 minutes after the injection. The same robot was also moved in automated fashion over similar tissue samples, using a synthetic pericardium analog to facilitate its movement.

E. Temperature Measurement

Outflow temperatures were measured with a rapid-response miniature bifilar thermocouple of 0.0095" maximum outer diameter (no. 12167, RTD, Inc.), inserted retrograde. Data were recorded with a dedicated computer interface device and software (Model HH127, Omega Instruments).

III. Results

A. Qualitative Injection Observations

In order to simulate a typical injection scenario in a patient, we manually guided a fully assembled HeartLander to 5 injection sites on the muscle tissue sample with the entire system submerged in human body-temperature water. We injected at a depth of 5 mm and waited approximately 60 s between injections, with the needle in the withdrawn position, to simulate the HeartLander in "locomotion" mode as it navigates from site to site. Cooling jacket flow was maintained at 0.25 ml/s throughout the experiment.

Injections of up to 0.5 cc took up to 30 s to accomplish using manual pressure on a 10cc syringe, owing to the resistance to flow of the long, narrow tubing and the relatively viscous hydrogel solution. Nevertheless, conductive cooling of the needle tip via its extension into the flowing water jacket was sufficient to prevent any premature gelling at all within this timeframe. Planar slices of the tissue sample revealed well-integrated solidified gel, with no observable leakage back through the track of the 25ga nitinol needle (see Fig. 3).

Optimization of the system will include manually cranked injection and reciprocation assemblies to allow the user the mechanical advantage to deliver greater injection pressures, and thus more rapid and volumetrically precise injection, while maintaining sensory feedback to the surgeon.

B. Quantitative Thermal Performance

In order to assess the operating safety margin of the system (i.e., its resistance to the premature gelling failure mode) with the needle in the injected position, extending more than 5 mm from the HeartLander working head, we recorded the outflow temperature of the hydrogel at various flow rates of ice-cooled saline (approximately 0-2°C) through the guide channel/jacket assembly. Results are shown in Fig 4. This data demonstrates a wide operational safety margin in staying below the target maximum temperature of 17°C, which is 3°C below the first observable trend up in viscosity of the gel [1]. These measurements

were performed under dynamic equilibrium conditions with constant flow of both jacket water and hydrogel. Flow rates as low as 0.1 ml/s maintained the hydrogel outflow at approximately 10°C, thus providing an excellent safety margin. These flow rates represent a non-negligible but minor physiologic cooling burden to the patient and the wasted fluid can be easily reclaimed via suction catheter introduced to the low point of the pericardium via the same surgical foramen as the robot.

C. HeartLander Locomotion Observations

A basic systems operability parameter for HeartLander is that any subsystem deployed through the working head not compromise its ability to freely crawl, turn, adhere and release on the cardiac surface. We had some concern the linear needle and water jacket assembly would impart excessive torsional rigidity to the head, between its two feet. If this were the case, reductions in diameter of the components might have been necessary. In operation, however, HeartLander crawled within its normal operational parameters for drive wire tension and chamber vacuum while crawling over both dry silicone rubber and wet tissue surfaces. No errors were returned from the navigational system.

IV. Discussion

We have successfully demonstrated an elegantly simple miniaturized cooling and injection system, fully integrated into the existing platform of the HeartLander crawling robot. Our ability to carry out repeated injections in multiple sites of warm animal tissue, while protecting the injected material from premature cooling, demonstrates the readiness of the system for *in vivo* trials, performing epicardial injections in swine via the subxiphoid approach to pericardial space, even without further optimization.

Moreover, by rapidly retooling and deploying the HeartLander platform in this challenging application, we have demonstrated the robustness and flexibility of the HeartLander system. This demonstration of HeartLander's ability to serve as the vehicle for an entirely novel surgical intervention system shows that the platform is intrinsically highly adaptable to a variety of instrumentation subsystems that will eventually be desired by the cardiac surgeon as end user.

Acknowledgments

This work was supported in part by the U.S. National Institutes of Health under Grant R01 HL078839.

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Fig. 1.
The HeartLander robotic system (arrow) crawling on the surface of a silicone rubber heart analog.

Fig. 2. Standard HeartLander system (bottom) and HeartLander modified to integrate the cooling and injection systems (top). (Refer to Methods section for labeling key.)

Fig. 3. Results of successful *ex vivo* injection experiment. The solidified hydrogel is visible as a white inclusion within the muscle bulk of this sample of chicken pectoralis muscle, approximately 5 mm below the surface (dashed oval). An absence of leak back and complete closure of the needle track can be observed.

Fig. 4.

Effluent hydrogel temperatures at various rates of cooling water flow in a 37 °C water environment, showing effective cooling of needle contents even in the extended (i.e., injected) position. Dashed Blue Trace (a): cooling water temp at exit point from HeartLander front foot. Purple Solid Trace (b): hydrogel temperature at needle tip with needle in withdrawn position. Red Dotted Trace (c): hydrogel temperature in needle tip with needle extended 5 mm out from HeartLander into the warm water environment, simulating the patient tissue target.