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 of catheter obstruction susceptibility. Extensive validation testing was performed confirming 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. Bovine skeletal muscle and *ex vivo* porcine heart testing identified injection forces and pressures for various tissue 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 delivery and retention
- Force Detection Feedback System specific to stem cell injection in the myocardium
  - Catheter placement and blockage assistance, identify infarct level
- Research tool for injection therapies
- Current injections devices → Insufficient for procedure

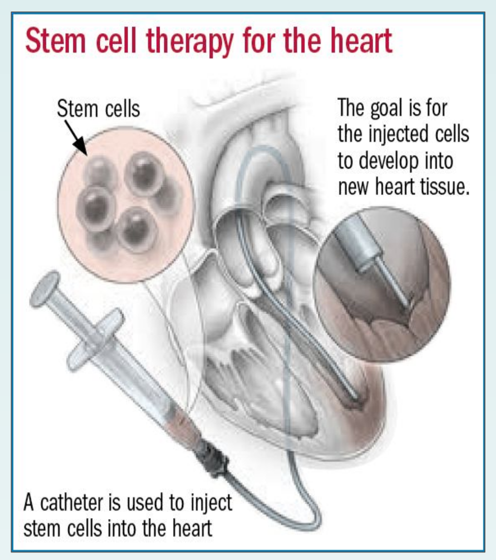

Figure 1: Stem cell therapy in the myocardium [2].

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
    - Damages cells [6]
    - Off-target effects
    - Cell Clumping
  - Rate inconsistency
- Force/Shear Stress

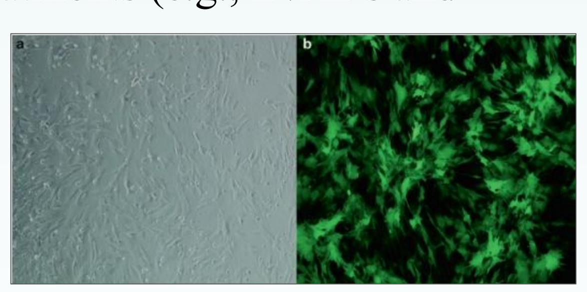

Figure 2: Mesenchymal stem cells in culture [7].

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
  - Identify obstruction threshold value
  - Applied force displayed throughout procedure (< 5% error)
- Generate MSC injection conversance
  - Correlate force applied with tissue stiffness and pressure
- Budget of $3000 and manufacture cost of $500 [9]

Final Prototype

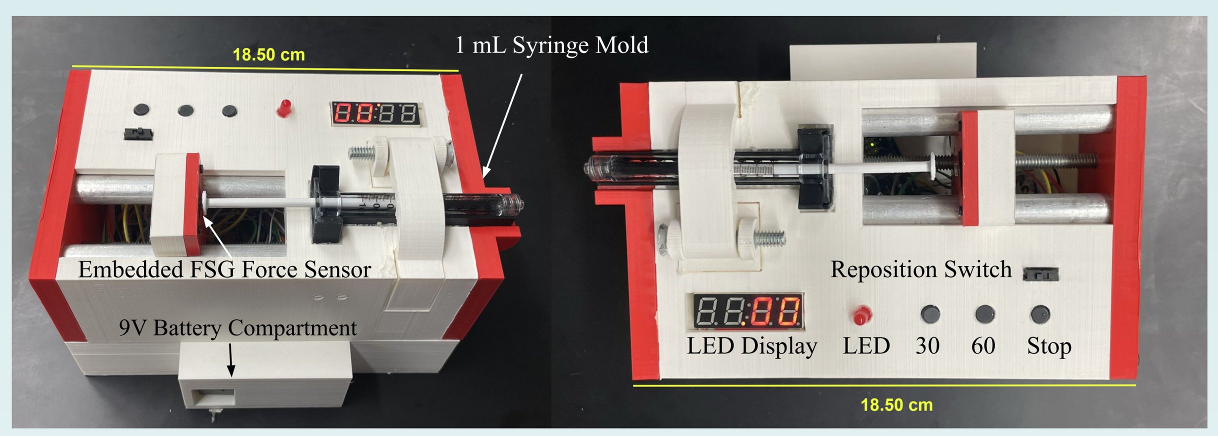

Figure 3: Left end and overhead view of the injector prototype displaying the force application system, injection buttons, syringe clamp, and feedback system.

