Automatic Intramyocardial Stem Cell Injection Device

Team Heartthrob
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Background

- Cardiovascular disease is the leading cause of death
  - 696,962 deaths in the U.S in 2020 [Prevention, 2019]
- Current cardiovascular disease treatment
  - 25 - 50% mortality rate within 5 years [Rheault-Henry et al., 2021]
  - Limited success with current treatments (e.g., LVADs and medications)

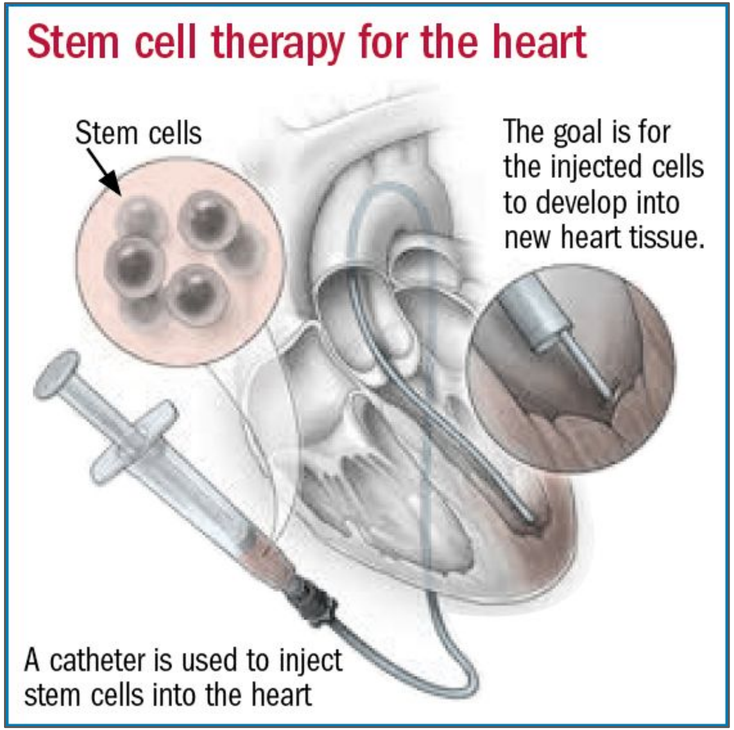


Figure 1: Stem cell therapy in the myocardium [Health.Harvard.edu].

Background

- Treatment via novel approach
  - Intramyocardial stem cell injections have therapeutic potential [Hmadcha et al., 2020]
    - Derived from bone marrow [Boyle et al., 2010]

Key Considerations:

- Flow rates
  - Too fast, slow, or inconsistent
    - Damaging to cells [White, 2016]
    - Off-target effects
    - Cell clumping
- Force / Shear stress

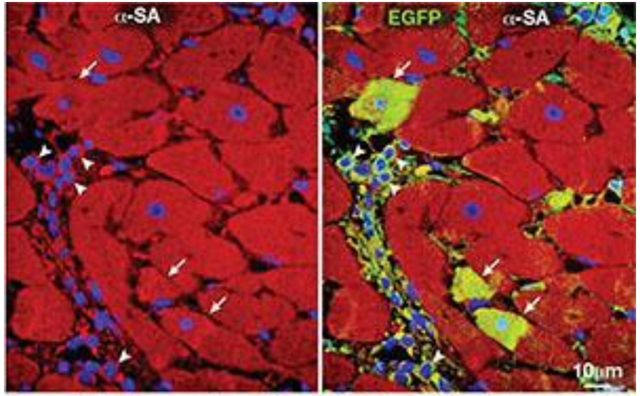


Figure 2: Successful stem cell therapy for heart failure [ncbi.nlm.nih.gov].

