Automatic Intramyocardial Stem Cell Injection Device

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Abstract

Treating heart failure by injecting mesenchymal stem cells (MSC) into the myocardium via an injection device and a needle-tipped catheter is a novel approach that can improve quality of life. The procedure is currently performed manually with 10 - 14 sequential injections of a 0.5 mL MSC aliquot solution over a 30 or 60 second duration. Unfortunately, manual injections result in an uncontrolled flow rate, inconsistent cell delivery, and operator fatigue. This can limit cell retention and induce cell reflux, damage, or clumping. Automating the injections can improve stem cell delivery and enhance the clinical success of intramyocardial MSC injections. Existing automatic injection devices are insufficient since they can not display intramyocardial MSC injection forces and are not approved or tailored for this procedure. As a result, a novel automatic injection device was fabricated that integrates with the procedural syringe-catheter system, limits operator intervention, provides controlled injection rates, maintains standard cell viability, constantly displays injection forces, and alerts the operator if catheter obstruction is imminent. Extensive validation testing was performed and the results confirmed that MSC viability does not decrease by more than 5% from initial viability, the force feedback system is accurate and consistent, and the device delivers 0.5 mL of solution in 30 and 60 second intervals. Thus, the device has the potential to enhance procedural success. Bovine steak and *ex vivo* heart testing determined typical injection forces for different tissue and stiffness values, demonstrating the injector's ability to function as a research device.

Problem Statement and Motivation

- Cardiovascular disease is the leading cause of death in the U.S.,
  - 696,962 deaths in 2020 [1]
- Automated injection device designed for intramyocardial stem cell delivery
  - Eliminate manual operations
    - Uncontrolled flow rates (rapid)
    - Operator hand fatigue
  - Improve efficacy
    - Cell retention
- Force Detection Feedback System specific to stem cell injection in the myocardium
  - Catheter placement and blockage assistance
- Research tool for injection therapies

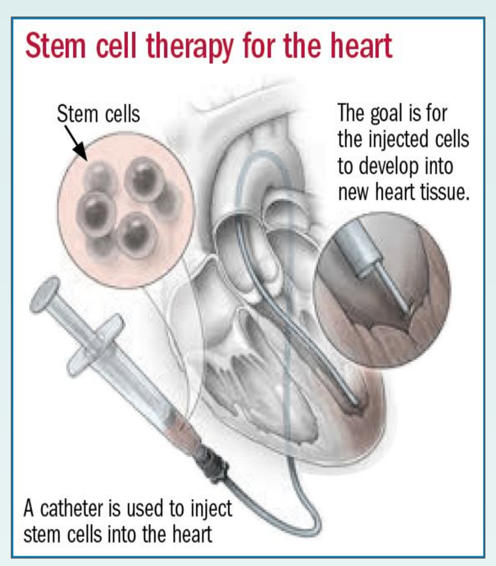

Figure 1: Stem cell therapy in the myocardium [2].

Background Research

- Current Cardiovascular Disease Treatment
  - 25 - 50% mortality rate within 5 years [3]
  - Limited success with current treatments (e.g., LVADs and medications)
- Mesenchymal stem cells (MSCs)
  - Derived from bone marrow [4]
  - Therapeutic potential [5]
- Flow rate
  - Too fast or too slow
    - Damaging to cells [6]
    - Off-target effects
    - Cell Clumping
  - Rate inconsistency
- Force/Shear Stress

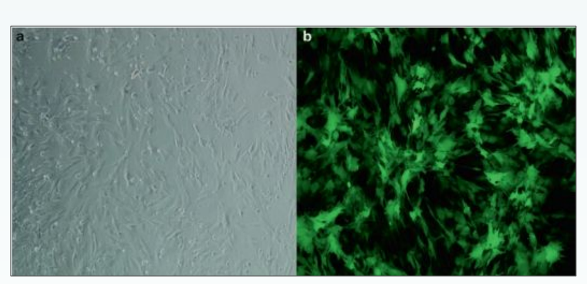

Figure 2: Mesenchymal stem cells in culture [7].

