Therapeutic Ultrasound and the Contribution of Bubbles

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UWAMIT
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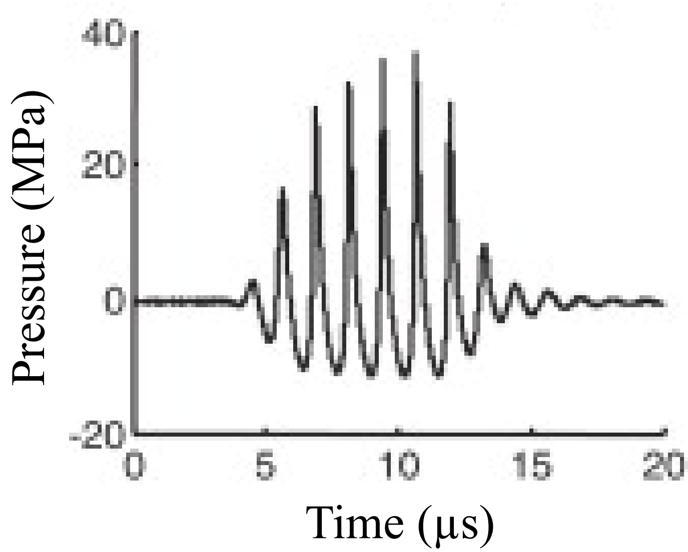
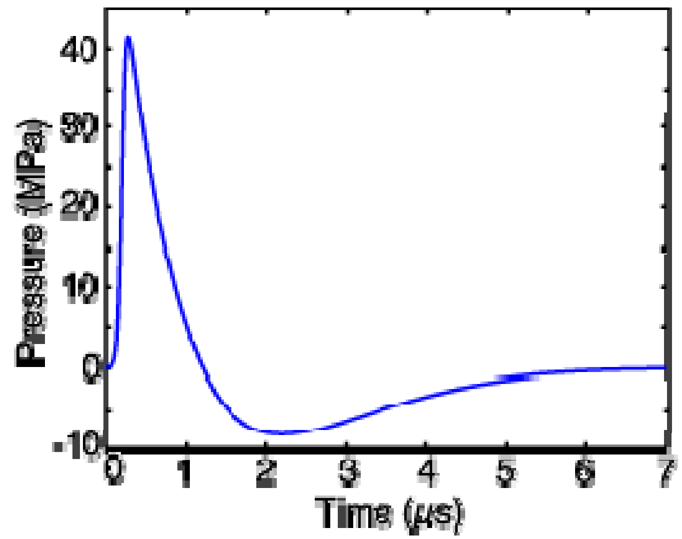
UNIVERSITY *of* WASHINGTON

Nonlinear Acoustic Pulses

HIFU or Histotripsy



Shock wave therapy

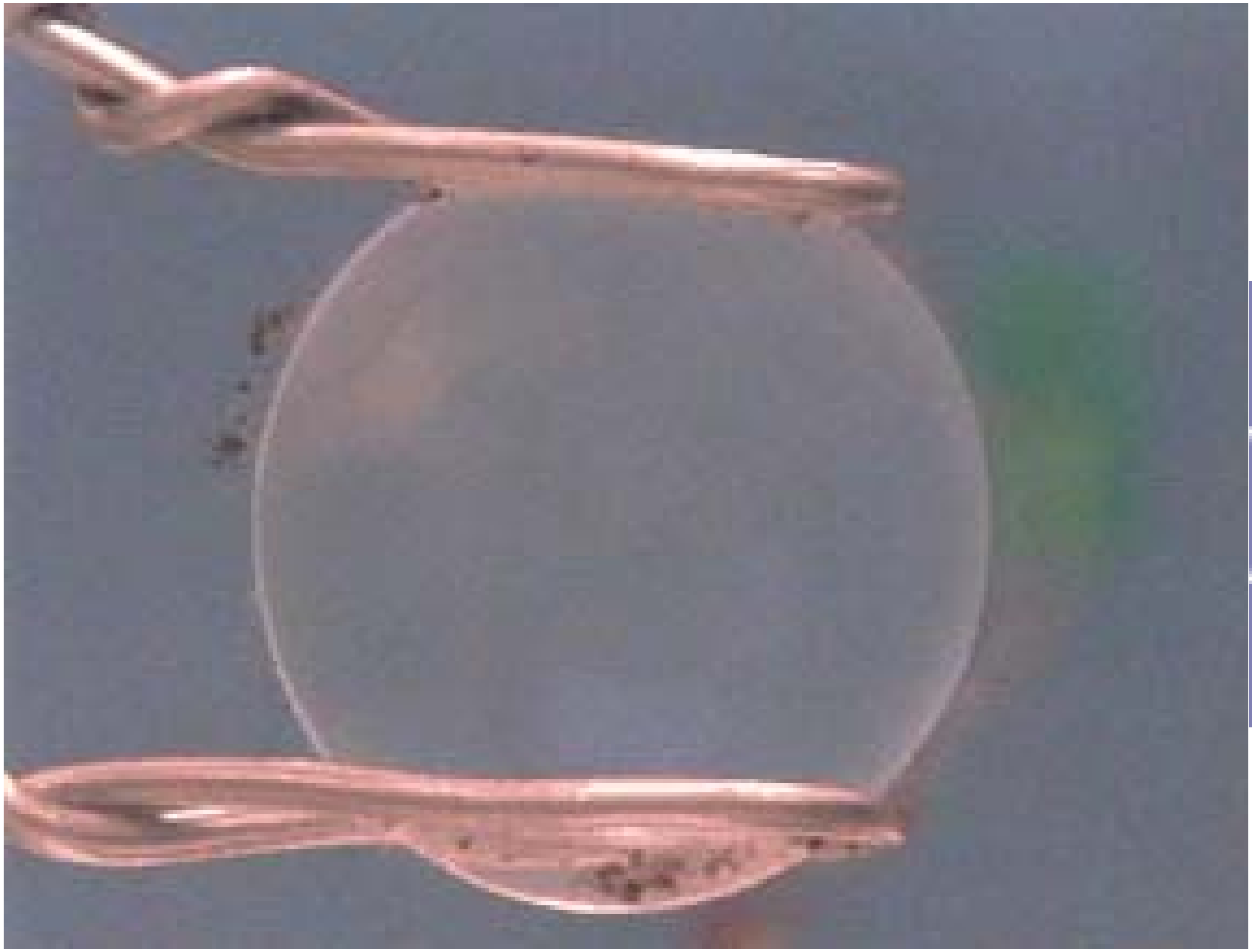


- Pulse can have thousands of cycles/sec
- **Heating** and/or mechanical bioeffects
  Heating – longer pulses