Problem Statement

- Automated injection device designed for intramyocardial stem cell delivery
  - Eliminate manual operations
  - Improve efficacy
  - Reduce issues such as hand fatigue
- Force detection feedback system specific to stem cell injection in the myocardium
  - Catheter placement and blockage assistance
- Research tool for stem cell injection therapies

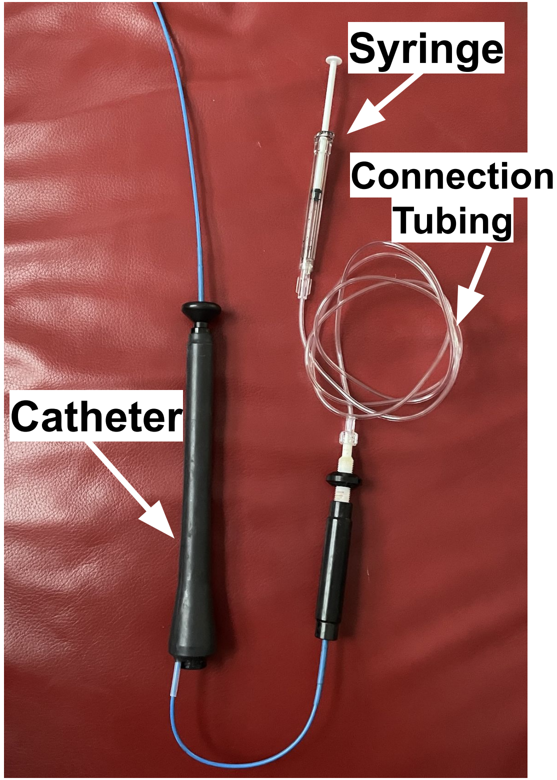


Figure 3: Set-up of the catheter, connection tubing and syringe.

Competing Designs

- Baxter Infus OR Syringe Pump ABC 4100 [Wilburn, 2020]
  - Controlled volume of anesthesia
  - Syringe is loaded, flow rate set, clicking start
  - Sense syringe plunger force and movement
- Pressure Sensing Syringe [DeVries, 1988]
  - Pressure sensitive piston between the syringe plunger and the thumb
  - Provides a tactile signal when a specified pressure is applied

Figure 4: The "Baxter Infus OR Syringe Pump ABC 4100" [Wilburn, 2020].

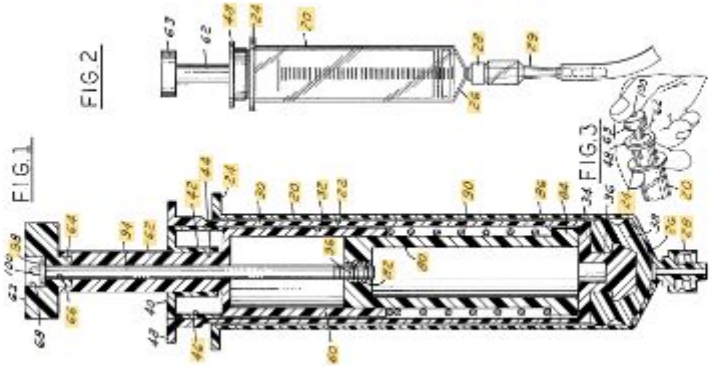


Figure 5: US Patent US4759750A [DeVries, 1988]

Product Design Specifications

- Electronically inject MSCs into the myocardium
  - Maintain cell viability - 5% reduction threshold
- Compatible with standard catheters, medical grade tubing, and 1 mL procedural syringes
- 30 and 60 second injection rates (± 1.0 second)
  - Deliver 0.5 mL of solution [Raval et al., 2021]
- Force sensing device and visual feedback
  - Threshold = 2.40 N [Doumit et al., 2016]
  - Continuously display applied force (< 5% error)
- Generate MSC injection conversance
  - Correlate force applied with tissue stiffness
- Budget of $3000 and manufacture cost of $500 [Raval, 2022]

