Heart Attack

on-a-chip

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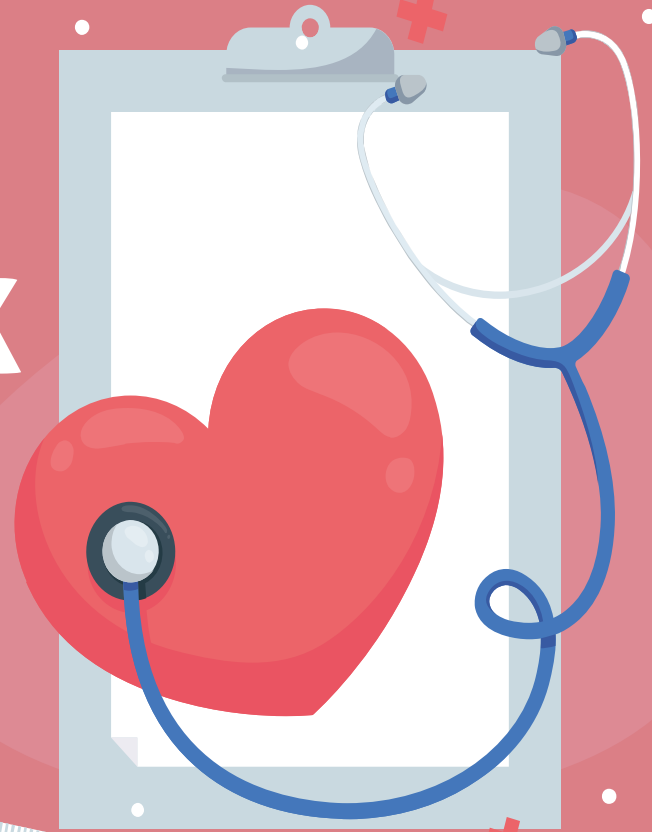

Overview

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2 Prior Models

3 Our Model

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Background

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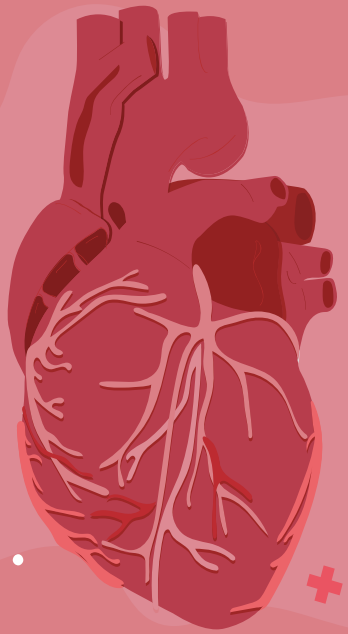
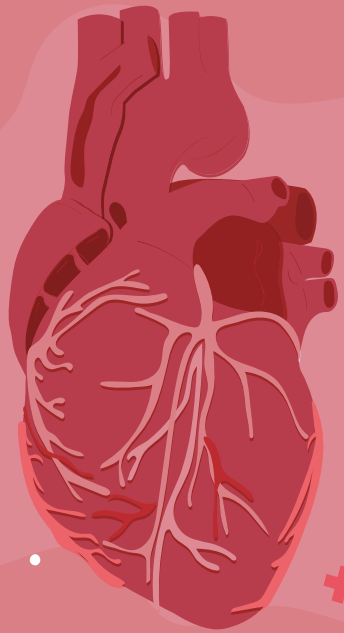
Definitions

- **Coronary Heart Disease** (CHD): A prevalent form of heart disease characterized by the narrowing or blockage of the coronary arteries, primarily due to atherosclerosis. [1]
- **Atherosclerosis**: A chronic condition where plaque (cholesterol, calcium, fatty substances, and fibrin) build up in the arteries. This plaque hardens limits the flow of oxygen-rich blood. [1]
- **Myocardial Infarction (MI)**: Occurs when the blood supply to a section of the heart muscle is abruptly interrupted. Caused by the breaking of plaque and the formation of a blood clot. [1]



Statistics

- Around 805,000 people in the United States have a heart attack each year. [2]
- Heart attacks can be silent or a drastic event leading to cardiac instability and sudden death. [2]
    - In 2019, 1 in 5 of heart attacks were silent and the person was not aware of it. [2]