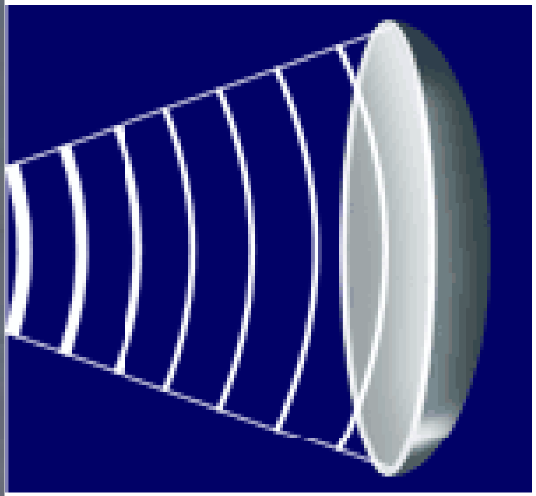
- Pulses have 1 cycle/sec
- Mechanical bioeffects only:
  Cavitation (negative tail)
  Shear (risetime of positive pulse)

Example of Heating: HIFU

Cow eye lens

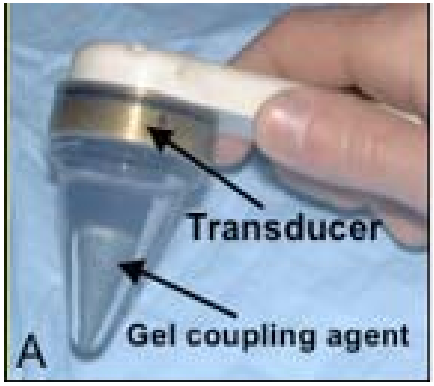


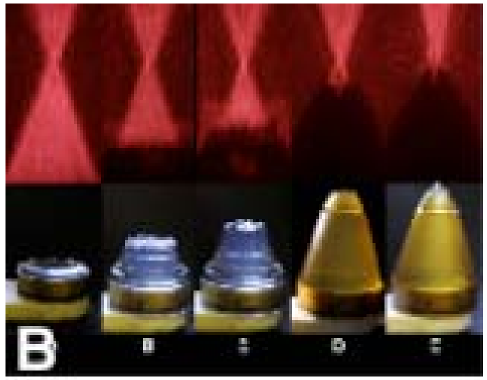
HIFU

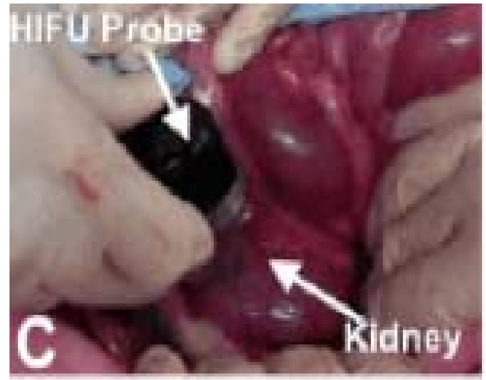


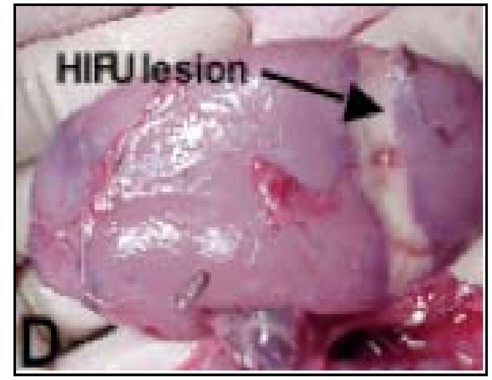
Application: HIFU for partial nephrectomy (Larry Crum, PI)

Focused Ultrasound

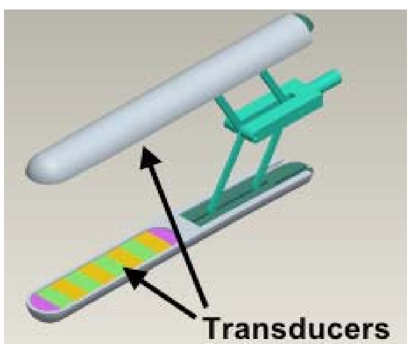


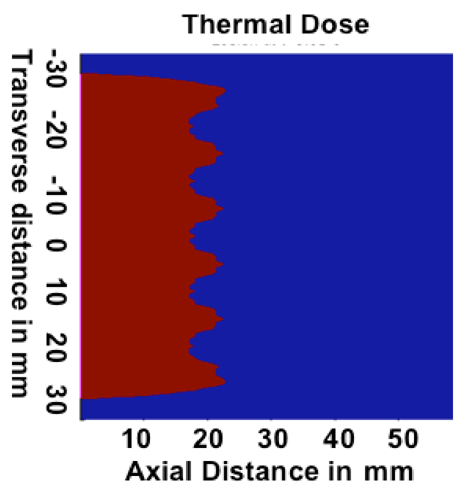






Unfocused Ultrasound Clamp



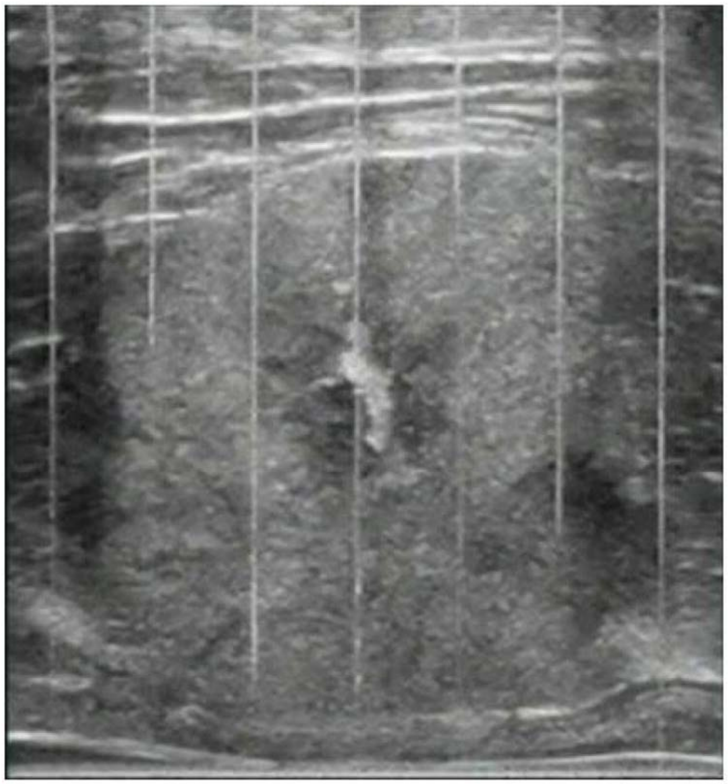


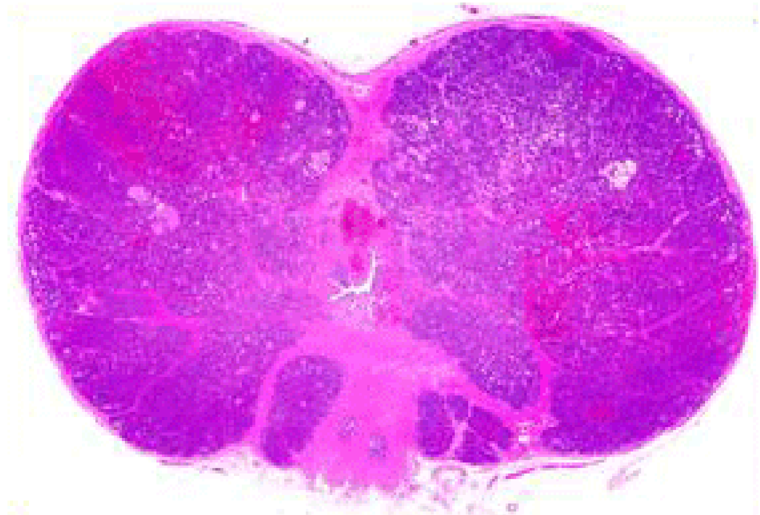
18 W/cm^2 Intensity; 25% DF; 120 S pulse duration; 11 Min treatment; 8532 J