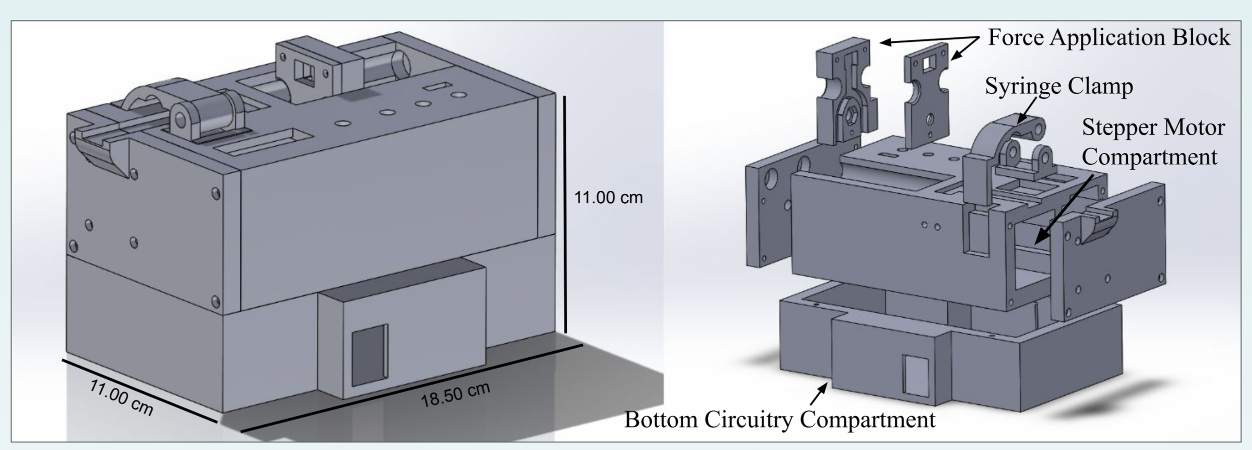

Figure 4: Solidworks assembly of final prototype.

- 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) [10]
      - 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 and clamp
  - Portable power supply

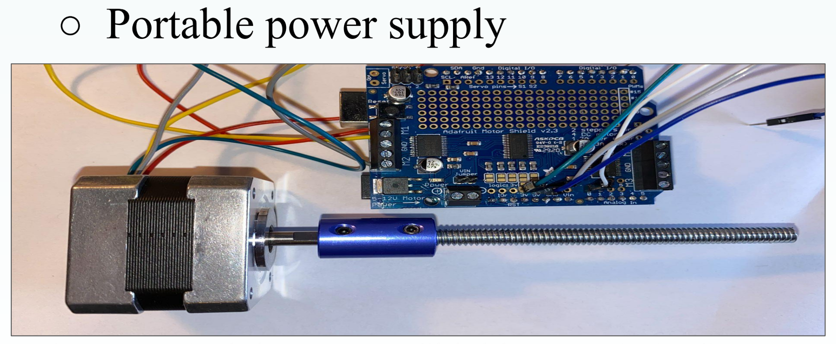

Figure 5: Arduino Motor Shield, NEMA-17 Stepper Motor, and 5 mm to 0.635 cm coupler.