Design Criteria

- Electronically inject MSCs into the myocardium
  - Maintain cell viability - 5% reduction threshold
- Integrate with standard catheters, medical grade tubing, and 1 mL procedural syringes
- 30 and 60 second injection rates (± 1.00 second)
  - Deliver 0.5 mL of solution (5% error margin) [8]
- Force sensor and visual feedback
  - Threshold = 2.40 N [9]
  - Applied force displayed throughout procedure (< 5% error)
- Generate MSC injection conversance
  - Correlate force applied with tissue stiffness
- Budget of $3000 and manufacture cost of $500 [10]

Final Prototype

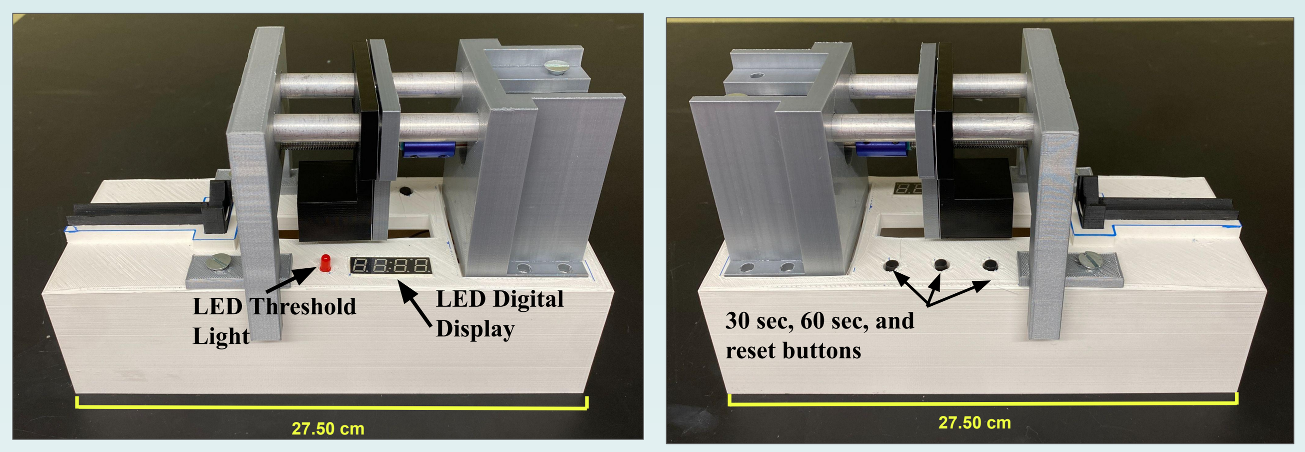

Figure 3: Right and Left end view of the injector prototype displaying the threaded bolt force system, injection buttons, and feedback system.