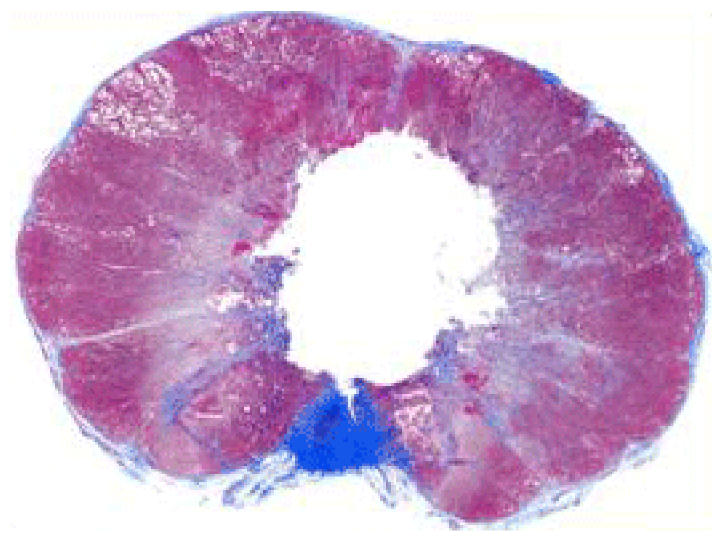
Example of Cavitation: Lithotripsy or Histotripsy

Pig kidney

Histotripsy





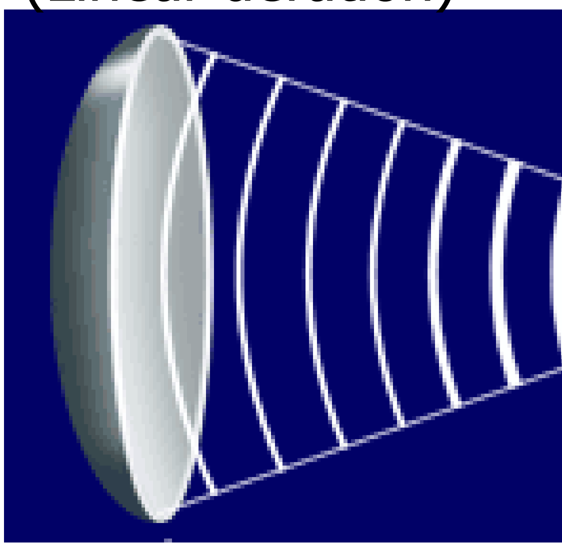


C.R. Hempel, *et al*., J. Urology, Vol 185, Pg 1484 (2011)

Histotripsy: Cavitation or Boiling?

Depends on pulse length

Exposure: 150 msec
Power: 160 W
12000 W/cm^2
(Linear deration)



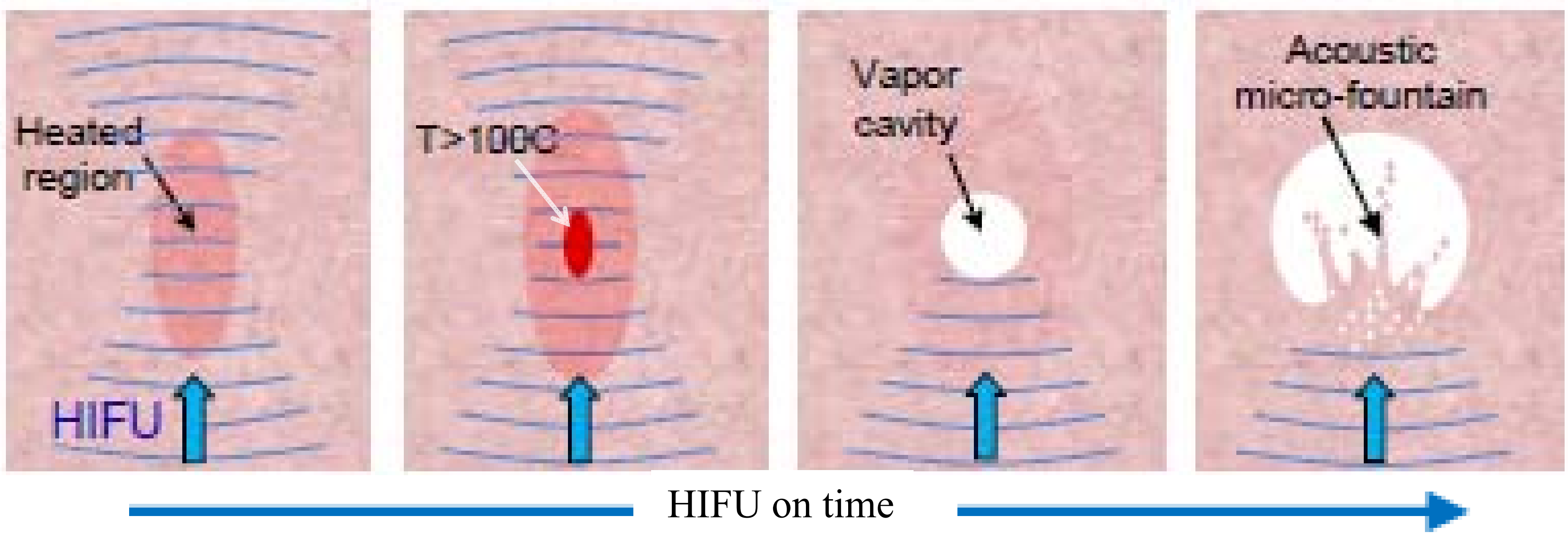
Predicted Time to boiling:

linearly: 380 ms

nonlinearly: 7 ms

Experiment: 9 ms

Proposed Role of Vapor / Gas Bubbles in Histotripsy



Pre-heating (µsec) Super-heating (msec) Boiling (msec) Atomization (msec)

Tissue Phantom Experiment with mm-sized "bubble"

HIFU Source:

2.165 MHz

F=45 mm, D= 45 mm

10 ms pulses, 1 Hz PRF

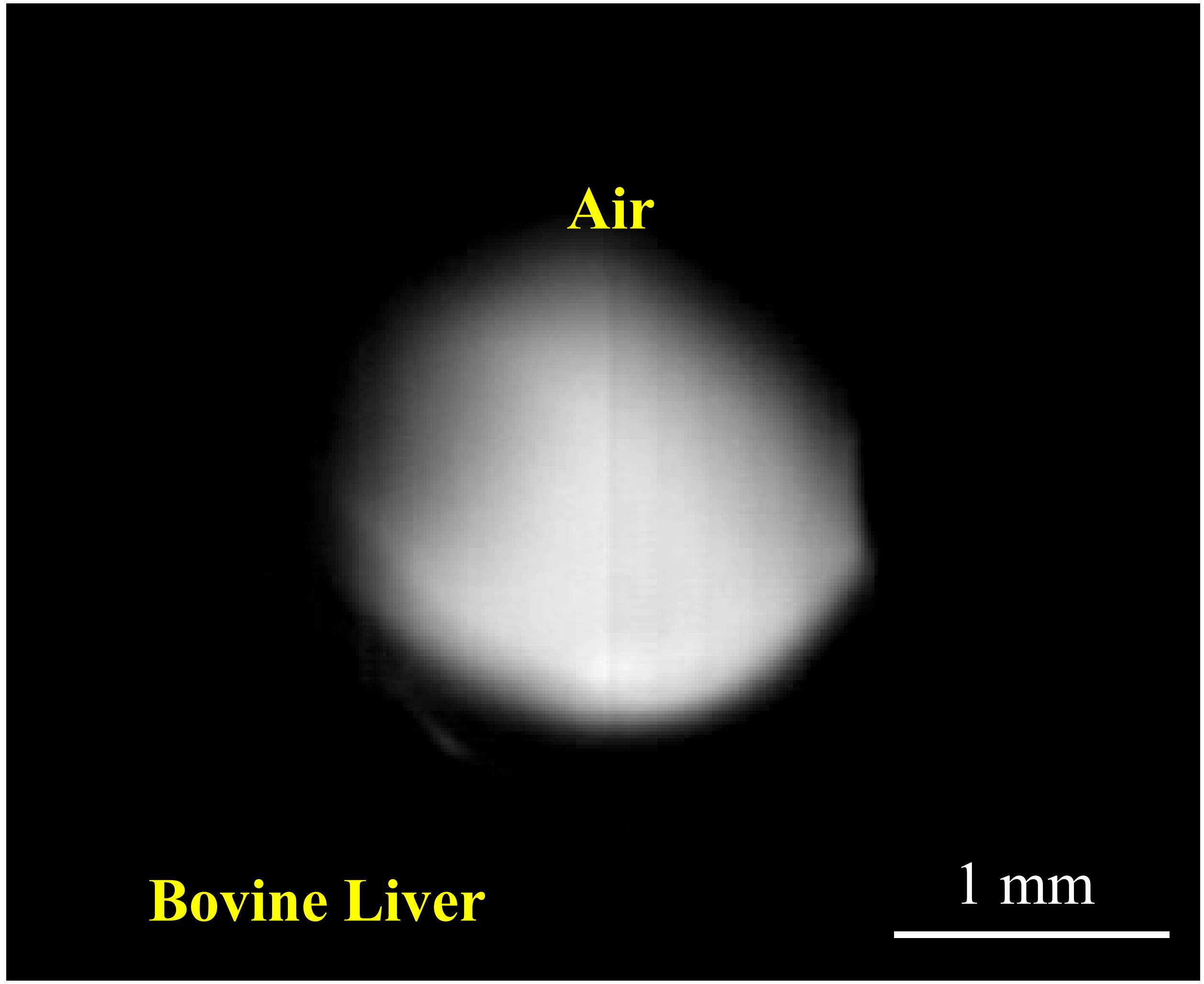
P+=65 MPa

P-=16 MPa

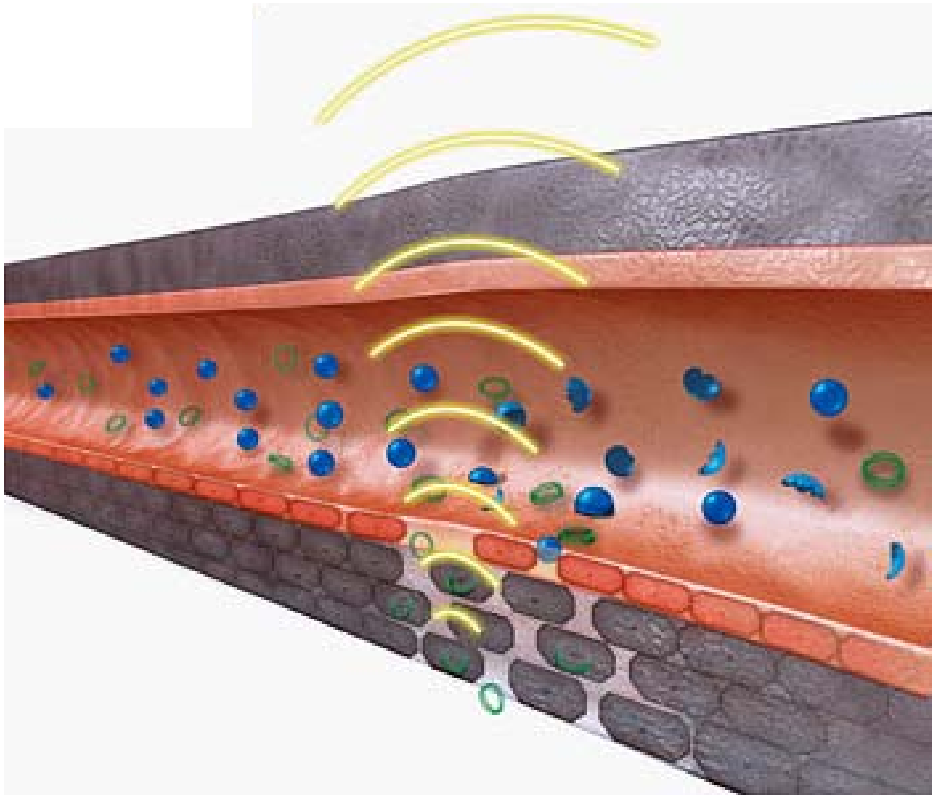
Camera (Photron Fastrax APX-RS):

20,000 frames/s

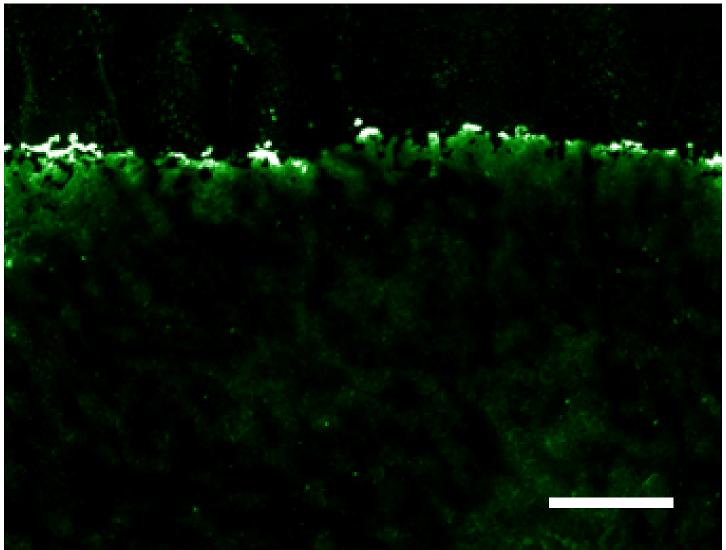
(50 µs/frame)