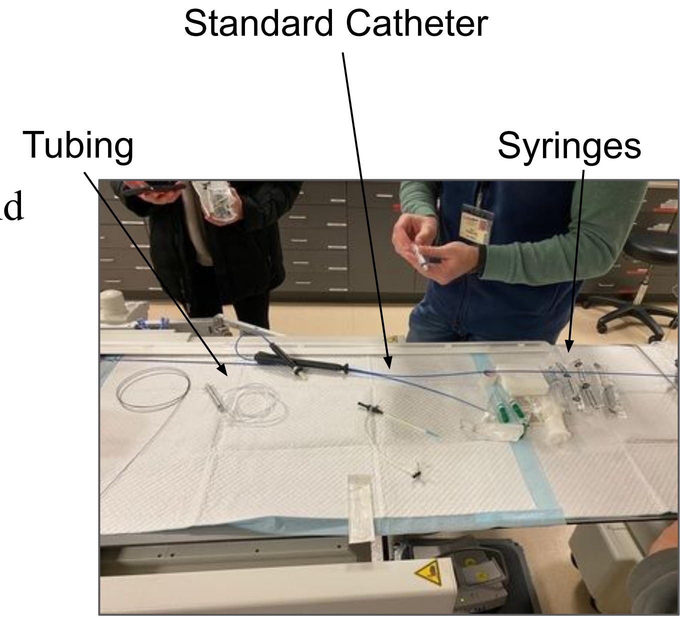


Figure 6: Standard catheters, medical grade tubing and procedural syringes

Current Design

Prototype Features

- 30 second and 60 second injection rates
  - Start, pause, reset, and adjust functions
  - NEMA-17 Stepper Motor
- Applied force feedback system
  - FSG-series force sensor
  - Arduino Microcontroller and calibration curve
  - LED threshold light warning and digital display
- 1 mL syringe mold

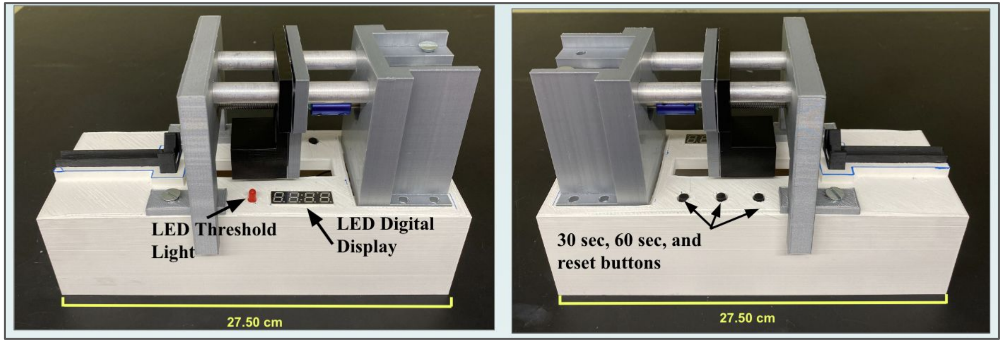


Figure 7: Solidworks drawing of final prototype assembly.

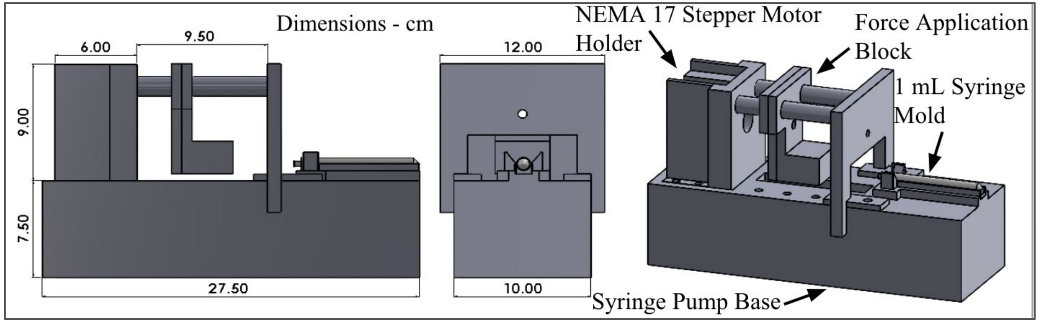


Figure 8: Right and Left end view of the injector prototype displaying the threaded bolt force system, injection buttons, and feedback system.