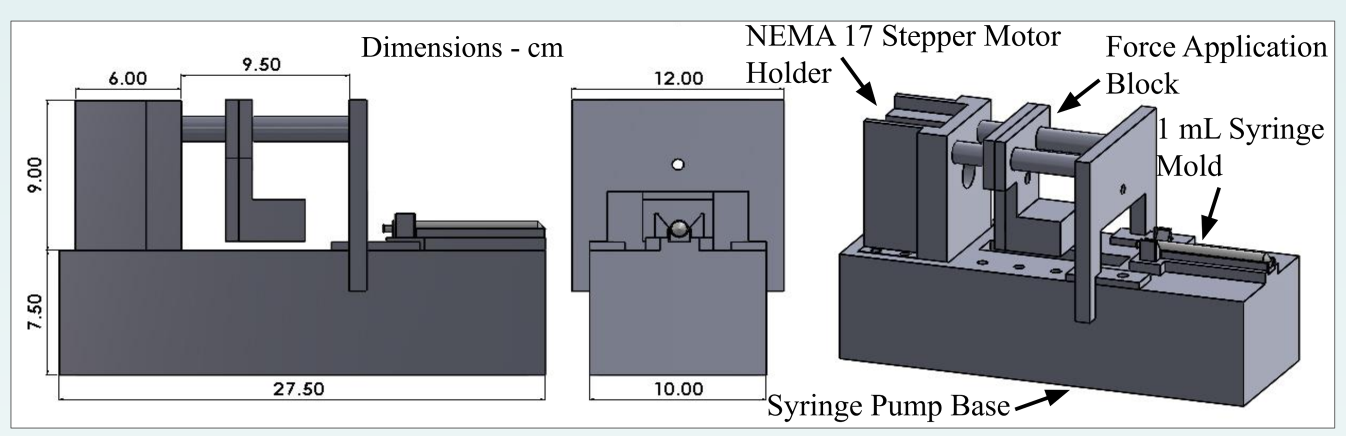

Figure 4: Solidworks drawing of final prototype assembly.

- Prototype features
  - 30 second and 60 second controlled injection rates
    - Start, pause, reset, and adjust functions
    - Regulated via NEMA-17 Stepper Motor (Figure 5)
  - Applied force feedback system
    - Detects force via an FSG force sensor (0.00 N - 10.00 N) [11]
      - Resolution = 0.0098 N
      - Response Time = 0.10 ms
    - Controlled by Arduino Microcontroller and calibration curve
    - LED threshold light and digital display
  - 1 mL syringe mold

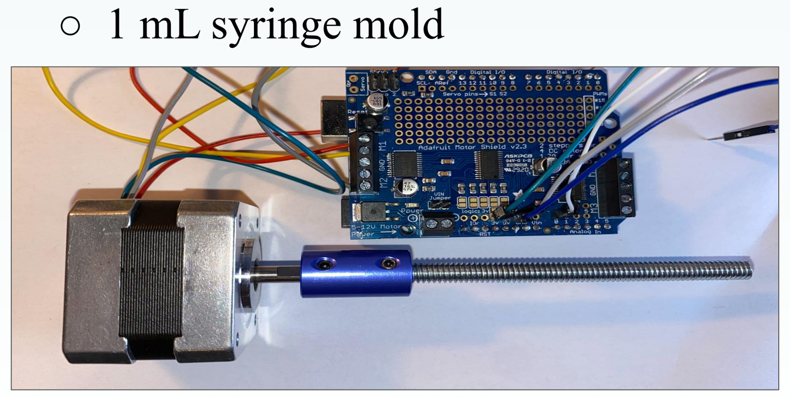

Figure 5: Arduino Motor Shield, NEMA-17 Stepper Motor, and 5 mm to 0.635 cm coupler.

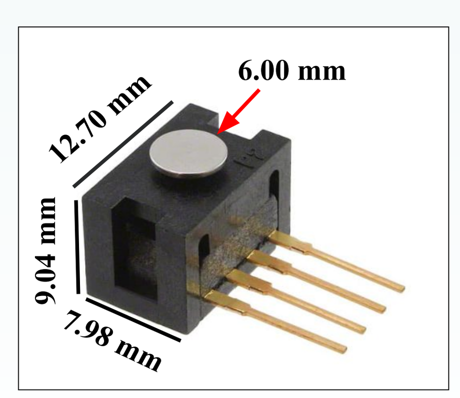

Figure 6: FSG Series Force Sensor highlighting its elevated sensor.

Testing and Results

- **Feedback System Calibration Testing** (n = 3)