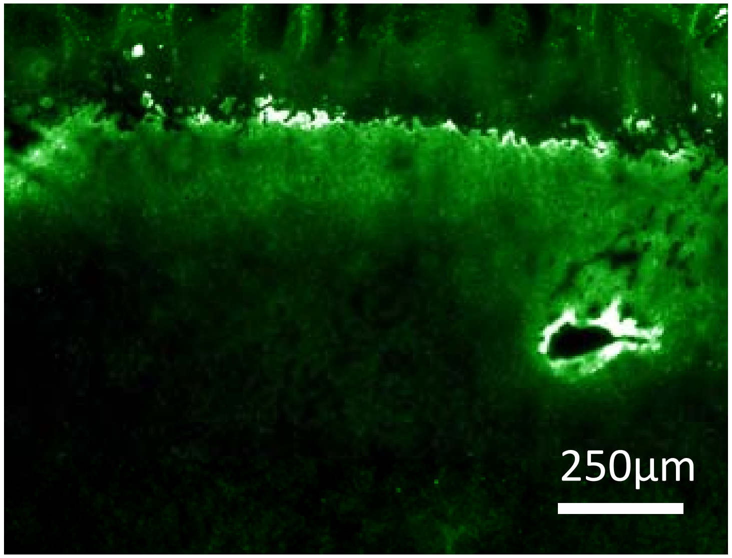
Drug and Gene Delivery Using Microbubbles



1. Focused ultrasound opens endothelial layer
2. Drug extravasates into the interstitium
3. Localized concentration of drugs



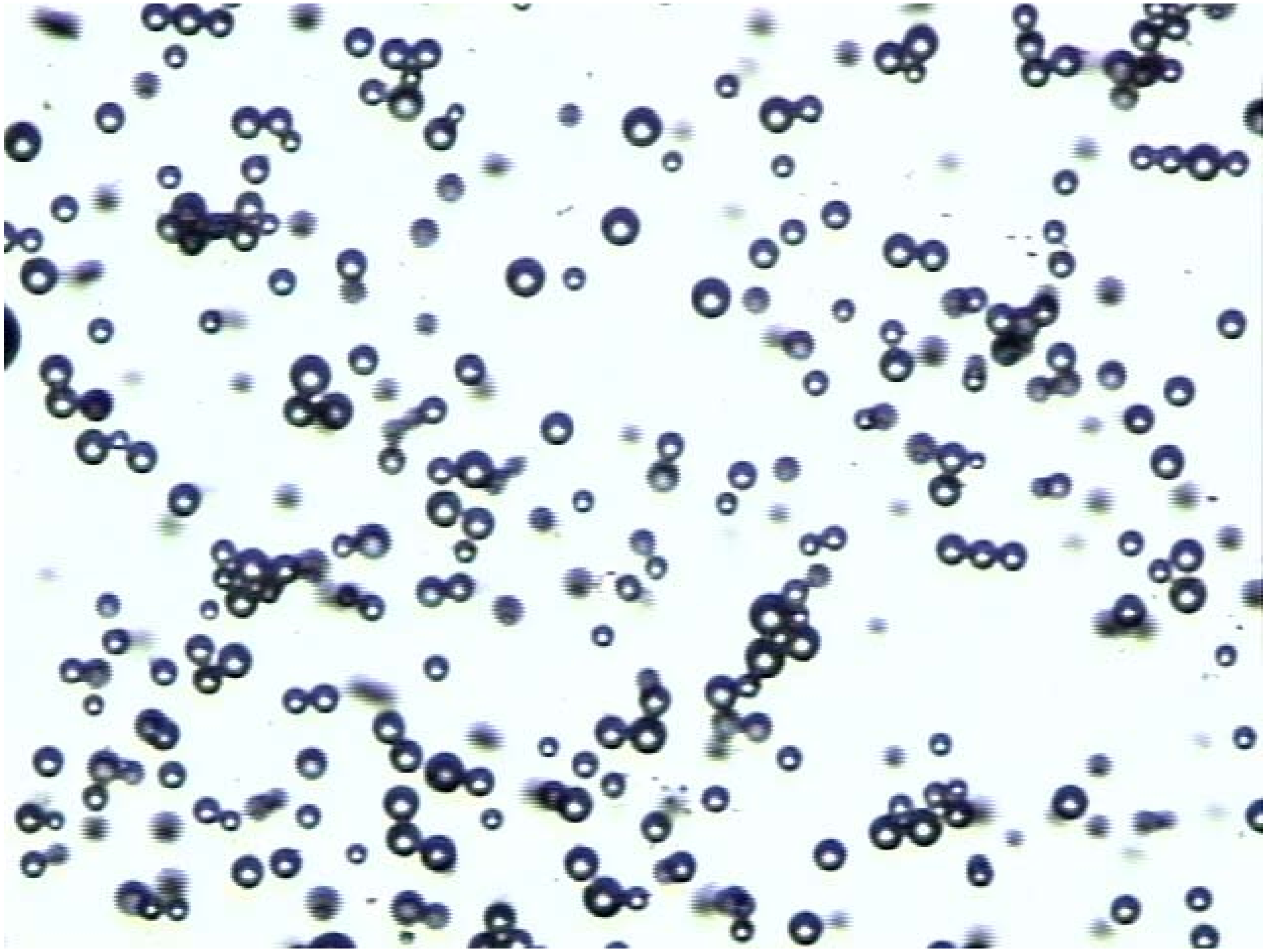
Control



Power– 1.37 W/cm^2

Data courtesy Joo Ha Hwang

Ultrasound Contrast Agents - Microbubbles



Micron-sized bubbles: Mean diameter between 1 – 3μm, Max < 10μm

Microbubbles go where RBCs go – throughout the vasculature.

Most are expelled from the lungs in minutes.

Contrast-Enhanced Ultrasound Imaging

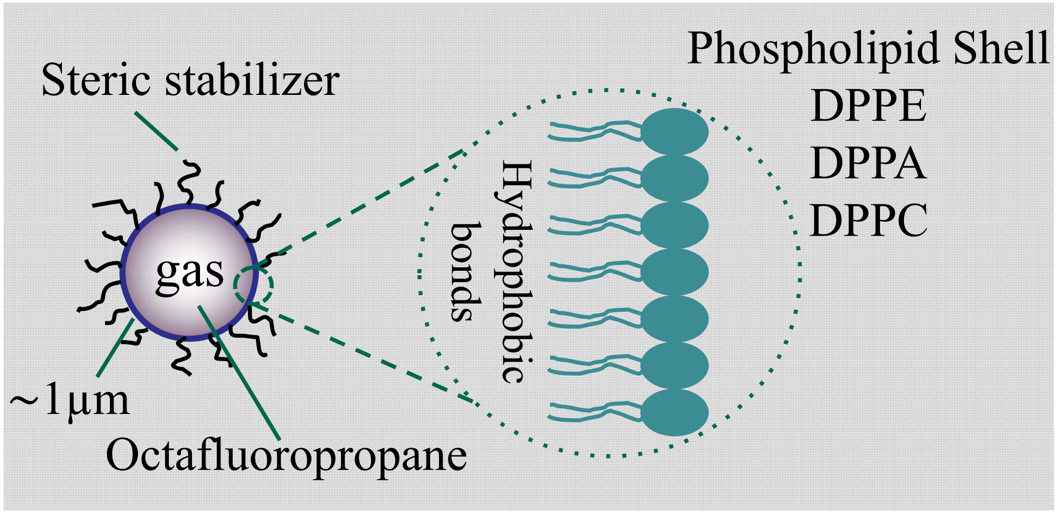
- Contrast agents perfusion in renal cortex and out to parenchyma in a mouse model.
- 13 MHz transducer, color Doppler.
- Image courtesy of Visualsonics