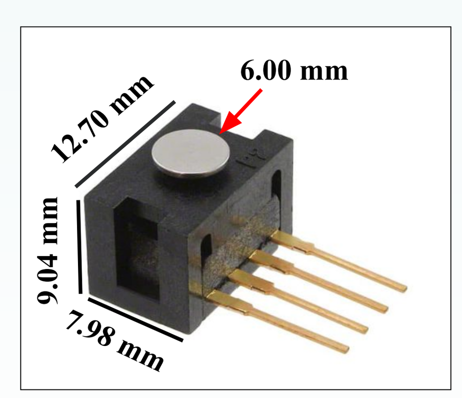

Figure 6: FSG Series Force Sensor highlighting its elevated sensor.

Testing and Results

- **Force Detection Testing** (n = 3)
  - Average error = 0.93% Standard error = 0.23%
- **Cell Viability Testing** (n = 3) - ANOVA p-value = 0.06

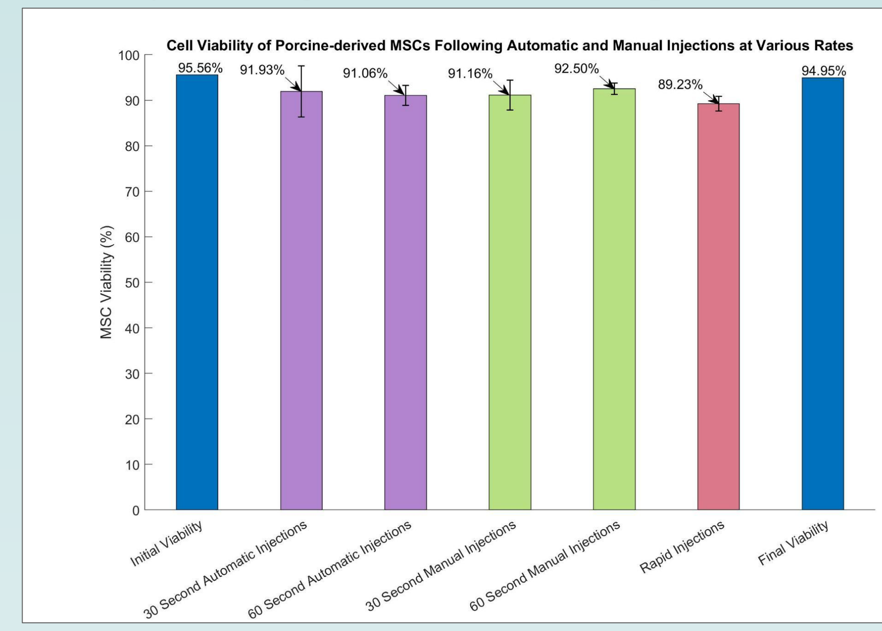

Figure 7: Boxplot comparing the viability of MSCs following automatic and manual 30 and 60 second injections.

- **Pressure Sensor Testing**

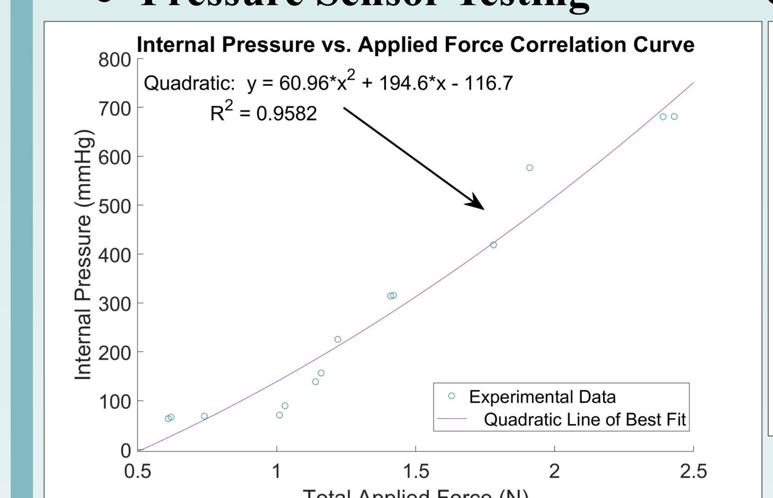

Figure 8: Internal injection pressure with respect to the applied force applied (n = 2).