Fabrication Plans

- FSG feedback circuit updates
  - 0.00 V and 9.00 V supply to INA129 amplifier
  - Develop a printed circuit board
- Reduce injector size
- Improve force application system
  - Partially threaded rod
    - Screw holes built in
  - More reliable coupler - Cyclic fatigue resistance
- 1 mL syringe clamp
- Procedural applicability
  - Operator rate selection

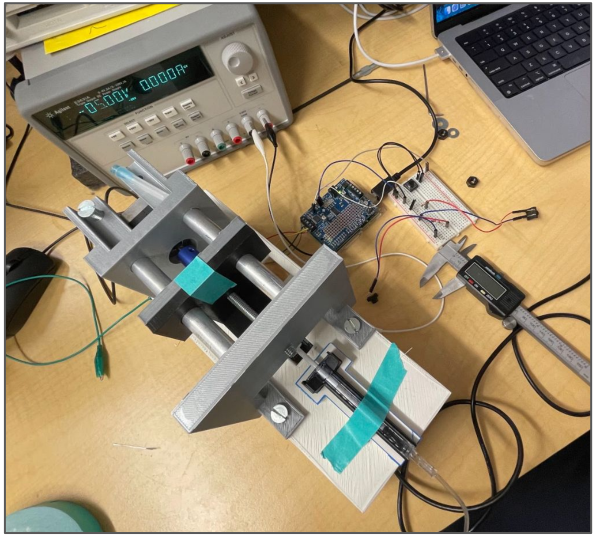
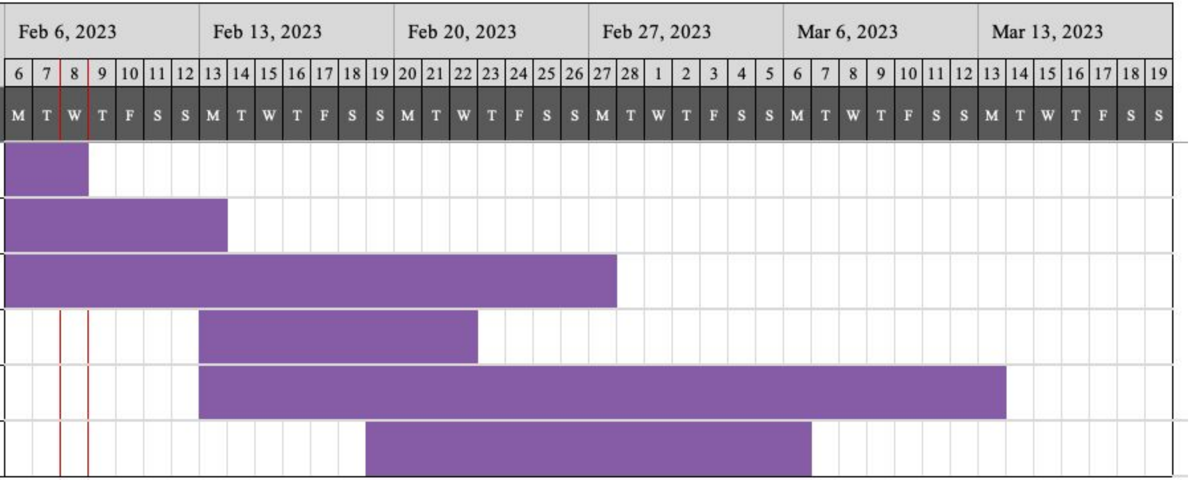


Figure 9: Injection testing of the system, displaying the required -5.00 V source for the FSG circuit via a power supply.

Fabrication Timeline

Table 1: Timeline outlining the current and anticipated workflow and completion of design modifications and fabrication.