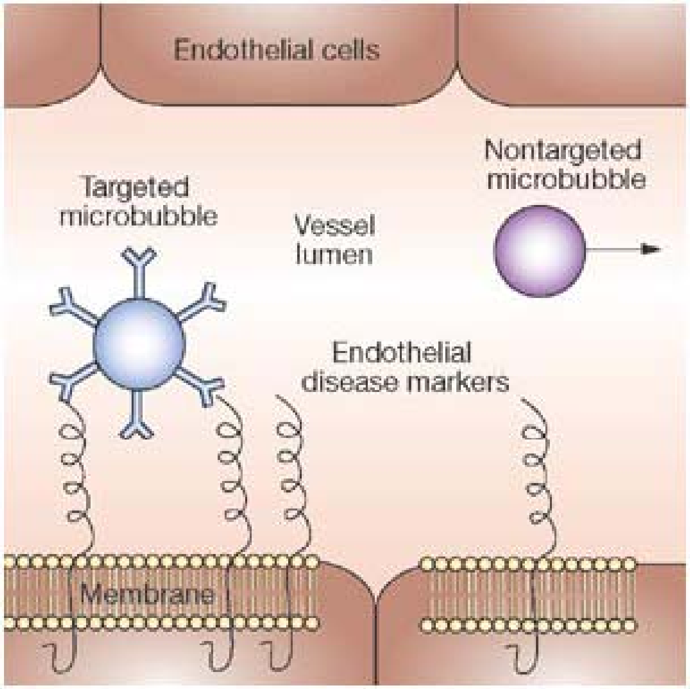
Does not cause the Bends: Requires Gas Supersaturation

An example of a supersaturated fluid subjected to an ultrasound pulse.

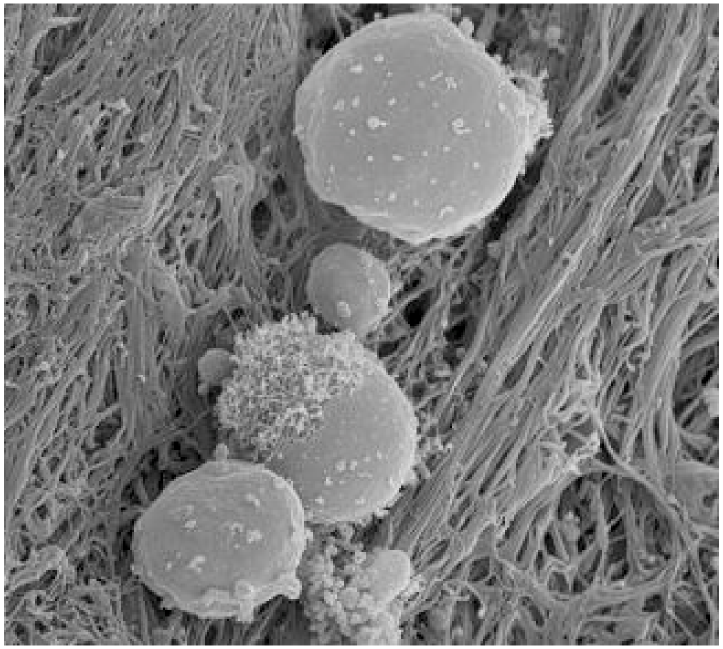
Bubbles injected into the vasculature do not grow,
they are expelled by the lungs.

Targeted Imaging and Therapy





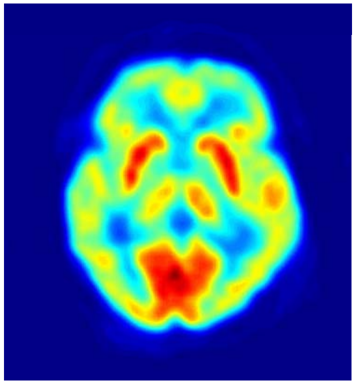
Villanueva FS and Wagner WR, "Ultrasound molecular imaging of cardiovascular disease," *Nat Clin Pract Cardiovasc Med*. (2008).



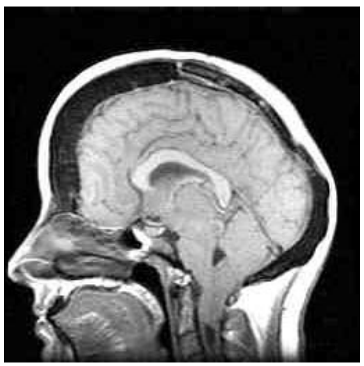
Targeting thrombosis: From E. Chung, University of Leicester, UK.

Targeson, Inc.
VisualSonics (now part of Sonosite)
Sonidel, LTD

Molecular Imaging: Why Ultrasound?




