UNIVERSITY OF Cincinnati | Image-Guided Ultrasound Therapeutics Laboratories

Ultrasound-mediated drug delivery for cardiovascular disease

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CVD Drug Delivery: Strategies

Conventional Drug Delivery Strategy:

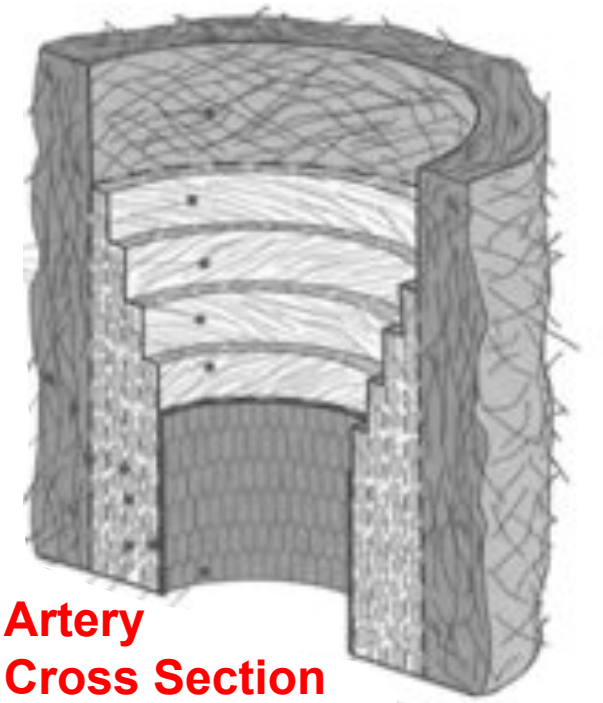
Perfuse entire vasculature with drug

tissue specificity

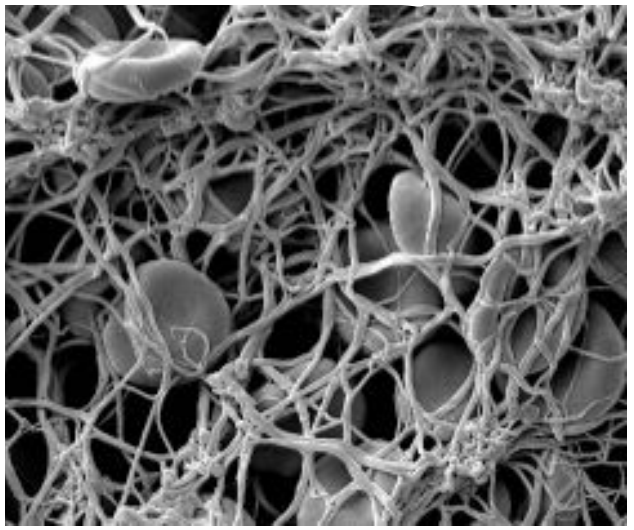
systemic effects

Ultrasound-mediated drug delivery:

1. ***Target*** drug/bubbles to pathologic tissu
   - Antibody conjugation
   - Molecular image-guidance
2. ***Trigger*** release & penetration
   - Permeabilize barriers
   - Drive drug penetration
3. ***Induce*** bioeffects
   - Stabilize plaques
   - Inhibit cell proliferation
   - Expedite clot lysis



Artery Cross Section



SEM: Human Blood Clot

Holzapfel and Gasser, *J Elasticity*, 2000.
Sutton et al. *Exp. Op. Drug Delivery*, 2013.

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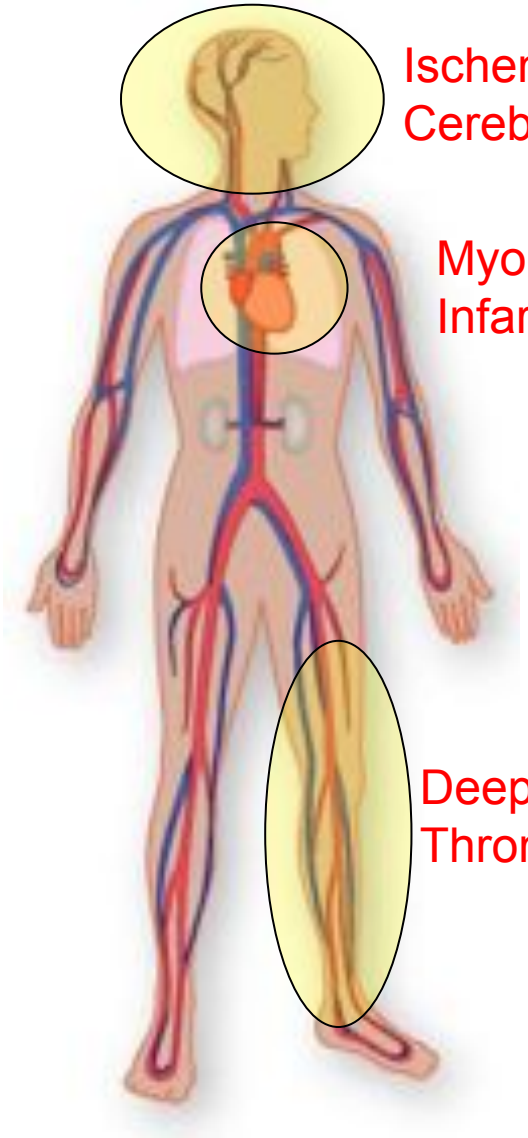
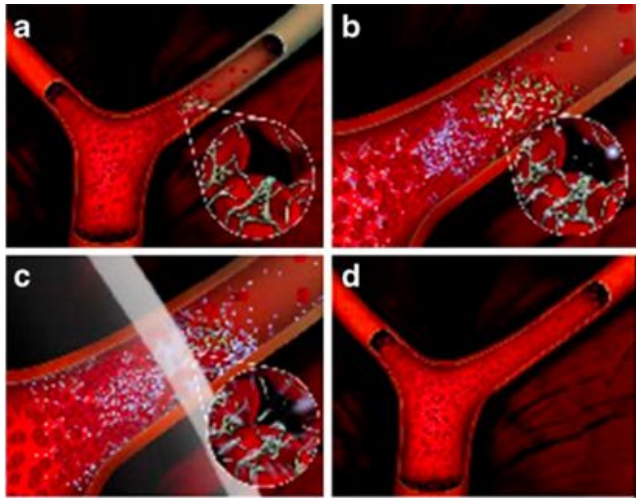


Ischemic Stroke
Cerebral Hemorrhage

Myocardial Infarction

Deep Vein Thrombosis



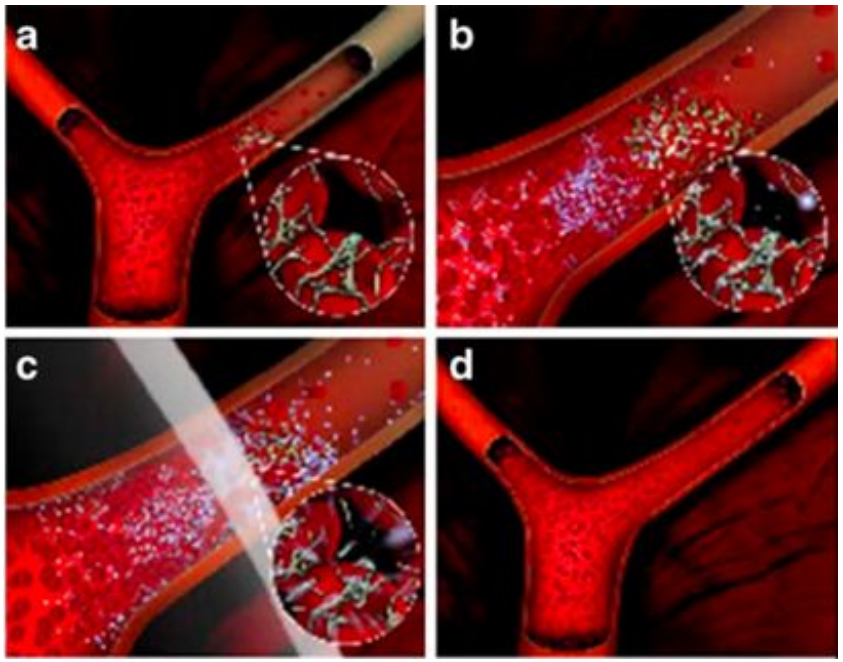
Sonothrombolysis

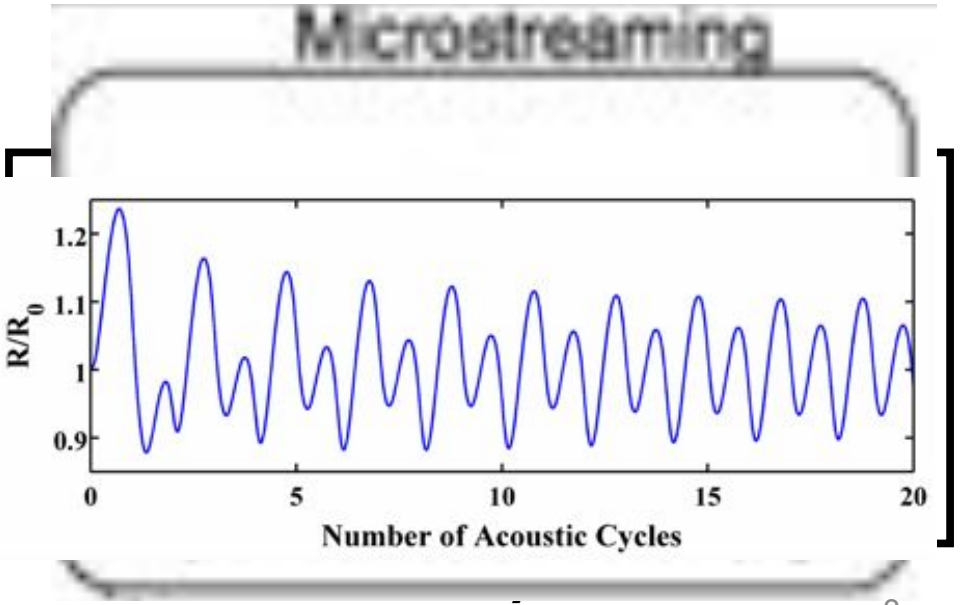
Sonothrombolysis: Background

Roger et al., *Circulation*. 2011.
Saver et al., *J Thromb Hemost,* 2011.