Symptoms of an MI

Nausea

Shortness of Breath

Chest Pain/Heart palpitations

Sweating

Upper Body Discomfort

[3]

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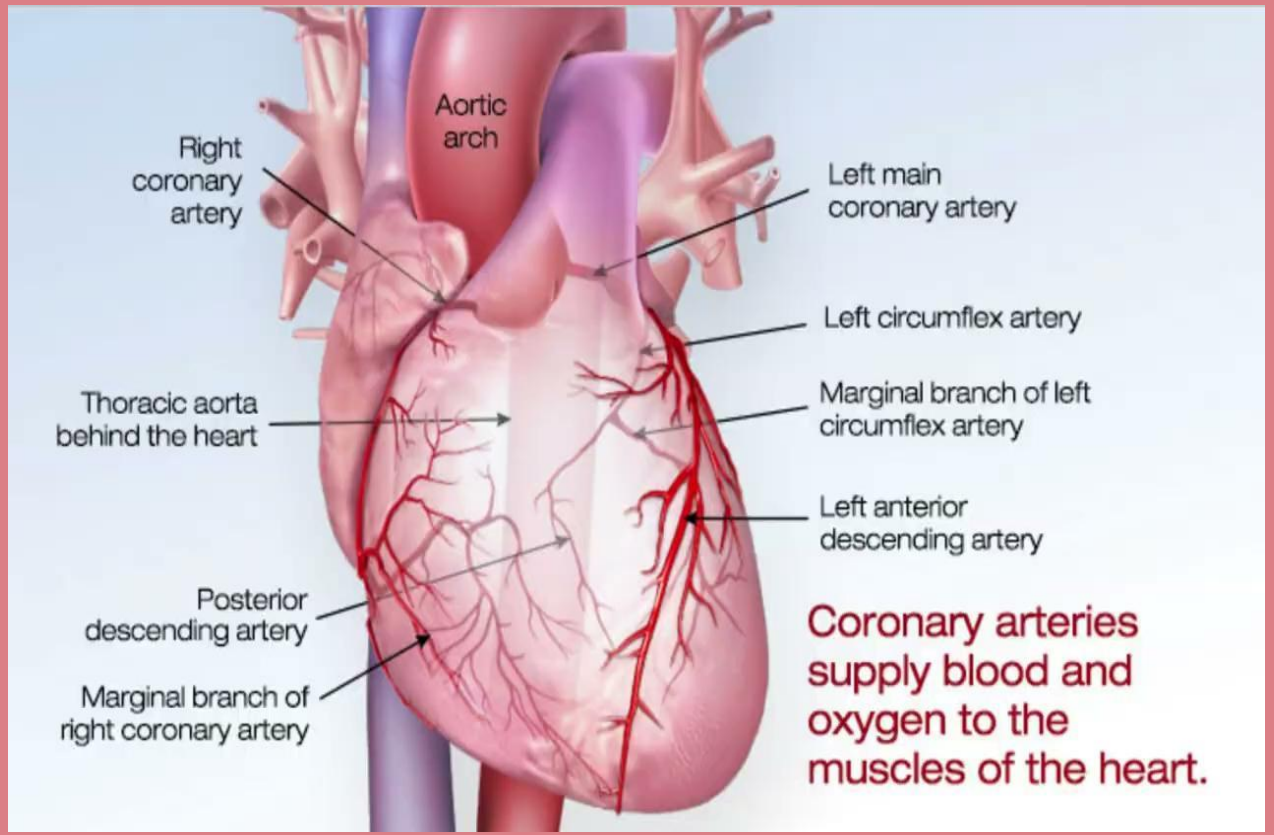
What does an MI look like?



[4]

Prior Models

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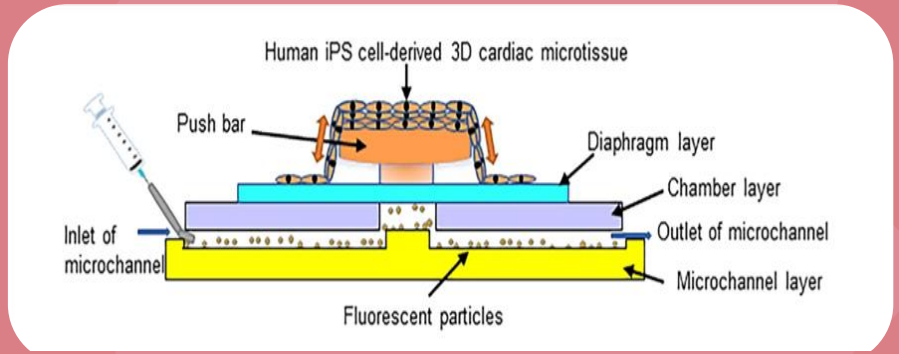
Previous Models

Our model is based on a previous studies by Abulaiti et al. [5] and McCain et al [6]. These articles did research with a heart-on-a-chip model and a failing myocardium on-a-chip model.