Catheter Obstruction Testing

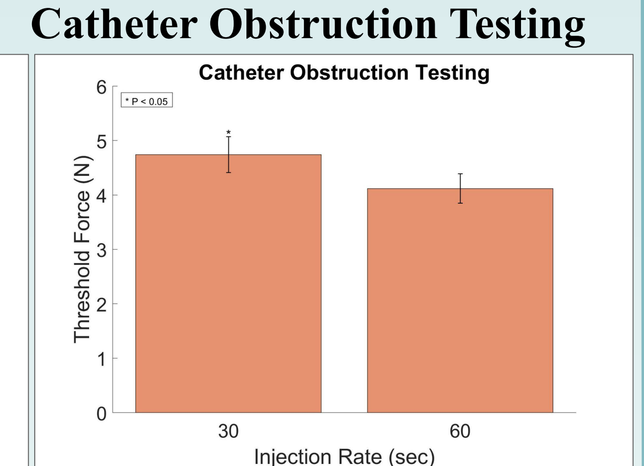

Figure 9: Catheter obstruction threshold force values for both injection rates (n = 5, p-value = 0.01).

- Peak pressure = 681.10 ± 0.42 mmHg
  - Onset force = 2.41 ± 0.06 N
- **Bovine Skeletal Muscle and *Ex Vivo* Heart Testing** (n = 3)

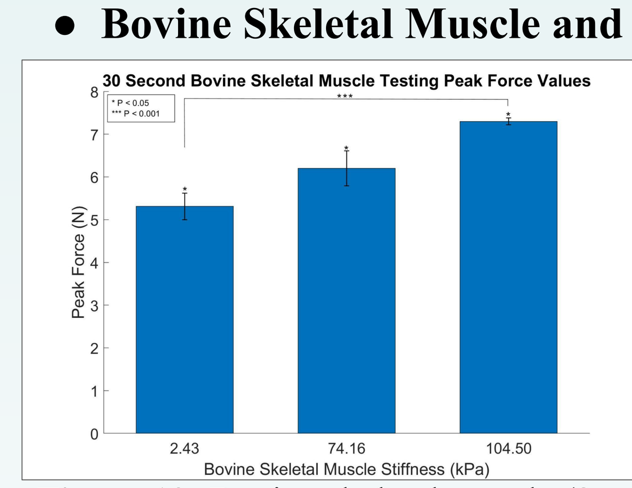

Figure 10: Bovine skeletal muscle (2 - 105 kPa) injection force values at the 30 second injection rate ($p = 5.92 * 10^{-4}$).

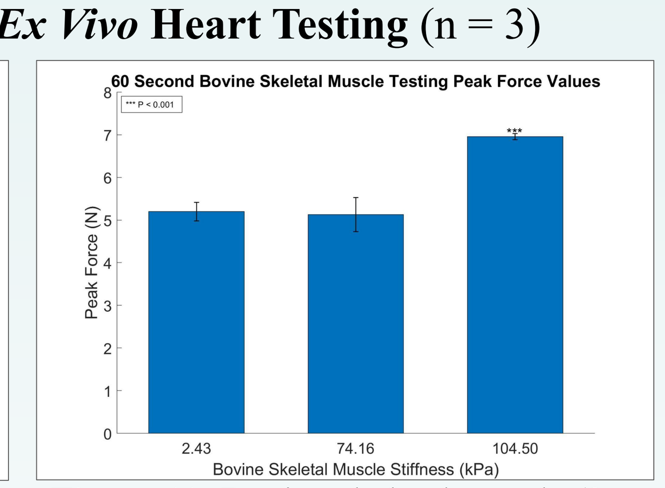

Figure 11: Bovine skeletal muscle (2 - 105 kPa) injection force values at the 60 second injection rate ($p = 2.35 * 10^{-4}$).