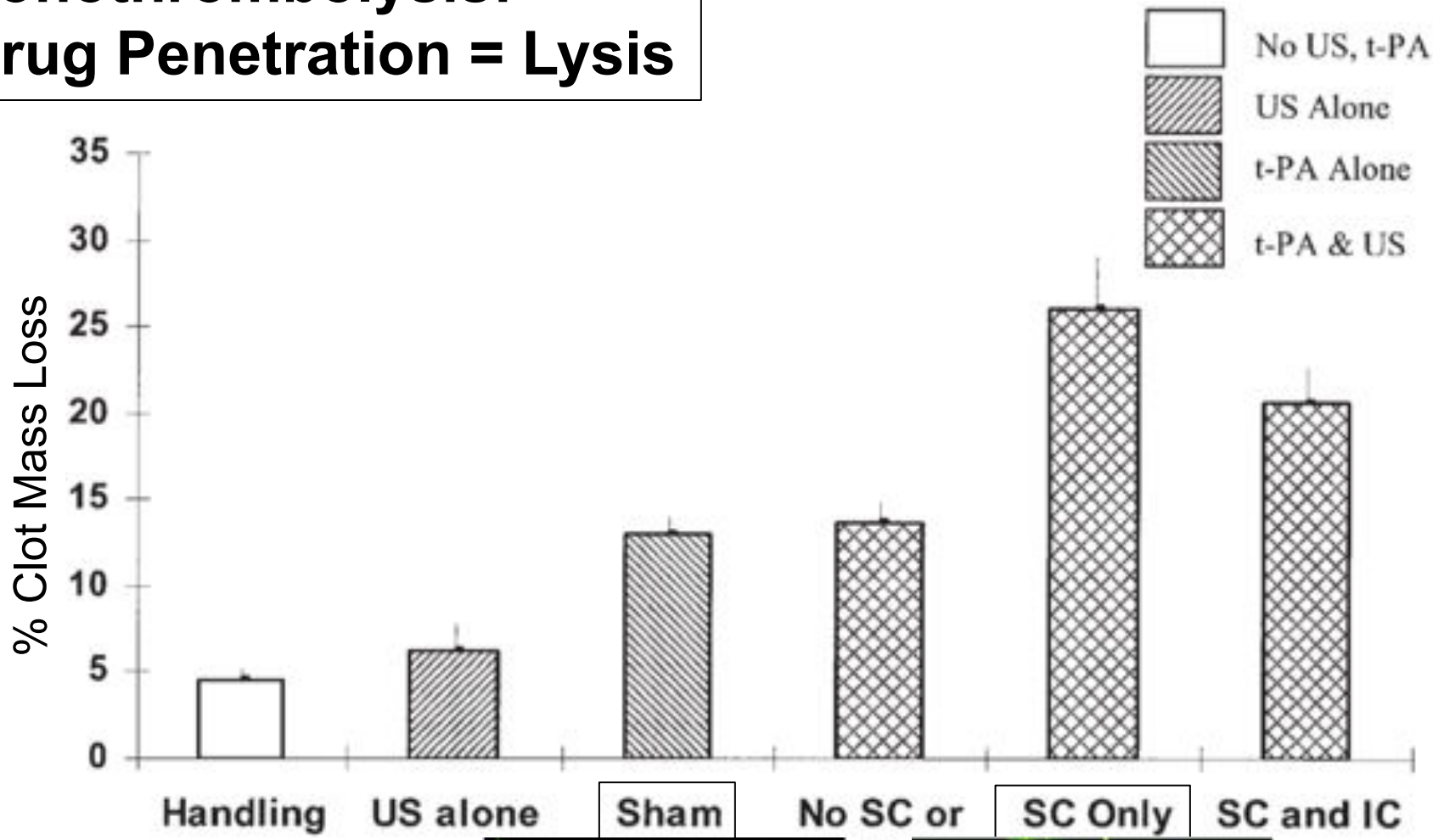
- Acute Ischemic Stroke: sudden cerebrovascular stenosis
- Treatment: I.V. recombinant tissue-type plasminogen activator (rt-PA)
  - 20 – 40% reperfusion, 4-7% hemorrhage, treatment window

- Progress: sonothrombolysis to expedite clot lysis

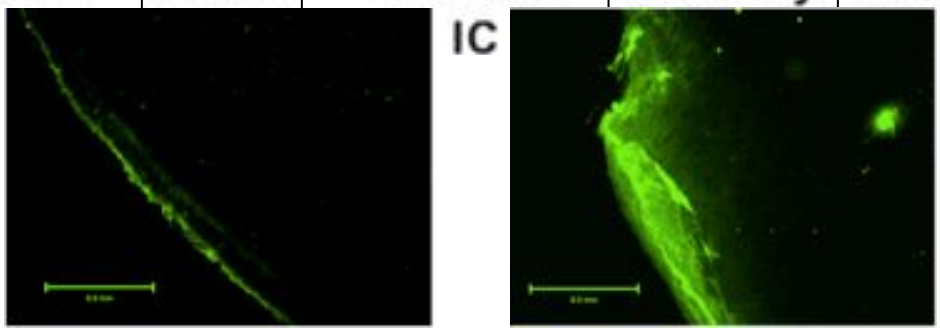




Sonothrombolysis: Drug Penetration = Lysis



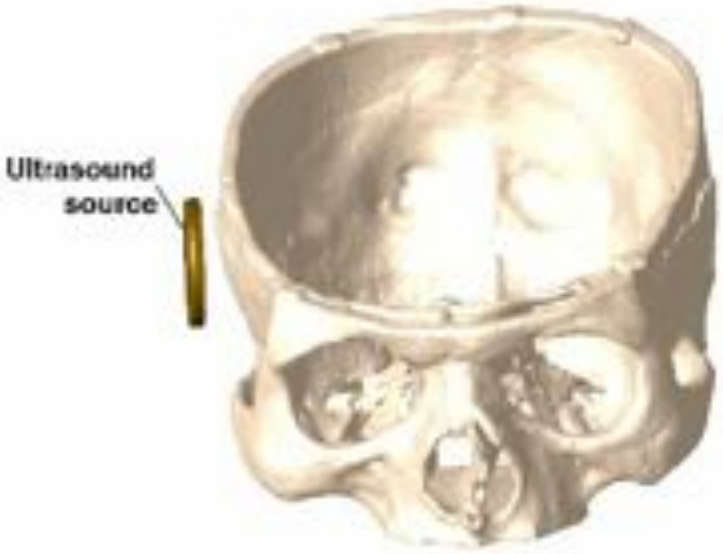
Enzyme penetration:
rt-PA



Datta et al. *UMB*. 2008

Sonothrombolysis: Know Thy Sound Field

G. Bouchoux, PhD

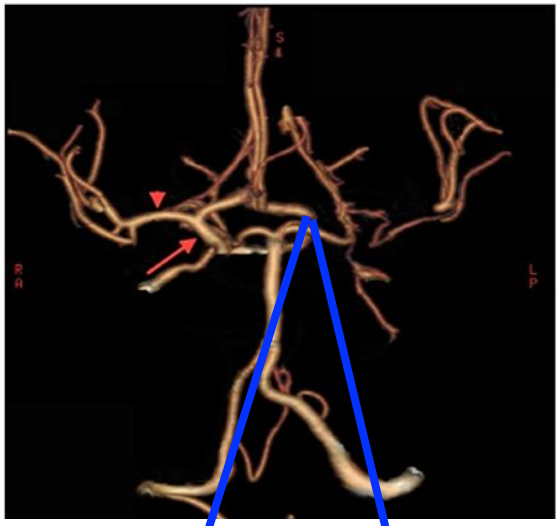


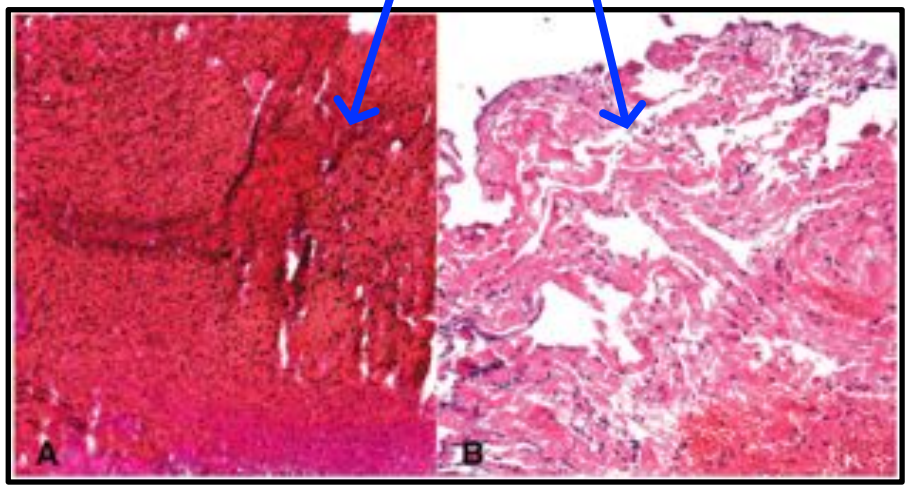
Implement an accurate transcranial propagation numerical model. Validate experimentally.