[5]

Heart-on-a-chip Model Fabrication Steps

Replica Molding Master Templates [7]

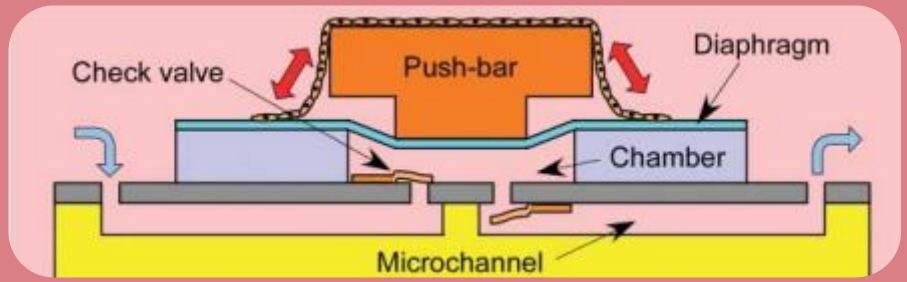
1. Silicon wafer
2. Spin-coated resist layer of SU-8
3. Hot plate to evaporate solvent
4. Exposed to collimated UV light through film masks
5. Baked to cross-link SU-8 resin
6. Developed in SU-8 Developer to remove unexposed areas of photoresist

1

Heart-on-a-chip Model Fabrication Steps

PDMS Elastomer Molding [7]

1. Prepared PDMS base with curing agent
2. Degassed under mild vacuum
3. Poured into silicon wafer master molds
4. Degassed
5. Cured for 1 hour at 120°C
6. Seperated from master

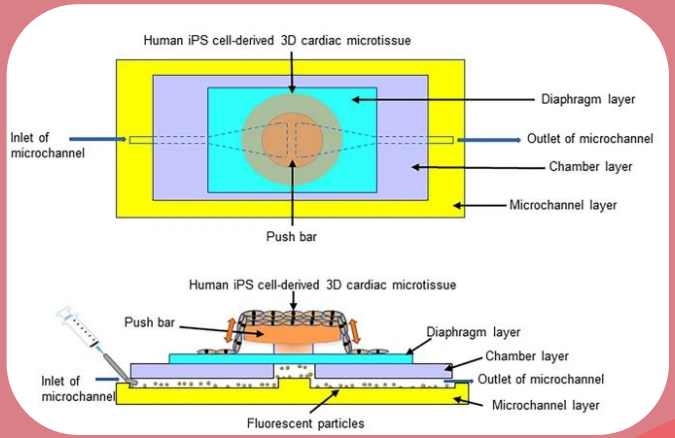


[7]

Heart-on-a-chip Model Fabrication Steps

Chip Assembly [7]

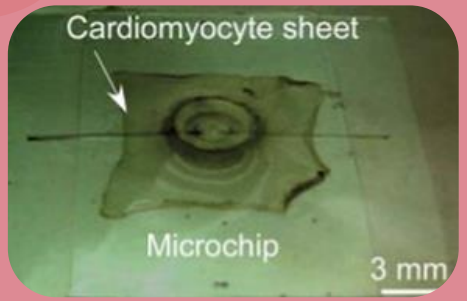
1. Diaphragm membrane attached to chamber layer
2. Silicon wafer spin coated with PDMS prepolymer
3. Heated at 120°C for 1 hour to harden PDMS
4. Align remaining components
5. Coated push-bar with fibronectin
6. Transplant cardiomyocyte or human iPS cell sheet onto microchip
7. Stainless steel check valve connected to chambers



[5]

Cardiomyocyte Seeding [7]