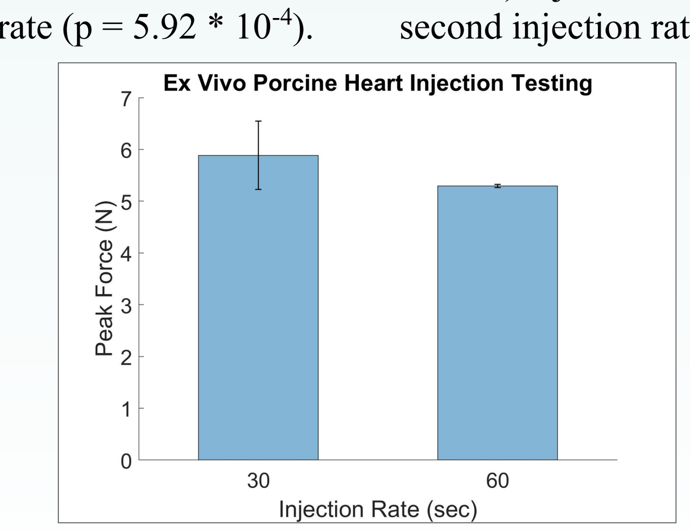

Figure 12: *Ex vivo* porcine myocardium (~ 20 kPa [11]) injection testing force values (p-value = 0.19).

Conclusion and Discussion

- Highly accurate FSG feedback system force detection
  - Displays force throughout each injection
  - Alerts the operator of catheter obstruction susceptibility
- Efficacy of the injection device validated
  - Provides required 30 and 60 second injection rates
  - Maintains cell viability and promotes cell retention
- Research capabilities inform and optimize treatment
  - Rapid injections induce cell lysing (> 5% viability reduction)
  - Novel internal pressure correlation methodology
  - Catheter obstruction threshold value implications
  - Force application identifies myocardial infarction extent
- Automatic MSC delivery limits operator intervention
  - Eliminates hand fatigue and rapid injections
- Improves intramyocardial MSC injections and clinical understanding, enhancing myocardial infarction treatment

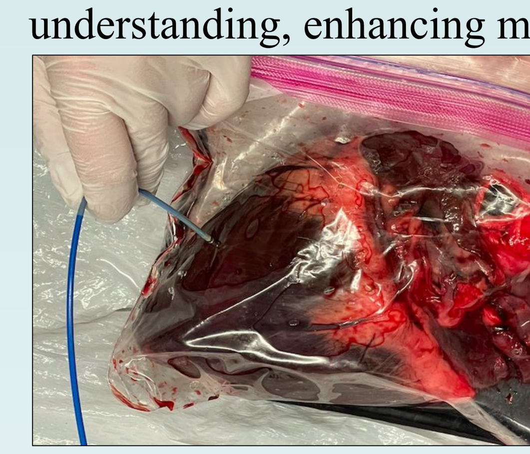

Figure 13: *Ex vivo* cervine heart injection testing

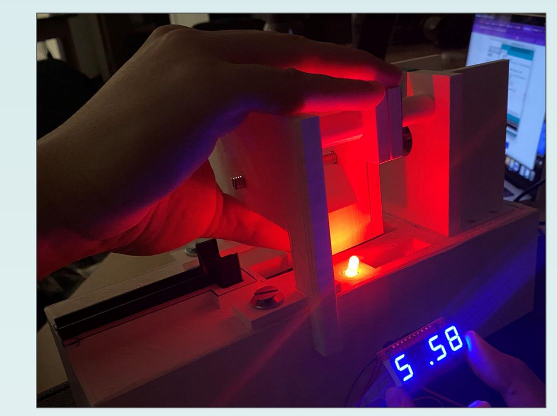

Figure 14: Illuminated threshold LED and digital display.

Future Work

- Design improvements
  - Improve system interface for universal applications
    - Multiple injection rates and syringe sizes
    - Display pressure values
  - Stronger motor for greater injection force application
  - Closed loop injection rate control
- Further testing
  - Cell viability rate optimization testing
  - Porcine clinical validation testing

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