	START	END
Order 9 V Battery and Holder	2/6/23	2/8/23
Complete Circuitry Updates	2/6/23	2/13/23
Create and Print New Solidworks	2/6/23	2/27/23
Fix Coupler	2/13/23	2/22/23
Create Keyboard for Multiple Rates	2/13/23	3/13/23
Copy Circuitry to PCB	2/19/23	3/6/23



Testing and Results

- Feedback system calibration testing (n = 3)
- Force detection testing
  - Average error = 1.70 ± 1.52%
    - FSR error = 10.31 ± 5.61%
    - p-value = 4.45×10^{-5}
- Cell viability testing (n = 5)
  - ANOVA p-value = 0.41

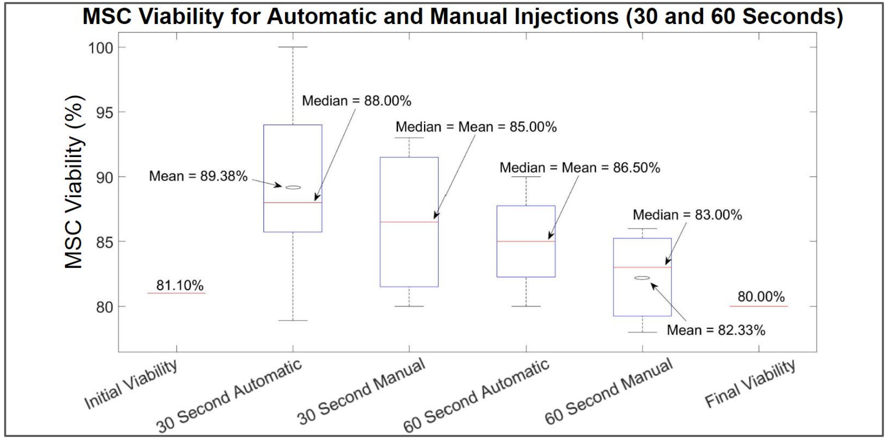


Figure 10: Boxplot comparing the viability of MSCs following automatic and manual 30 and 60 second injections.

Testing and Results

- Catheter obstruction testing (n = 3)
  - 30 second threshold = 3.47 ± 0.33 N
  - 60 second threshold = 4.29 ± 0.07 N
- Bovine steak testing (n = 3)
  - 70 - 260 kPa stiffness
- *Ex vivo* cervine heart testing (n = 3)
  - 30 second peak force = 9.01 ± 1.83 N
  - 60 second peak force = 4.69 ± 0.14 N

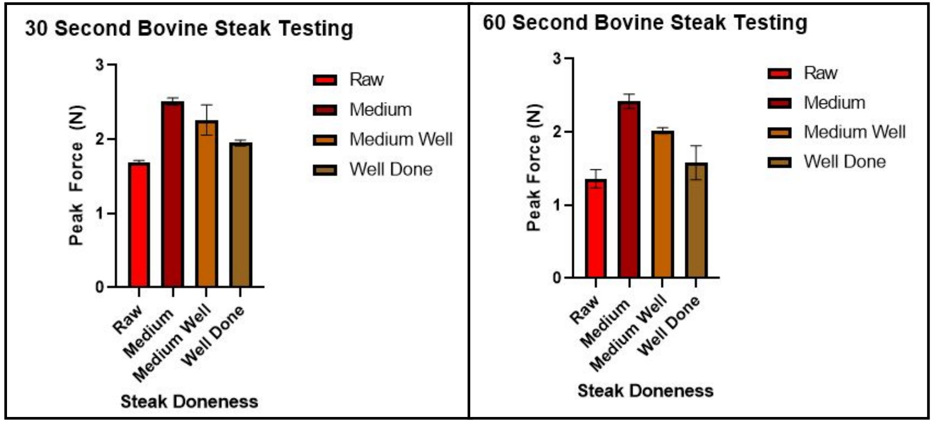


Figure 11: Bovine steak testing results for the peak force during 30 (left) and 60 (right) second injections into steaks with various stiffness levels.