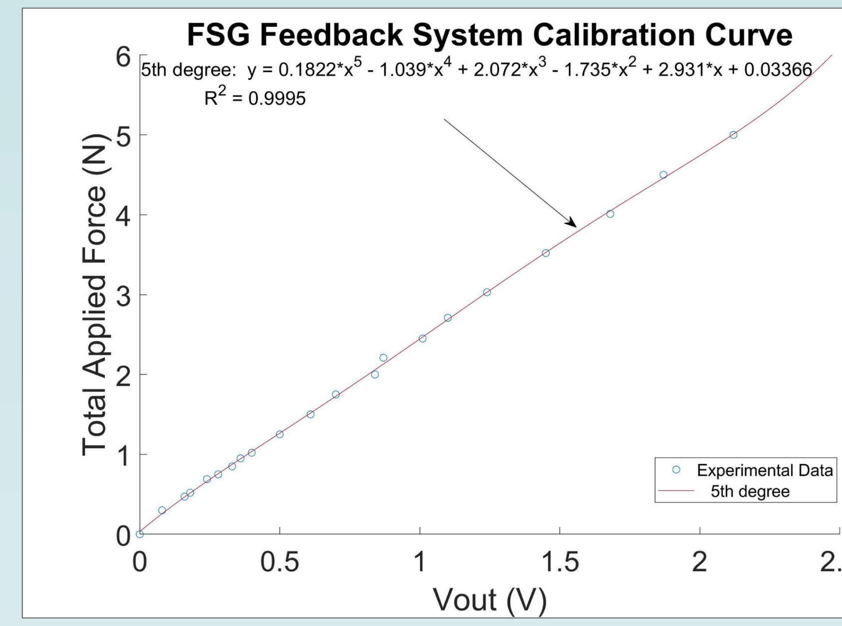

Figure 7: Calibration curve for the FSG feedback system under various loading enabling applied force calculation.

- **Force Detection Testing**
  - Average error = 1.70 ± 1.52%
- **Cell Viability Testing** (n = 5) - ANOVA p-value = 0.41

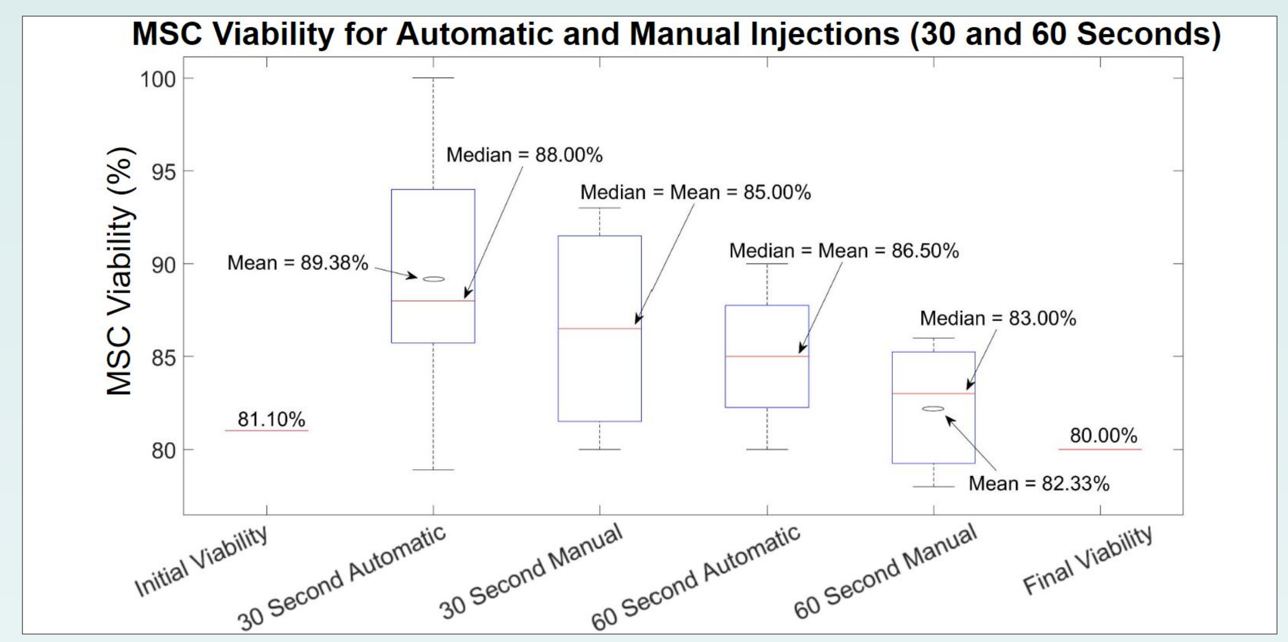

Figure 8: Boxplot comparing the viability of MSCs following automatic and manual 30 and 60 second injections.