- 1 cycle, 120 kHz sinusoidal excitation
- Simulations compared with hydrophone measurements
- Degassed human skulls
- 15 – 33% pressure reduction (rel. FF)
- Shift in peak pressure position < 2.5 mm
- Homogenous acoustic pressure in MCA

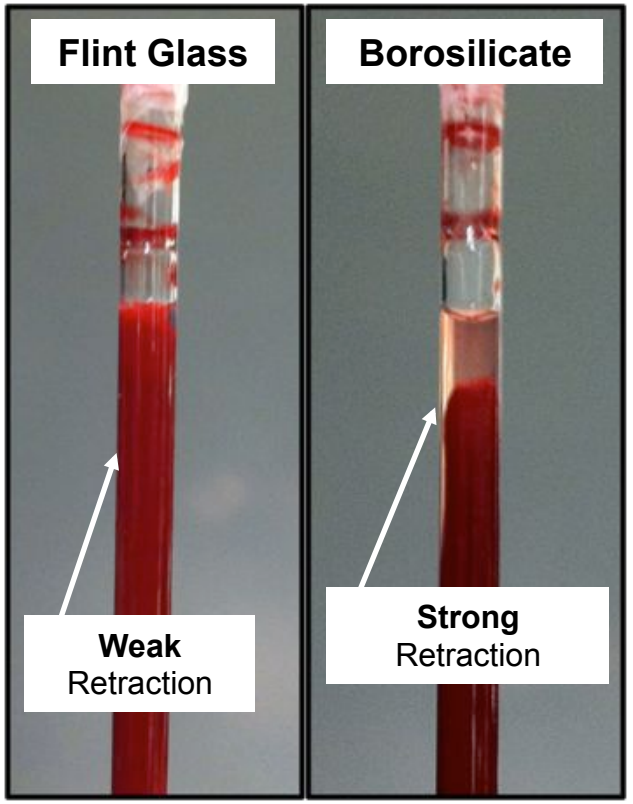
Bouchoux et al. *PMB*. 2012.

Sonothrombolysis: Barrier Permeability





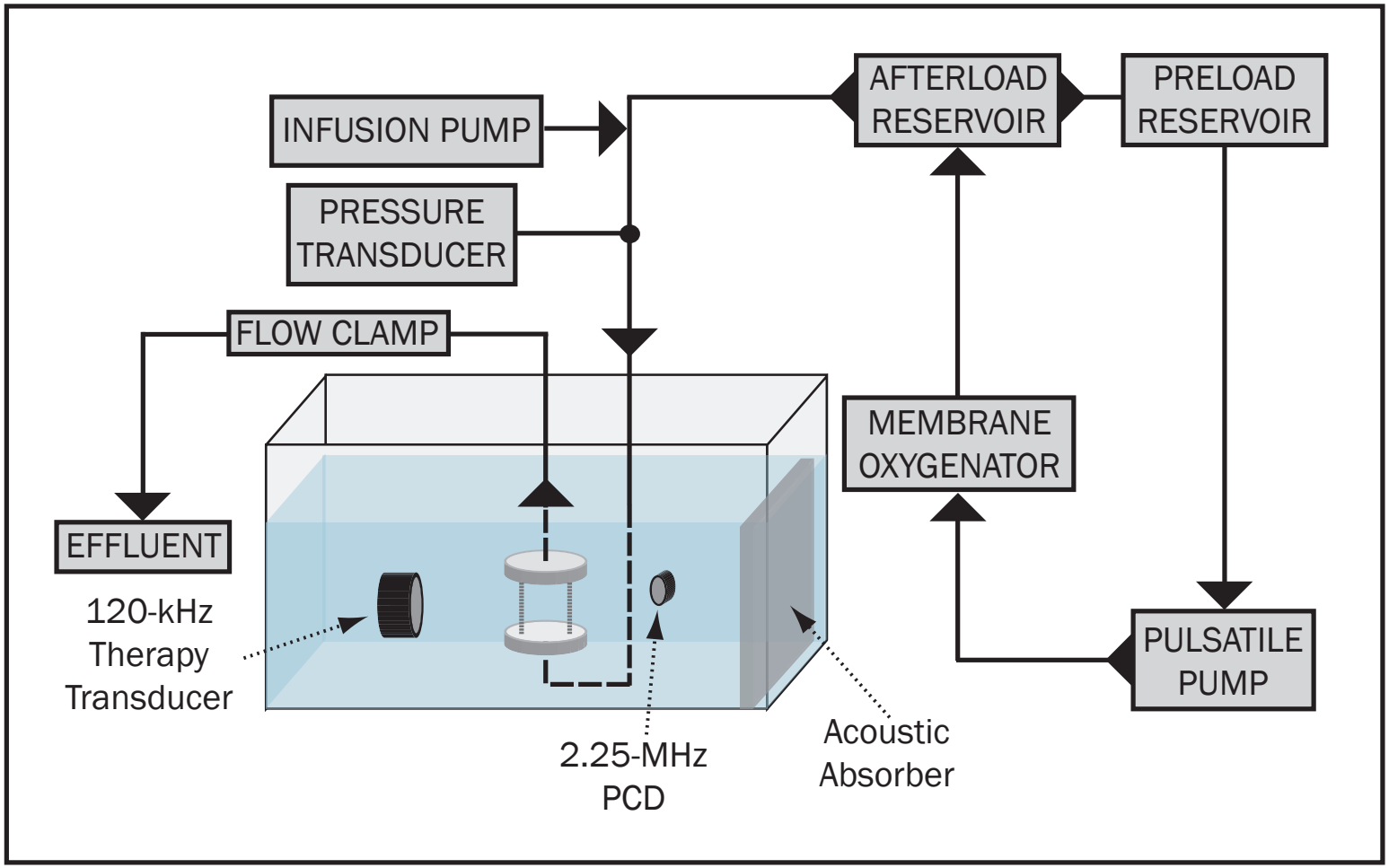
Erythrocytotic Fibrin-enriched



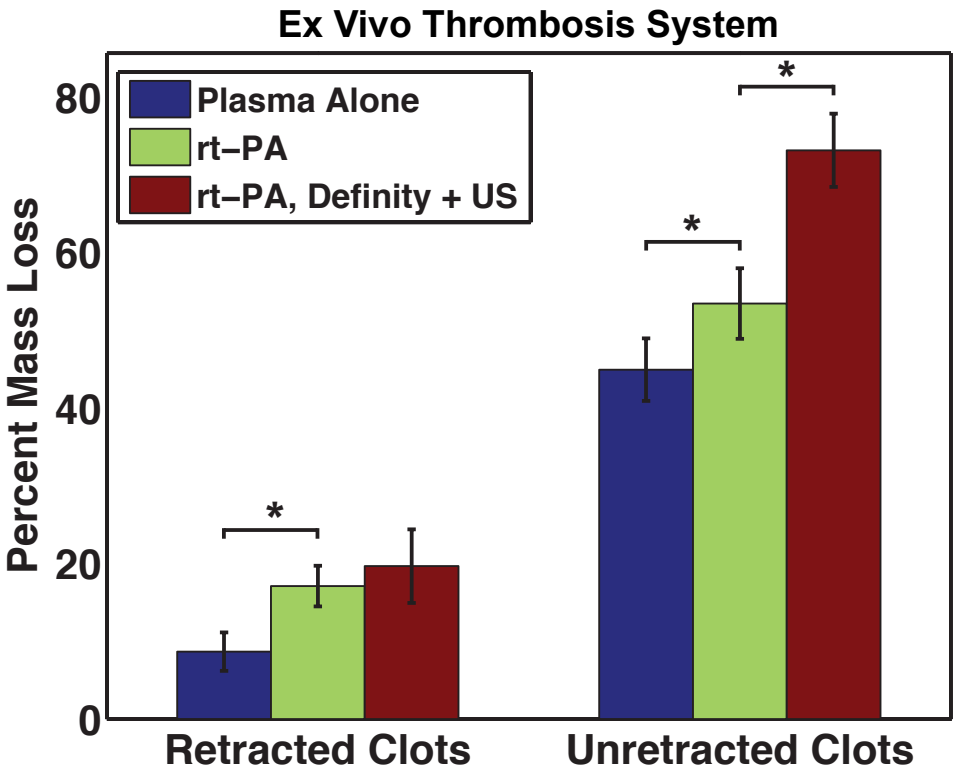
<u>Research Question:</u>
Does clot retraction affect extent of sonothrombolysis?

Liebeskind et al. *Stroke,* 2011.