- Fabricated from primary cell (cardiomyocyte) suspensions using polystyrene culture dishes and thermo-responsive polymer
- Pulsed during culturing using the thermo-responsive polymer
- Cells released from culture using standard methods such as trypsin
- Entire cell sheet was moved to device and attached to push-bar using fibronectin-coating

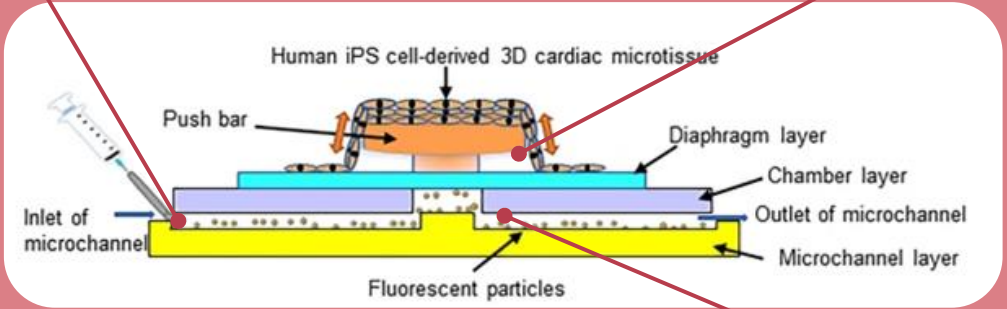


[7]

Biomimetic Strategies

Microchannel Fluid Flow

Pulsatile Stressed



[5]

Check Valves

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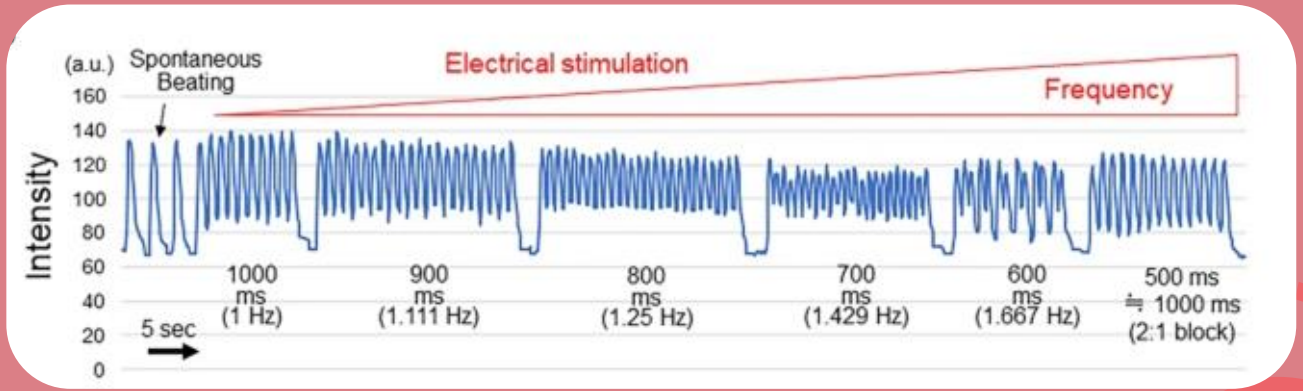
Model Characteristics [5]

- Fluorescent particles allowed for quantization of particle displacement relative to ‘beating’
- Electrical stimulation to produce particle displacement
- Stroke volume calculation
- MUSCLEMOTION contractile function analysis
- Calcium sensor to evaluate intracellular calcium ion release



[5]

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Pros and Cons of Current Heart (Attack)-on-a-chip Models

Pros	More accurate representation than 2D cultures	Highly tunable	Enable beating and fluid flow
Cons	Cell viability	Not complete heart model	Not integrated into other organ systems

[8]

Our Model

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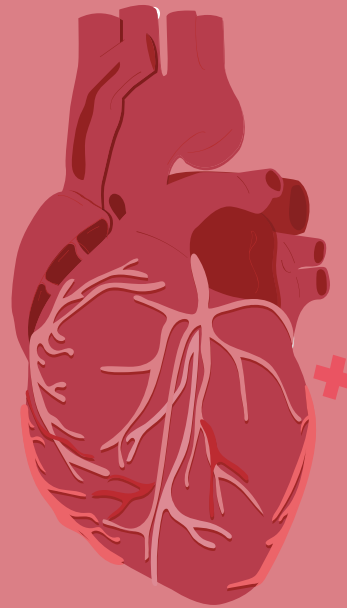
How to Mimic a Heart Attack

- Establish oxygen flow within the fluid chamber to simulate blood flow and introduce epithelial cells into the chamber.
- Introduce a plaque mixture containing cholesterol, calcium, fatty substances, and fibrin into the chamber.
- Observe for clot formation, detectable visually or through particle displacement monitoring.