PET/CT



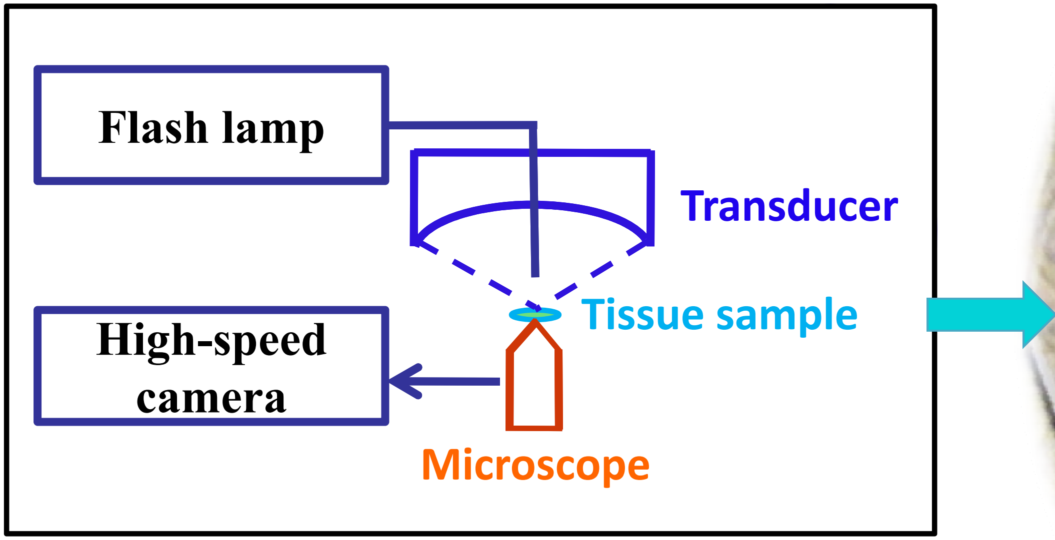
MRI

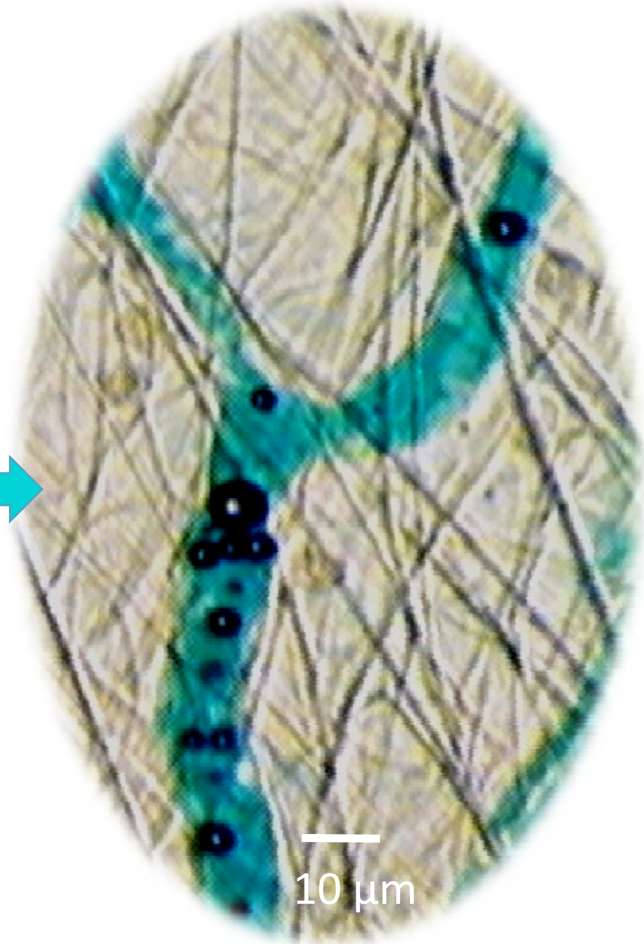
Ultrasound

- Low cost
- No radiation
- Non-invasive
- Highly portable
- Real time imaging

How do microbubbles respond in real blood vessels?

Experimental Schematic





Transducer :