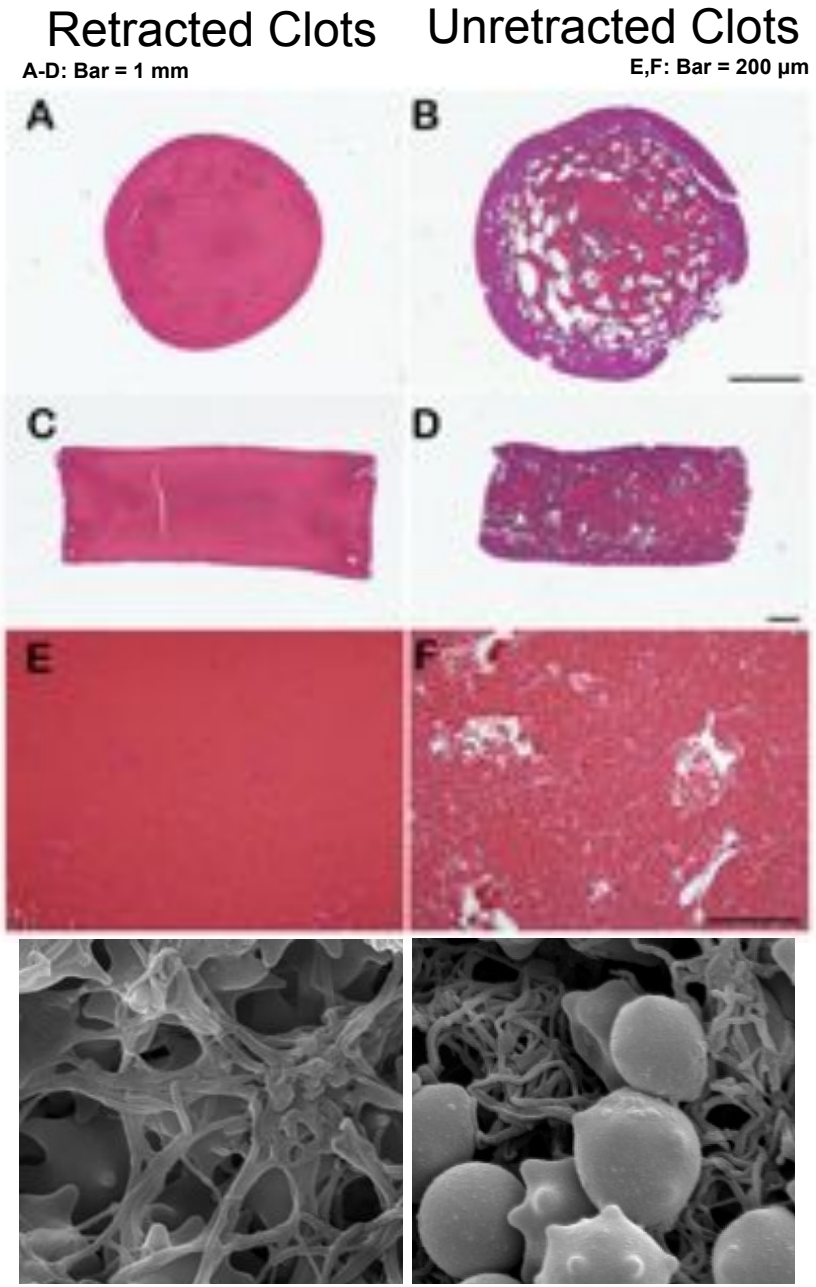
Sonothrombolysis: Ex vivo perfusion model



Sonothrombolysis: Bioeffects



US: 120 kHz, 0.48 MPa_{PK-PK}, CW



Sutton et al., *UMB.* 2012.

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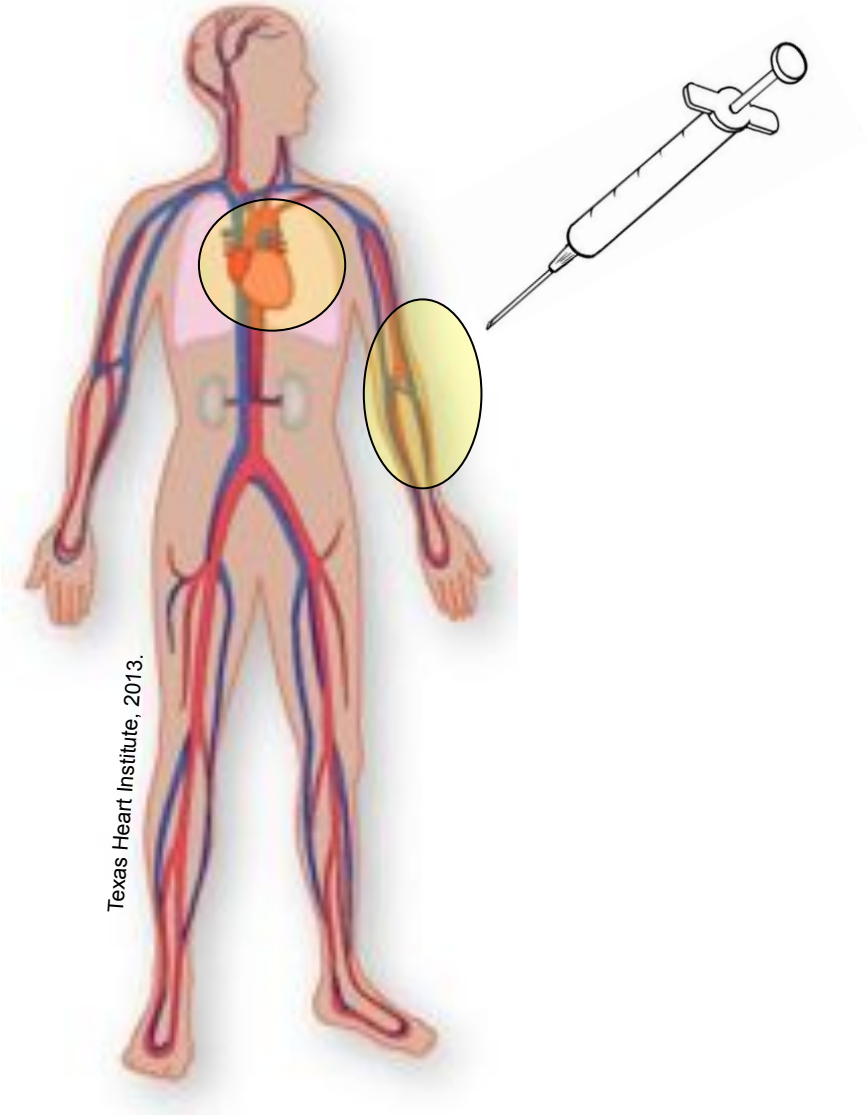
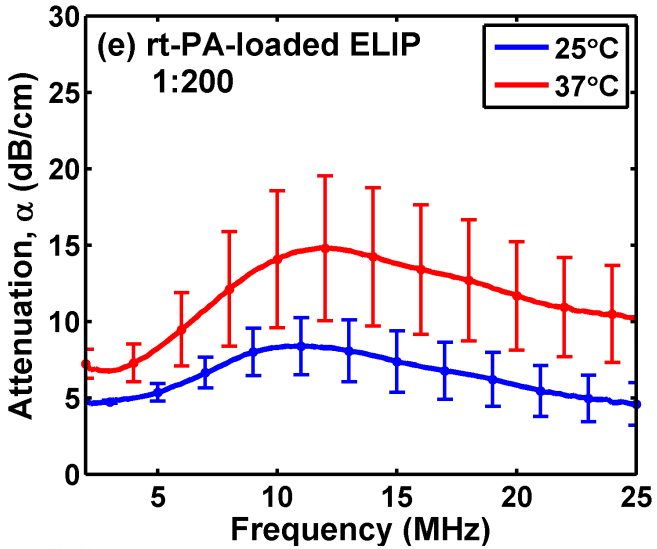


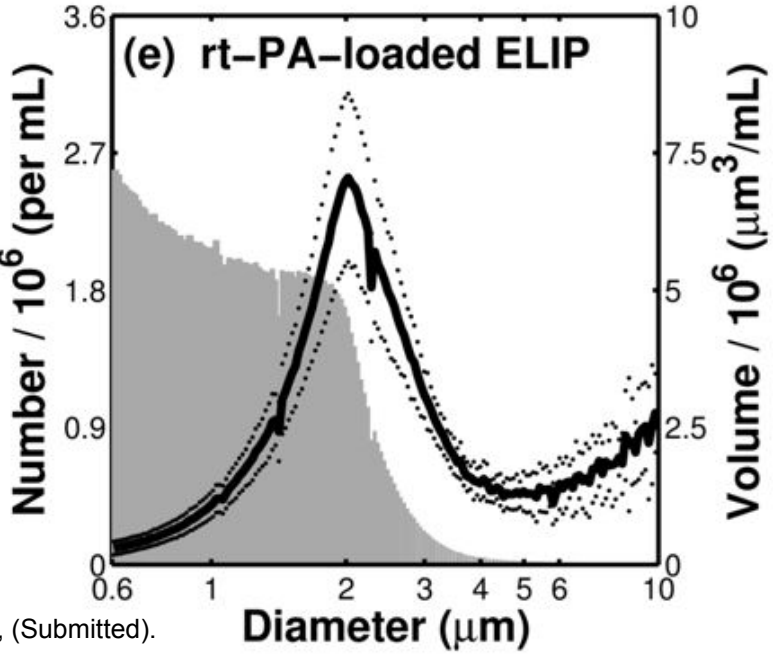
Texas Heart Institute, 2013.