Goals for Heart attack–on–a–chip

- Induce a single heart attack to generate scar tissue in the model.
- Simulate a second heart attack and assess its impacts, focusing on:
  - Heparin efficacy [10] after a 2nd heart attack
  - Epithelial cell damage
  - Investigating any changes to electrical function



Materials

- Heart on a chip model with characterization methods as described earlier
- Continuous flow of oxygen in the microchamber
- Epithelial cells
- Cholesterol
- Calcium
- Fatty substances
- Fibrin
- Human blood
- Microscope
- Oxygen sensor

Methods and Measurements

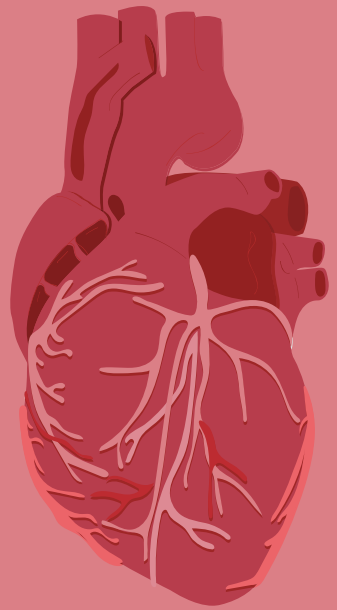
- Seed the epithelial cells in microchannel, ensuring attachment
- Introduce human blood
  - Use fluorescent particles to measure the displacement of the blood
  - Use microscopic imaging with the fluorescent particles
- Introduce fatty substances, fibrin, calcium, and cholesterol to microchannel walls
- Add oxygen flow into microchannel
  - Add oxygen sensor to monitor levels
    - An oxygen gradient would indicate a blood clot has formed

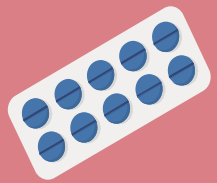
Testing

- Monitor calcium and oxygen levels using sensors to detect changes indicative of a blood clot. [11]
  - Observe blood flow and clot presence using fluorescent particles.
- Evaluate contractile changes with MUSCLEMOTION.
- Administer Heparin to disrupt the clot.
- Use microscopic imaging to examine epithelial cells for any damage.
  - Monitor calcium, oxygen, and fluorescent particle flow until stable; time the clot dissolution process.
- Collect epithelial cell samples.
- Repeat the procedure to induce and analyze a new clot formation.

Analysis

- Compare contractile responses using MUSCLEMOTION data after the first and second heart attacks to understand the variations.
- Analyze and differentiate the epithelial cell samples collected post-first and second heart attacks.
- Evaluate the time required for clot resolution after heparin administration following each heart attack event.





Conclusion

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Summary

- The "heart-attack-on-a-chip" simulates heart attack conditions in a controlled environment, enabling the study of heart attack mechanics and therapeutic responses.
- It uses innovative methods like oxygen sensors, MUSCLEMOTION, and fluorescent particles to monitor changes in blood flow, clot formation, and cellular responses.
- This model facilitates the analysis of the effects of successive heart attacks on scar tissue formation, epithelial cell damage, and the efficacy of treatments such as Heparin.

Limitations

- Not a full organ system
  - Cannot produce all of the same proteins and signals such as troponin, which is released when a heart attack occurs.
  - Does not contain functioning blood vessels, just heart model
- Not a complete heart model
  - Does not account for various blood movements/flow that occurs as blood pumps through arteries/veins/ventricles/atrium
  - Does not account for other tissues

Importance

- Study the injury and repair mechanisms.
- Low cost option for future cardiovascular research
- Accelerate discovery and testing of new treatments aimed at heart attack recovery and prevention.
- Analyze how different risk factors impact severity
- Reduces reliance on animal testing

Future Directions

- Look at other cardiovascular issues.
- Creation of layered vasculature with all three tunics.

REFERENCES

THANK YOU!