- **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)
- **Catheter Obstruction Testing** (n = 3)
  - 30 Second Threshold = 3.47 ± 0.33 N
  - 60 Second Threshold = 4.29 ± 0.07 N
- **Bovine Steak and *Ex Vivo* Heart Testing** (n = 3)

Table 1: Bovine steak (70 - 260 kPa) injection rate durations and delivery volumes with

Measurement	30 Second Injection	60 Second Injection
Average Injection Time (Seconds)	30.72 ± 0.22	60.52 ± 0.18
Average Injection Volume (mL)	0.49 ± 0.01	0.48
Percent Error Between Injection Time and Target Time (%)	2.42 ± 0.74	0.86 ± 0.30
Percent Error Between Injection Volume and 0.5 mL (%)	3.60 ± 1.67	4.00

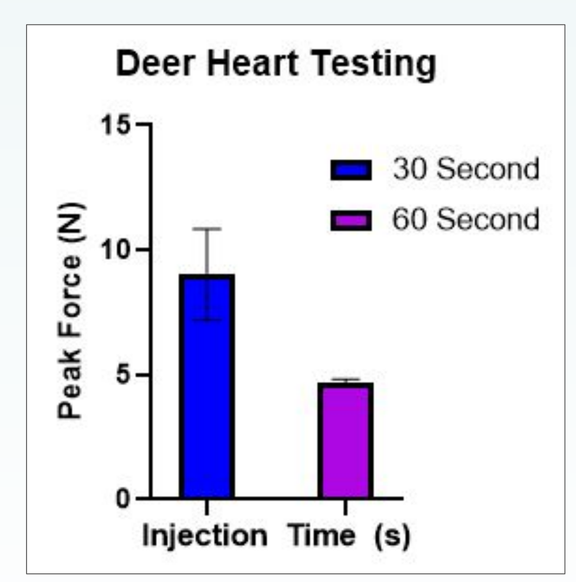

Figure 9: *Ex vivo* cervine myocardium (8 - 15 kPa [12]) injection testing force values.

Conclusion and Discussion

- FSG feedback system allows for greater force detection accuracy (FSR error = 10.31 ± 5.61%, p-value = 4.45×10^{-5})
  - Displays force throughout each injection
  - Alerts the operator when catheter obstruction is imminent
- Efficacy of the injection device validated
  - Provides required 30 and 60 second injection rates
  - Maintains cell viability and promotes cell retention
- Research utilization in academia and industry
- Reliable and Accurate - Clinical applicability
- Automatic MSC delivery limits operator intervention
  - Eliminates operator hand fatigue and rapid injections
- Implication: Improve intramyocardial MSC injections, enhancing myocardial infarction treatment

Figure 10: *Ex vivo* cervine heart injection testing

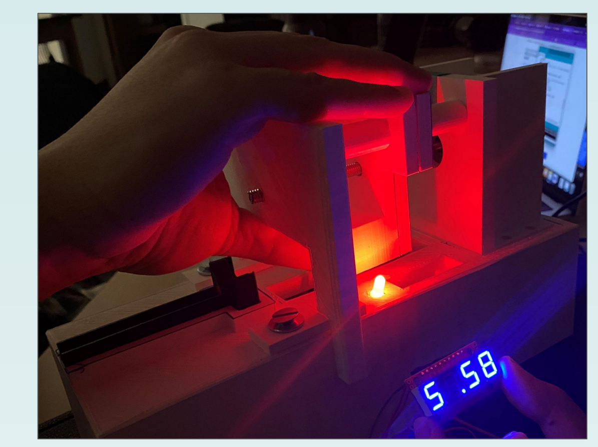

Figure 11: Illuminated threshold LED and digital display.

Future Work

- Design improvements
  - Transition the injector into battery operation
  - Implement a syringe clamp design
  - Improve system interface for universal applications
- Further testing
  - Porcine clinical validation testing
  - Establish force ranges associated with different myocardium locations
  - Additional viscosity and pressure sensor testing

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