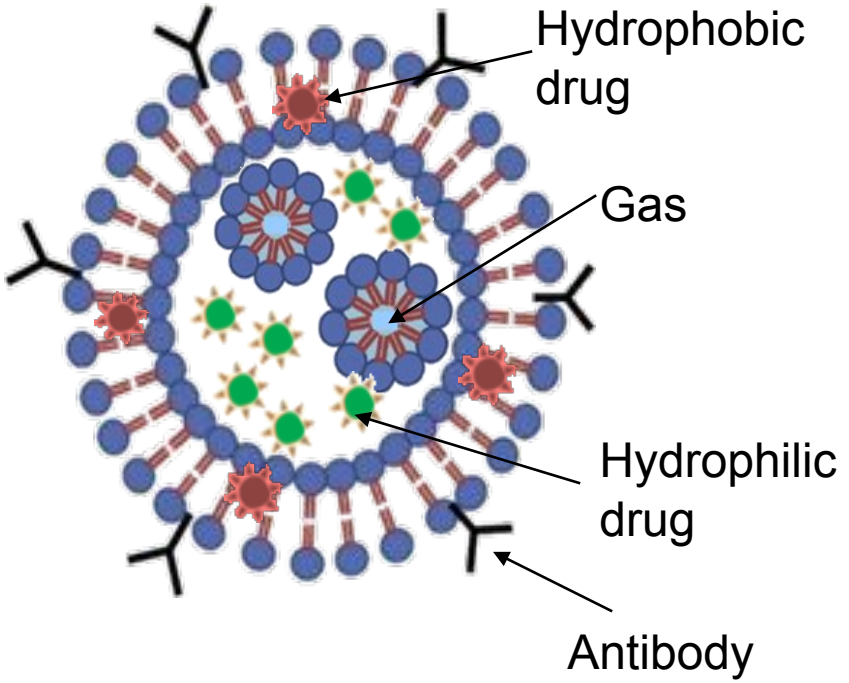
Cardiovascular Drug Delivery: US Contrast Agents

Drug Targeting & Image-Guidance: ELIP

J. Raymond



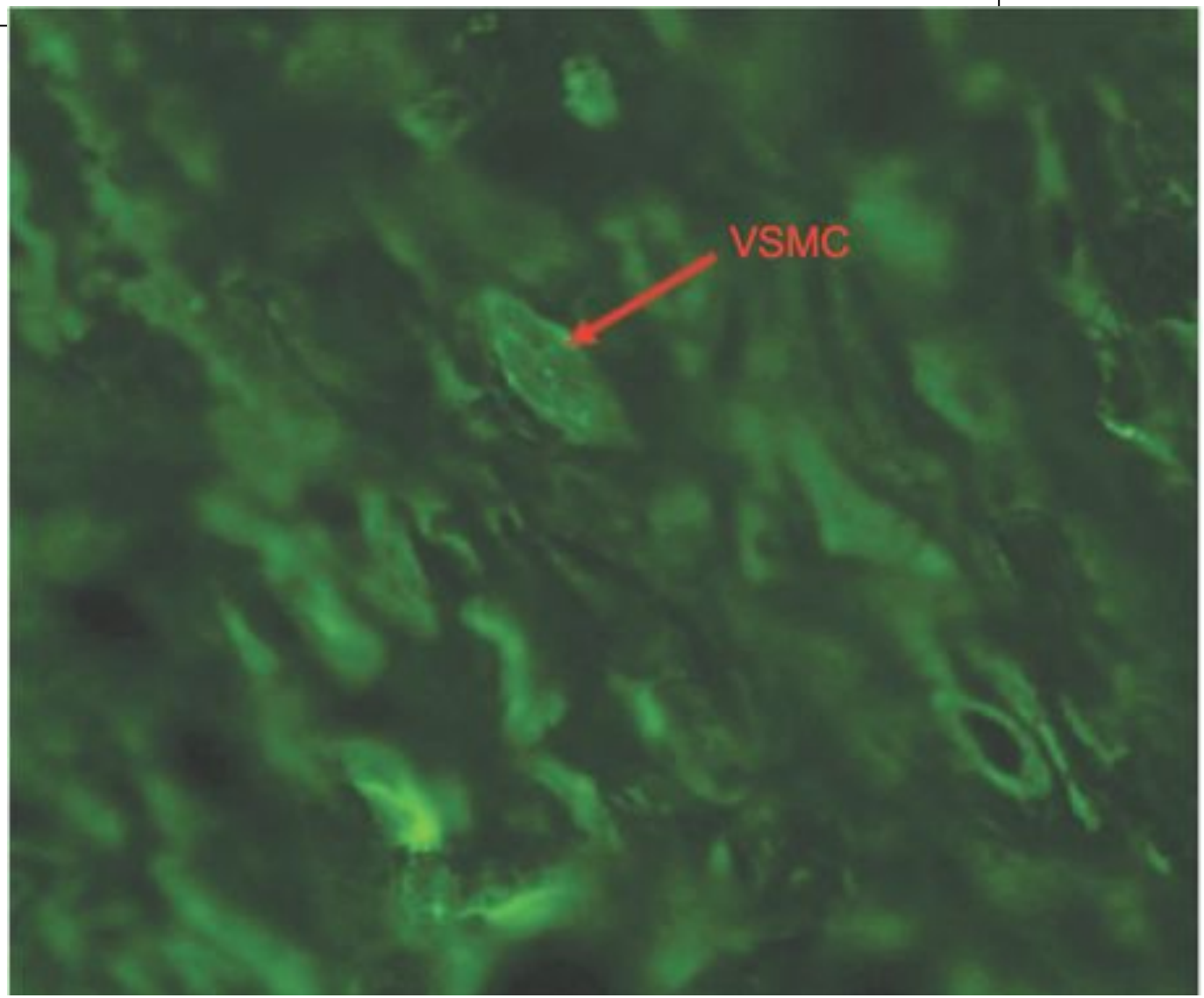




Proposed schematic of an Echogenic Liposome (ELIP)

Raymond et al. *UMB*, (Submitted).

Drug Targeting & Image-Guidance: ELIP Targeting to Smooth Muscle



Laing et al. *J. Liposome Res*. 2010.

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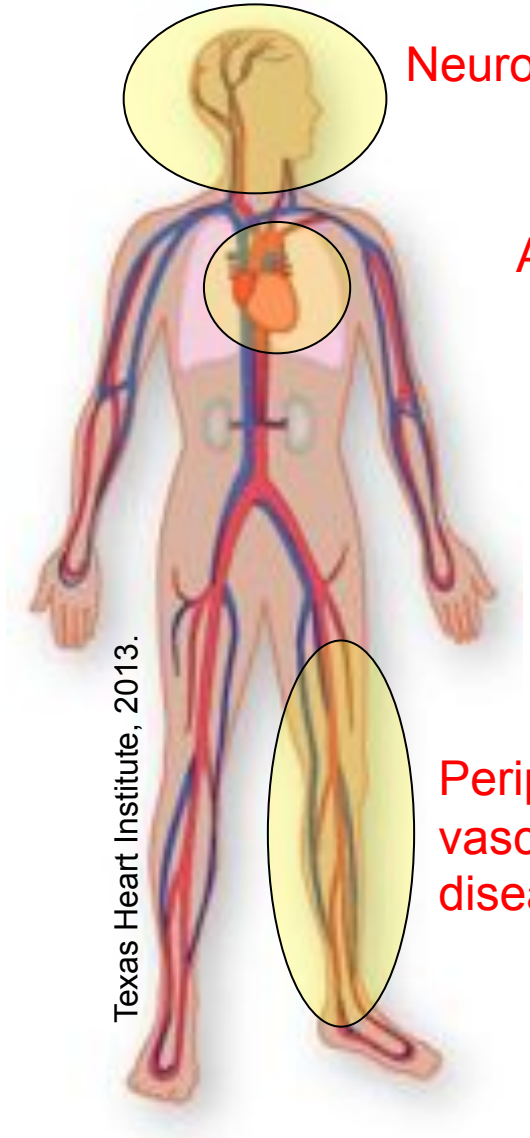
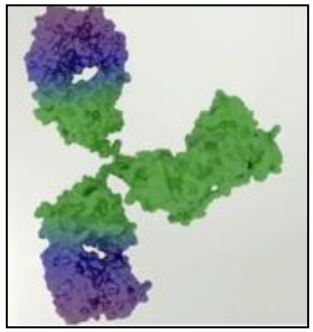


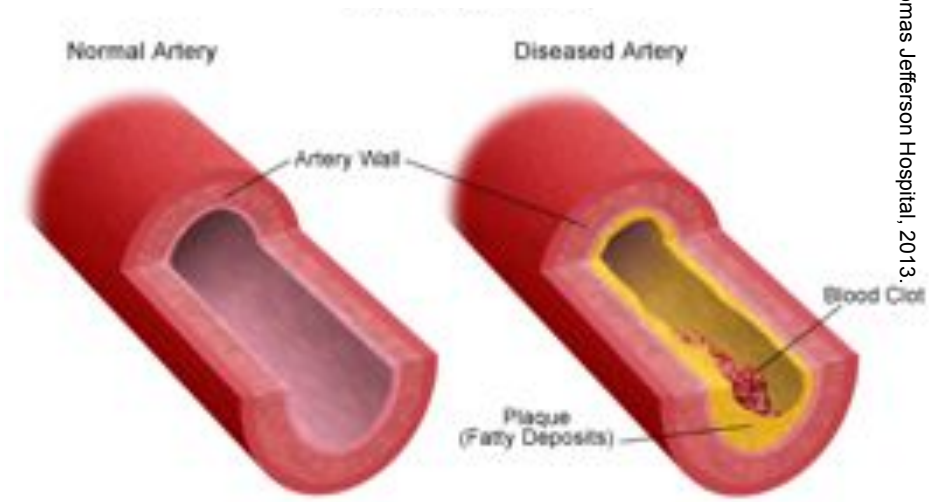
Texas Heart Institute, 2013.

