A Comparison of Thrombus Dissolution Efficacy With Single and Multiple-Cycle Histotripsy Pulses In Vitro

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Motivation: Chronic Deep Vein Thrombosis

• DVT is a burden on the public health
• Need treatment for thrombolytic resistant clots\(^1\)
• Histotripsy enhances thrombolytics in non-responsive clot model\(^2\)

1 Augustinos Circulation 2004
Histotripsy: Shock Scattering Cavitation

- 3-20 cycle excitations
- Incident shock wave scattered by intrinsic nuclei
- Requires highly asymmetric waveforms
- Potential off-target cavitation


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Histotripsy: Intrinsic Threshold Cavitation

- Single cycle excitations
- Only peak negative pressure matters
- Large tensile phase needed for inertial cavitation
- Contained in vessel

Bader et al. *Ultrasound Med Biol* 2019

[Image showing pressure comparison]

*Zhang Ultrasound Med Biol 2017*
Research Questions

• How does pulse duration affect thrombolytic efficacy?

• Can thrombolytic efficacy be assessed by passive cavitation imaging?
Methods: Experimental Setup

- Human plasma alone or mixed with 2.68 μg/mL of rt-PA
Methods: Experimental Setup

- Human plasma alone or mixed with 2.68 μg/mL of rt-PA
- 1 (intrinsic threshold) and 5 (shock scattering) cycle pulses
- 1 MHz fundamental frequency
- Peak negative pressures of 0, 15, 20, 25, and 30 MPa
- 2000 pulses per location at 40 Hz pulse repetition frequency
Methods: Acoustic Power Dose from Passive Cavitation Imaging

Haworth et al.  
*IEEE Trans Ultrason Ferroelectr Freq Control 2017*
Results: Thrombolytic Efficacy

Significant increase w.r.t. rt-PA alone
Results: Thrombolytic Efficacy

- **plasma alone**
- **rt-PA alone**
- **1 cycle**
- **1 cycle, rt-PA**
- **5 cycles**
- **5 cycles, rt-PA**

Mass Loss (%) vs. Peak Negative Pressure (MPa)

Five Cycle

Pressure (MPa)

Amplifier Voltage (V)
Results: Thrombolytic Efficacy

Intrinsic threshold for water-based media\textsuperscript{5-7}

\textsuperscript{5}Bader et al. *Ultrasound Med Biol* 2019
\textsuperscript{6}Maxwell et al. *Ultrasound Med Biol* 2013
\textsuperscript{7}Vlaisavljevich et al. *Ultrasound Med Biol* 2015
Results: Thrombolytic Efficacy to Acoustic Power Dose
Results: Thrombolytic Efficacy to Acoustic Power Dose

- Mass Loss (%) vs. Acoustic Power Dose/10^6 (V^2)
- Graph showing data points for different conditions:
  - Plasma alone
  - rt-PA alone
  - 1 cycle
  - 1 cycle, rt-PA
  - 5 cycle
  - 5 cycle, rt-PA
Conclusion

• Enhancement in thrombolytic efficacy in combination with histotripsy depends on mechanism based threshold
• Thrombolytic efficacy correlates with acoustic power dose, independent of pulse duration

Contact Information

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Results: Particle Debris

Subcellular (between 4 and 6 μm)

Cellular (between 6 and 8 μm)

Supercellular (between 8 and 38 μm)

Legend:
- plasma alone
- rt-PA alone
- 1 cycle
- 1 cycle, rt-PA
- 5 cycle
- 5 cycle, rt-PA

Graphs showing particle debris levels across different peak negative pressures for subcellular, cellular, and supercellular fractions.
Methods: Whole Blood Clot Model

Protocol
• Venous blood drawn from volunteer patients at the catheter lab
• Aliquots of 2 mL were transferred into Pasteur pipettes
• Incubated at 37 °C for 3 hours
• Stored at 4 °C for 3 days to allow for full retraction

Subject Demographics
• 15 volunteer patients
• 55 ± 12 years of age
• 8 African American, 7 white
• 9 female, 6 male
Results: Acoustic Power Dose Inside Clot
Methods: Spectrum from Maximum Pixel Location
Results: Normalized Spectra of Bubble Cloud Emissions

1 cycle, 15 MPa

Normalized PCl Emission (dB)

Frequency (MHz)

-50 -40 -30 -20 -10 0 10

2 4 6 8 10

5 cycles, 15 MPa

Normalized PCl Emission (dB)

Frequency (MHz)

-50 -40 -30 -20 -10 0 10

2 4 6 8 10

1 cycle, 25 MPa

Normalized PCl Emission (dB)

Frequency (MHz)

-50 -40 -30 -20 -10 0 10

2 4 6 8 10

5 cycles, 25 MPa

Normalized PCl Emission (dB)

Frequency (MHz)

-50 -40 -30 -20 -10 0 10

2 4 6 8 10