Testing and Results

- Viscosity testing (n = 3)
  - Water
    - 30 second peak force = 1.44 ± 0.54 N
    - 60 second peak force = 1.12 ± 0.08 N
  - Canola oil
    - 60 second peak force = 2.03 ± 0.05 N
  - Glycerol - Experimental design complications
- Pressure sensor testing (n = 2)
  - 30 second peak pressure = 429 mmHg
    - 2.21 ± 0.01 N
  - 60 second peak pressure = 429 mmHg
    - 2.22 ± 0.06 N

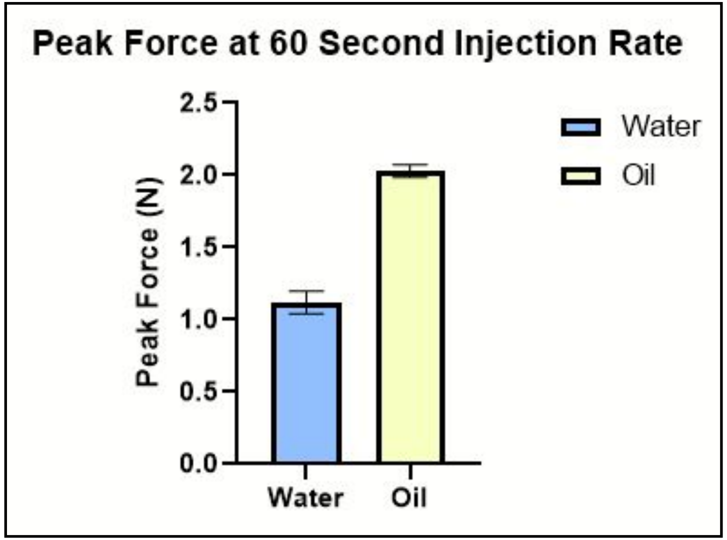


Figure 12: Peak 60 second injection forces for water and oil injectates.

Testing Plans

- FSG calibration testing
  - Using 9.00 V battery
  - 0.00 N - 10.00 N range
- Further cell viability testing
  - Connect to catheter
- Additional viscosity, catheter obstruction, and bovine steak testing
  - Previous results were inconclusive
- Further pressure sensor testing
- Porcine *ex vivo* heart injection testing

Figure 13: *Ex vivo* cervine heart injection testing.

Testing Timeline

Table 2: Timeline outlining the target schedule for injector efficacy testing in order to validate the design.

Feb 13, 2023 | Feb 20, 2023 | Feb 27, 2023 | Mar 6, 2023 | Mar 13, 2023 | Mar 20, 2023 | Mar 27, 2023 | Apr 3, 2023

	START	END
FSG Calibration Testing	2/17/23	2/24/23
Cell Viability Testing	2/27/23	3/3/23
Pressure Sensor Testing	3/5/23	3/10/23
Viscosity Testing	3/5/23	3/10/23
Catheter Obstruction Testing	3/5/23	3/10/23
Bovine Steak Testing	3/20/23	3/26/23
***Ex Vivo* Heart Injection Testing**	3/26/23	4/1/23

Budget

Table 3: Fall and Spring 2022 semester expenses.

Total Budget	Expenses Spring 2022
$3000	$163.64

Expenses Fall 2022	Remaining Budget	Estimated Expenses Spring 2023
$201.33	$2635.03	**~$127**

Table 4: Predicted Spring 2023 expenses.

Item	Cost
9 V battery [Nuoxing Battery, 2023]	$10
9 V battery holder [Lampvpath, 2023]	$6
Printed circuitry [PCBWay, 2023]	~$35
3D printed PLA parts	~$55
Partially threaded rod [Small Parts, 2023]	$11
New coupler [UxCell, 2023]	$10
	Total: ~$127

Commercialization

- Packaging
  - Sterile bag to ensure sterility
- Documentation
  - User manual
    - System activation
    - Stop, start, and rate selection
  - Safety cautions and warnings
    - Dispose as biohazardous waste
    - Moving components
    - Risk of patient or operator harm with misuse

Figure 14: FisherBrand Sterile Bags [Fishersci.com].

Acknowledgements

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Dr. Aviad Hai

Figure 15: The team at the UW Health University Hospital

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