Neuroprotection

Atherosclerosis

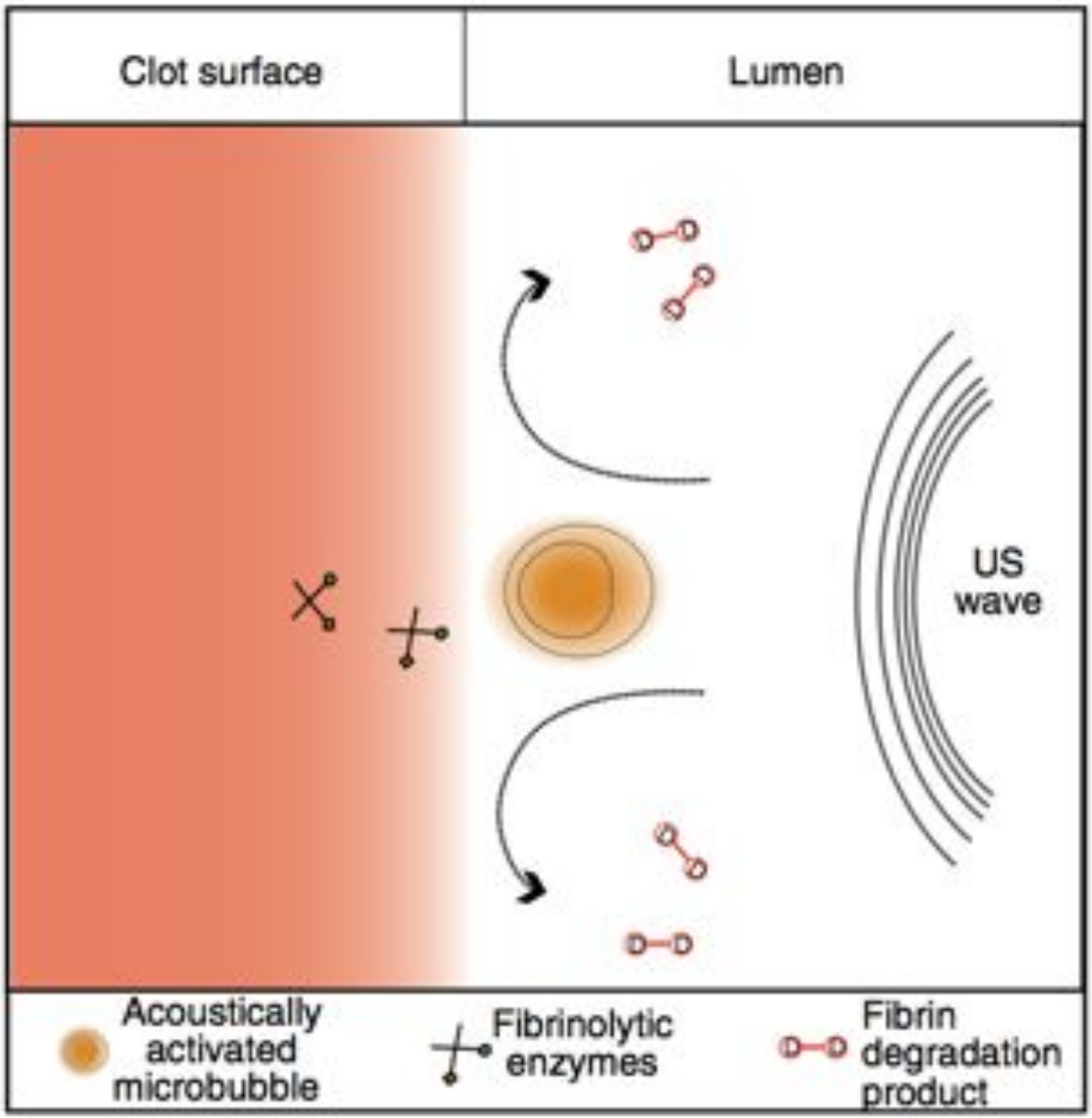


Peripheral vascular disease



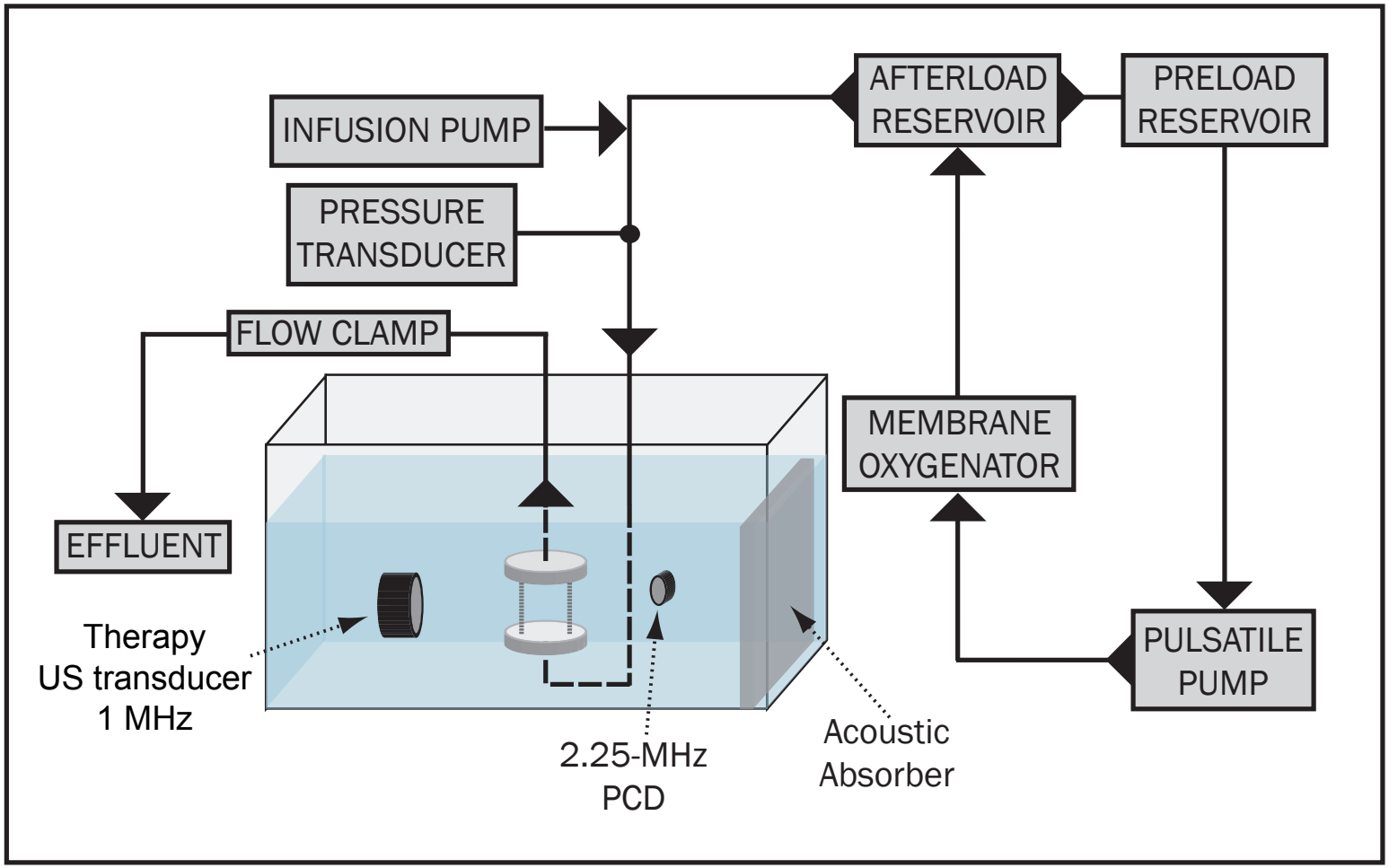
Thomas Jefferson Hospital, 2013.

Cardiovascular Drug Delivery: Therapeutics



Sutton et al. Expert Opinion in Drug Delivery. 2013.

Sonothrombolysis: Ex vivo perfusion model



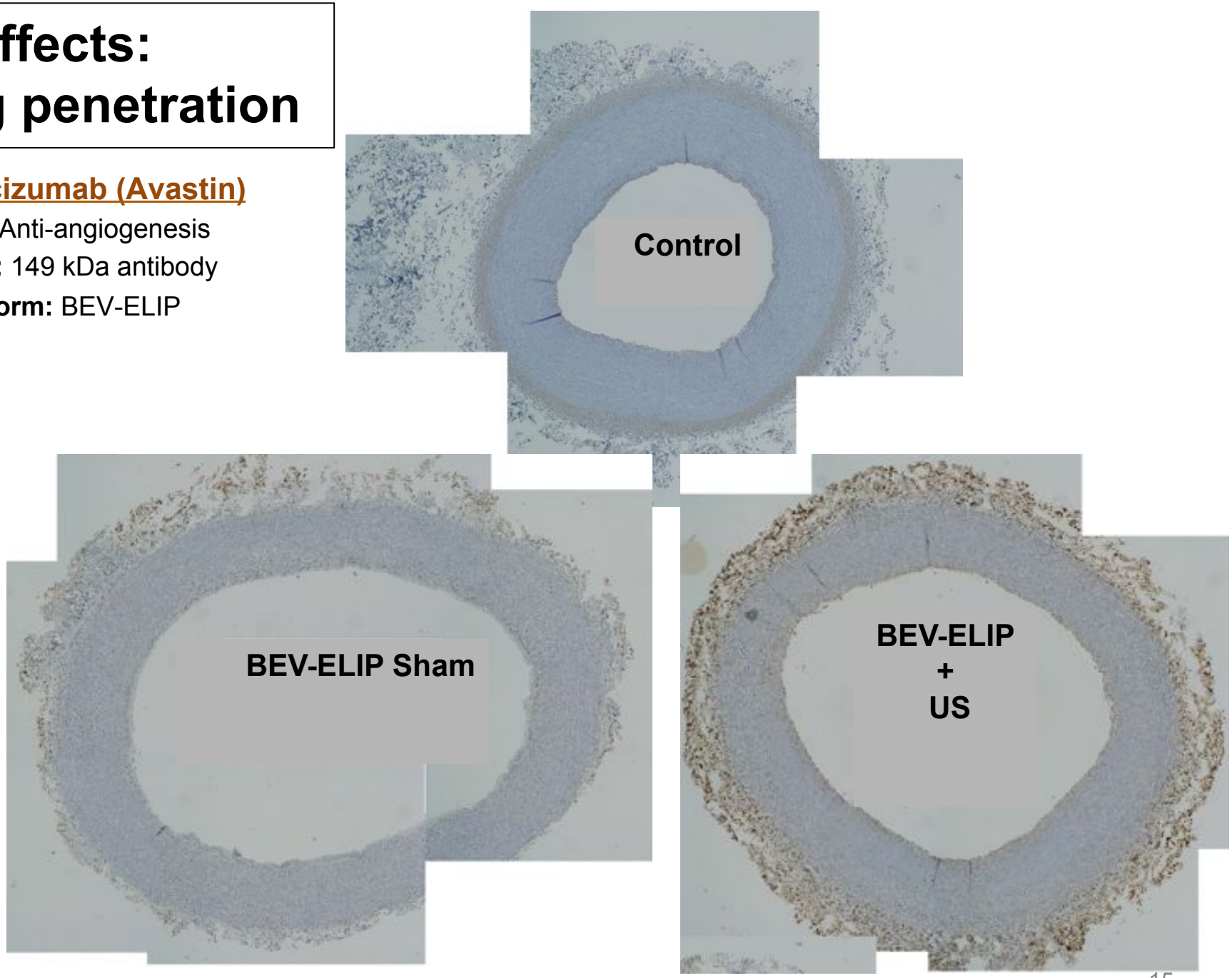
Bioeffects: Drug penetration

Bevacizumab (Avastin)

Rx: Anti-angiogenesis

Size: 149 kDa antibody

Form: BEV-ELIP



US: 1 MHz, 0.58 MPa_{PK-PK}, CW

Bioeffects:
Bioactive gas delivery

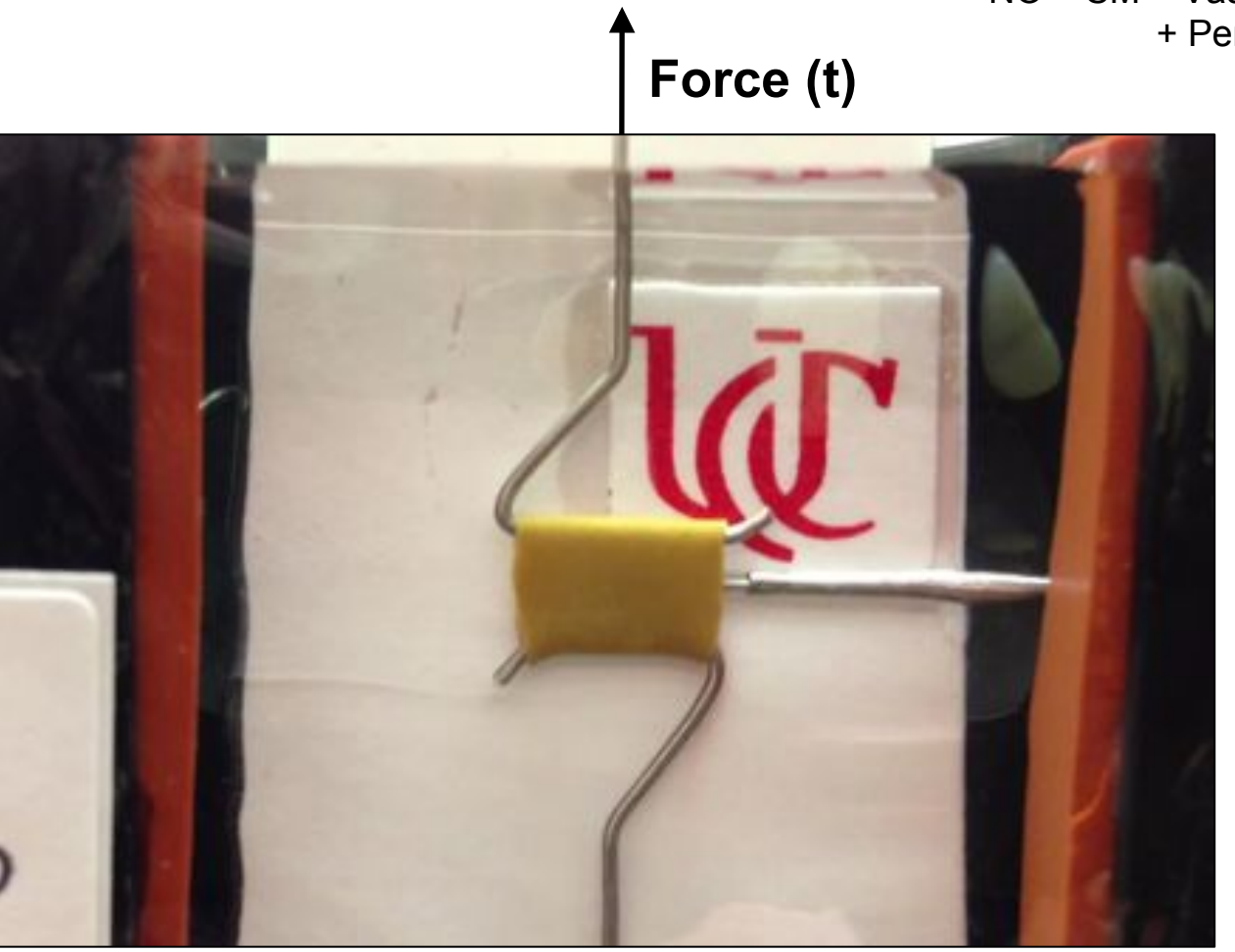
Nitric Oxide (NO)

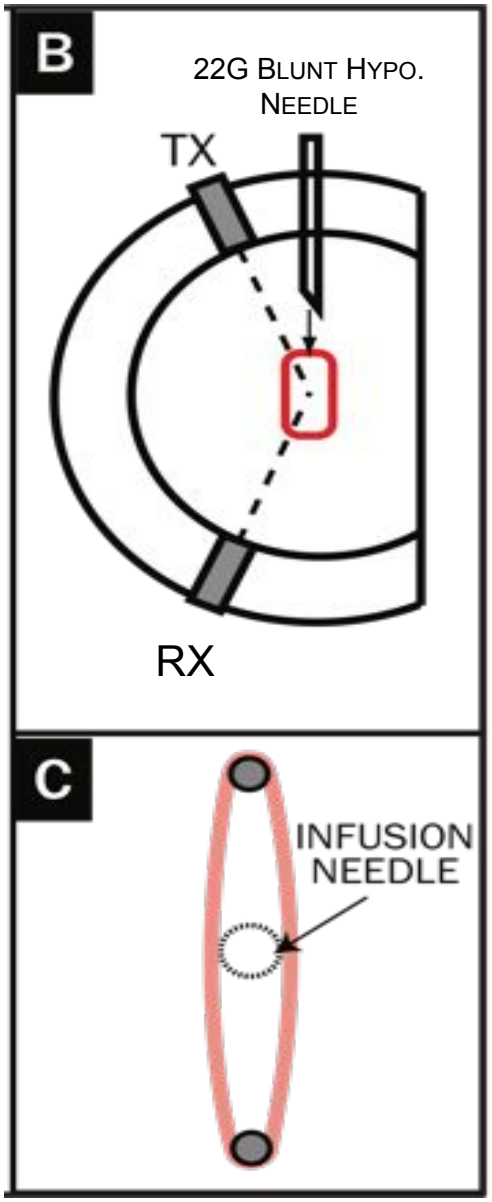
Size: Soluble gas, 30 Da

Form: NO Liposomes

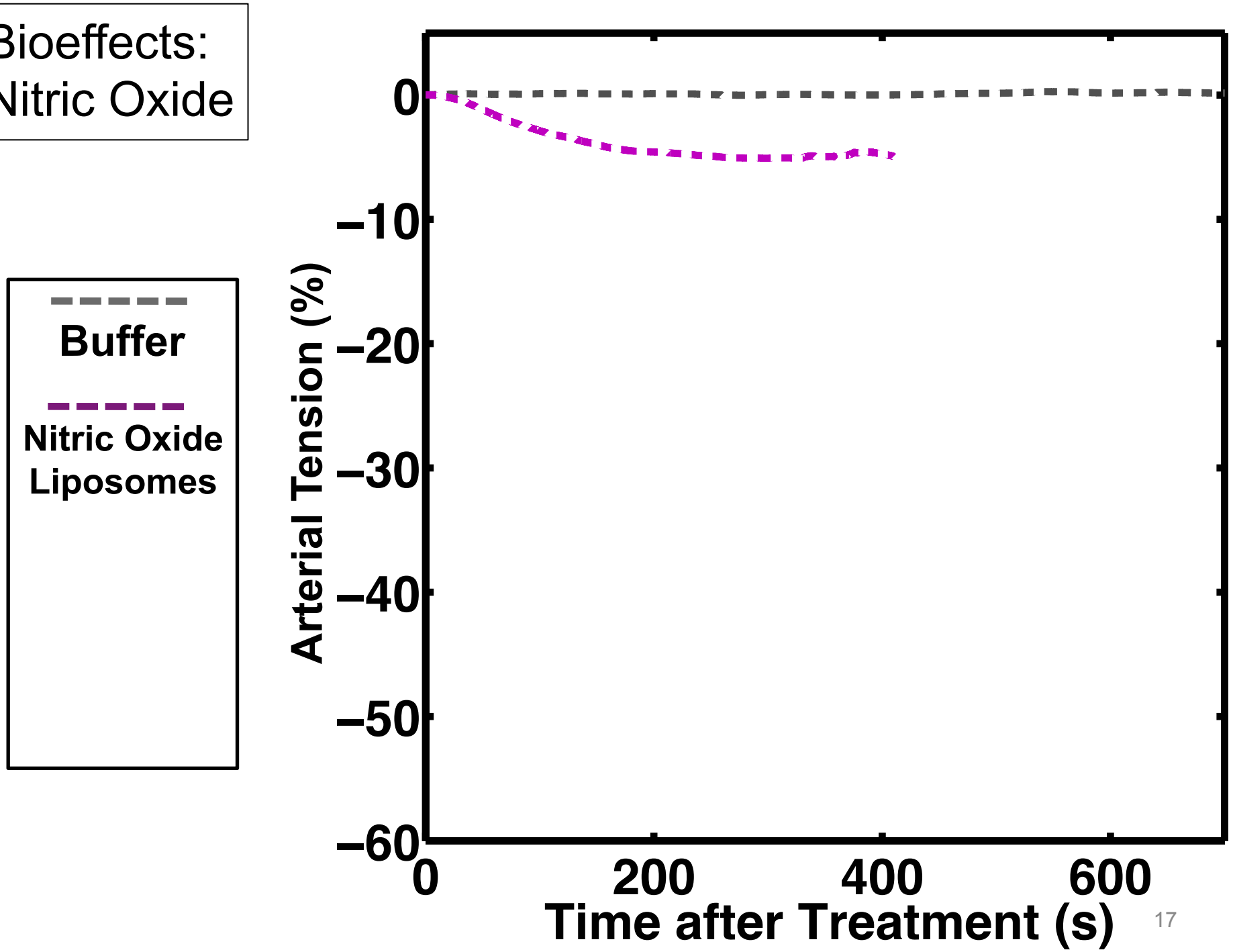
Mechanism:

NO + SM = Vasodilation
+ Permeability

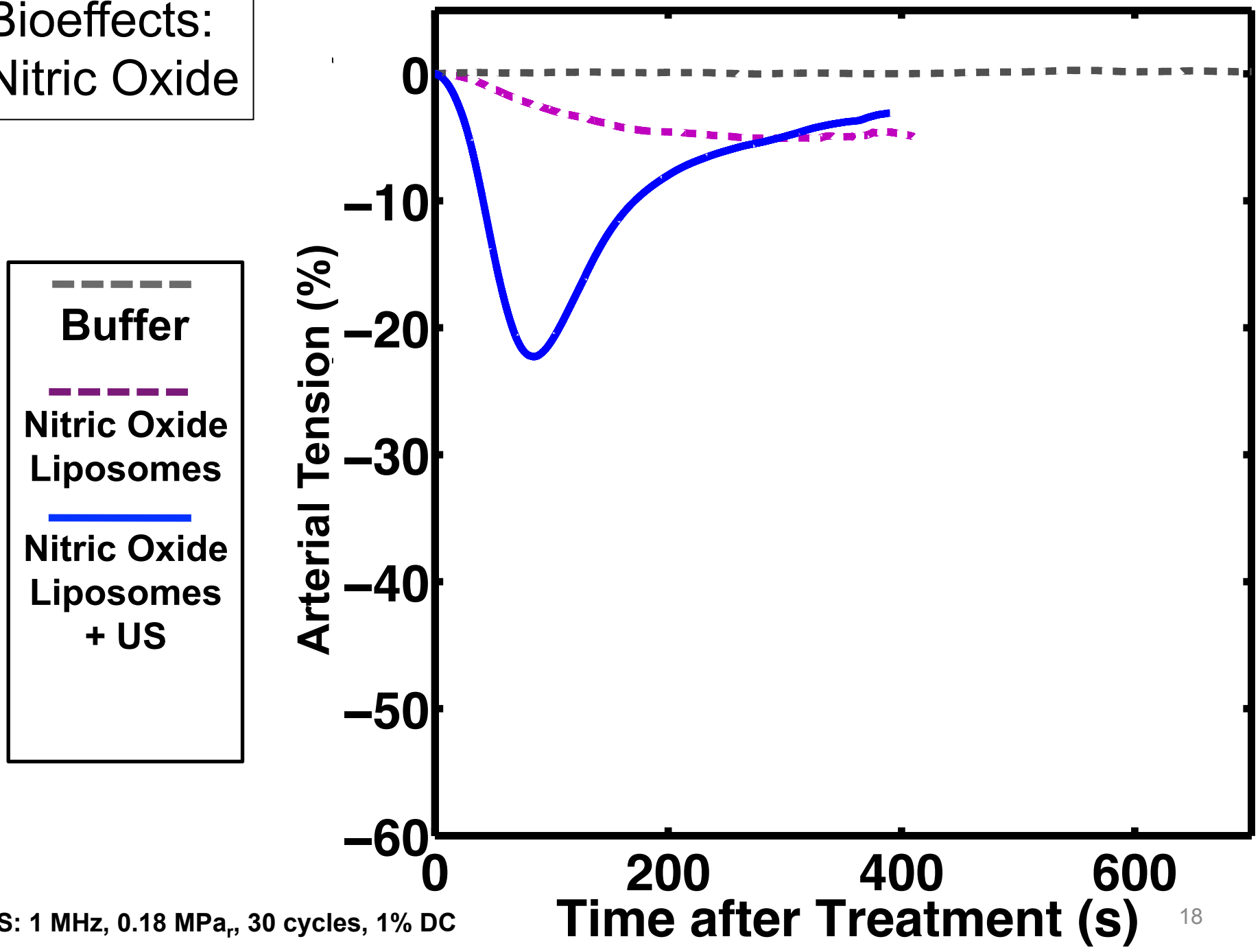




Bioeffects:
Nitric Oxide

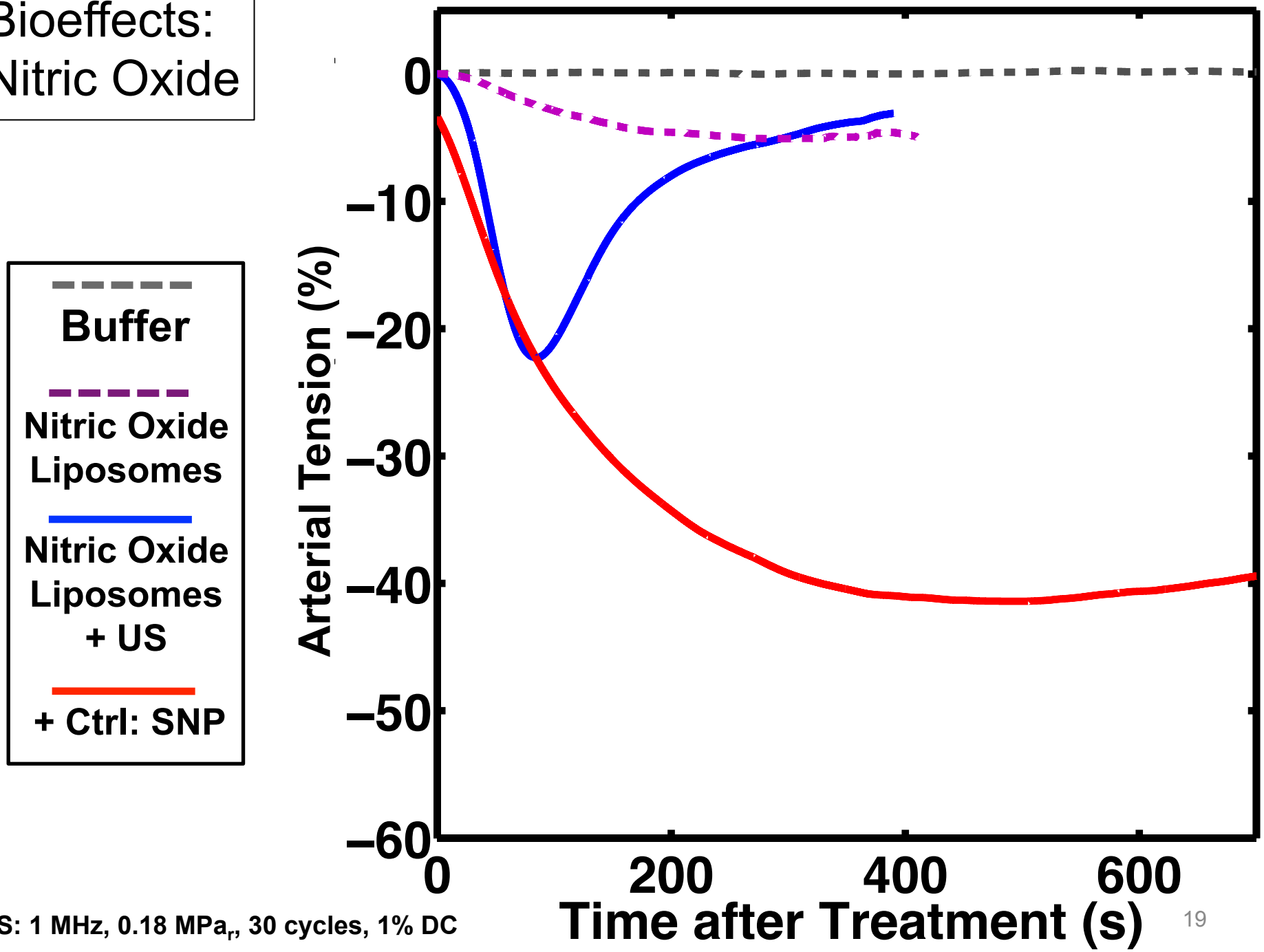


Bioeffects: Nitric Oxide



US: 1 MHz, 0.18 MPa_r, 30 cycles, 1% DC

Bioeffects: Nitric Oxide



US: 1 MHz, 0.18 MPa_r, 30 cycles, 1% DC

CVD Drug Delivery: Summary

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Goal of UC IgUTL:

Investigate possible role of ultrasound to treat cardiovascular disease

- circulatory stability of drug carriers
- ultrasound image guidance, molecular imaging
- tissue targeting
- promote bioeffects, understand mechanism

Current Work:

- Developing/assessing novel drug carrier & US contrast agent (ELIP)
- sonothrombolysis
- drug penetration into tissue & resulting bioeffect
  - fibrinolytic enzymes, bevacizumab, nitric oxide

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Thank You

Questions, Comments?

Cardiovascular Institute

The University of Texas Health Science Center at Houston

Cincinnati Children's Hospital Medical Center

Texas Heart Institute at St. Luke's Episcopal Hospital