Frequency:1MHz

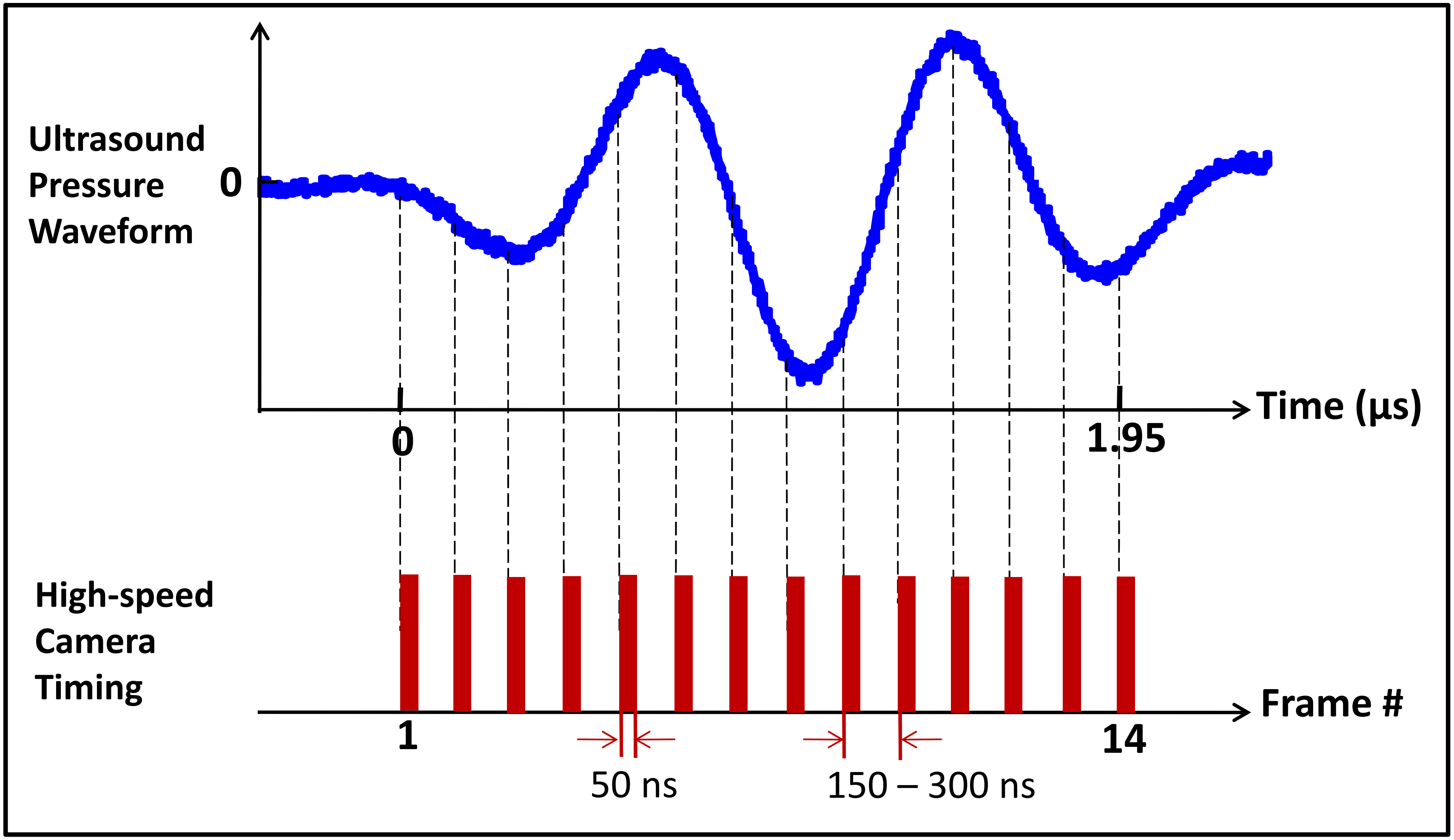
Cycle #: 1

P^{-}: 0.8 – 7 MPa

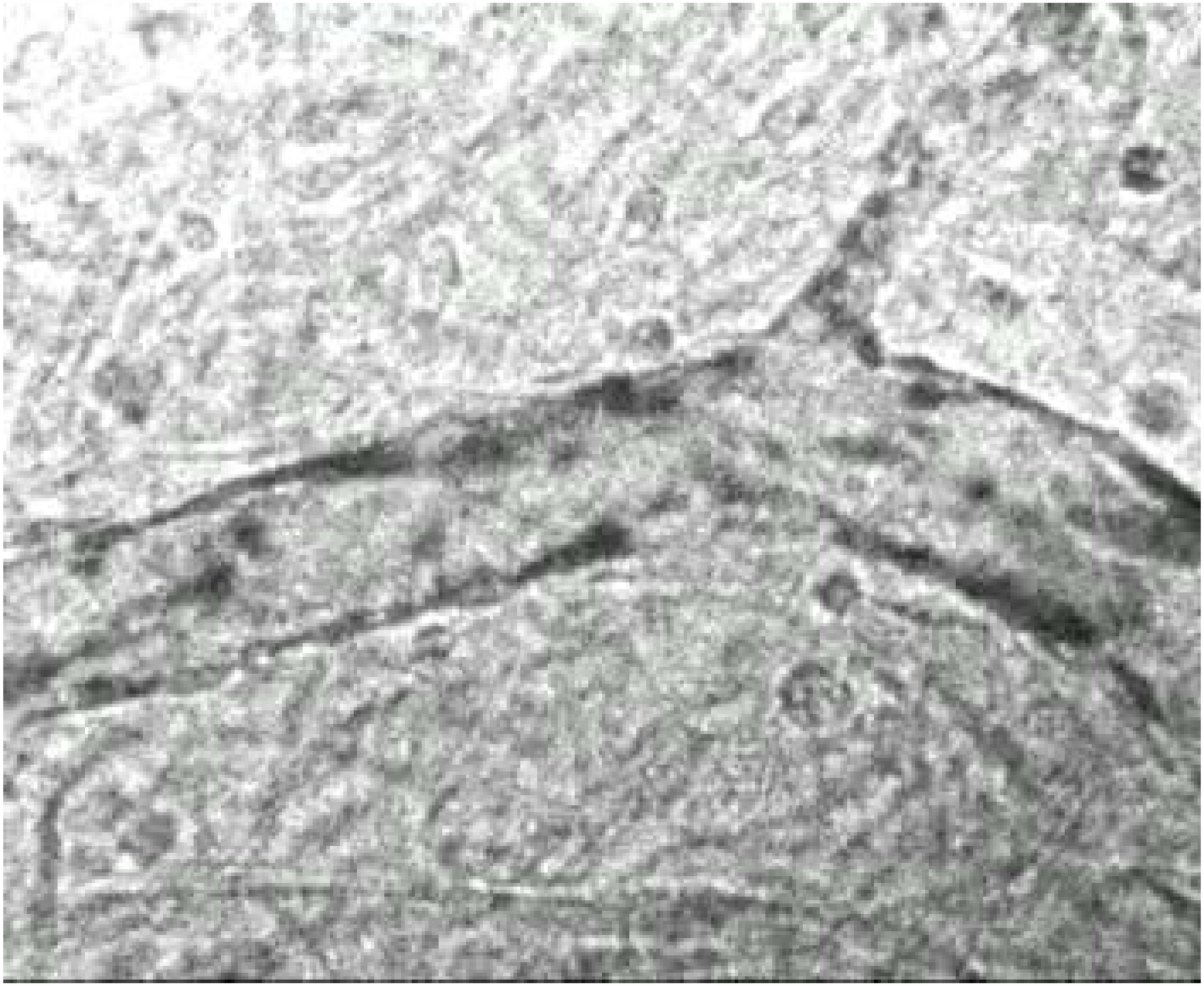
Ultra High-Speed Imaging

Imacon 200:
1360 x 1024 pixel resolution per frame
10-bit CCD sensor
200,000,000 frames per second
5 nsec per frame minimum
14 total frames, 7 twice

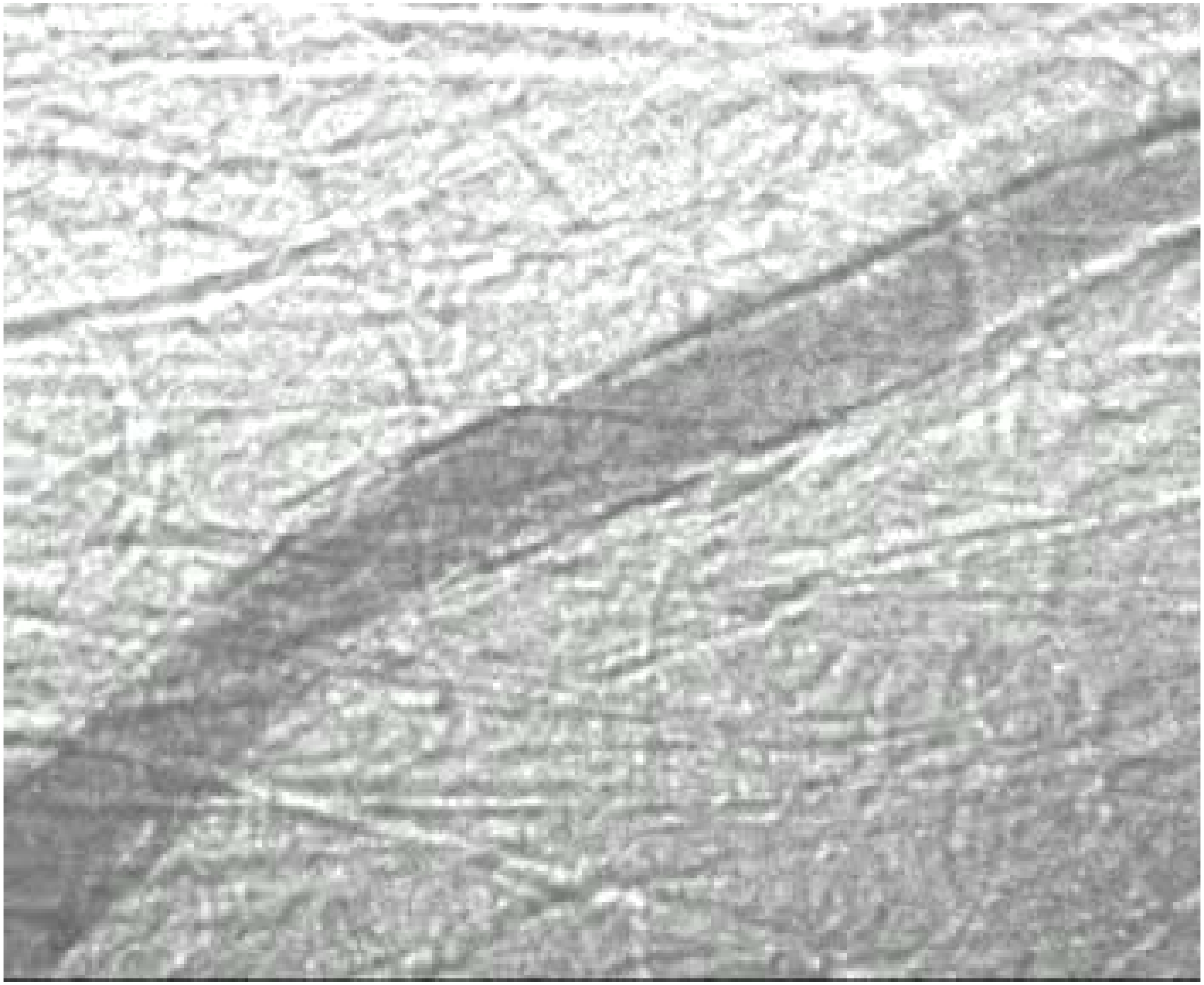
Timing Diagram



Vessel Response to Bubble Oscillations

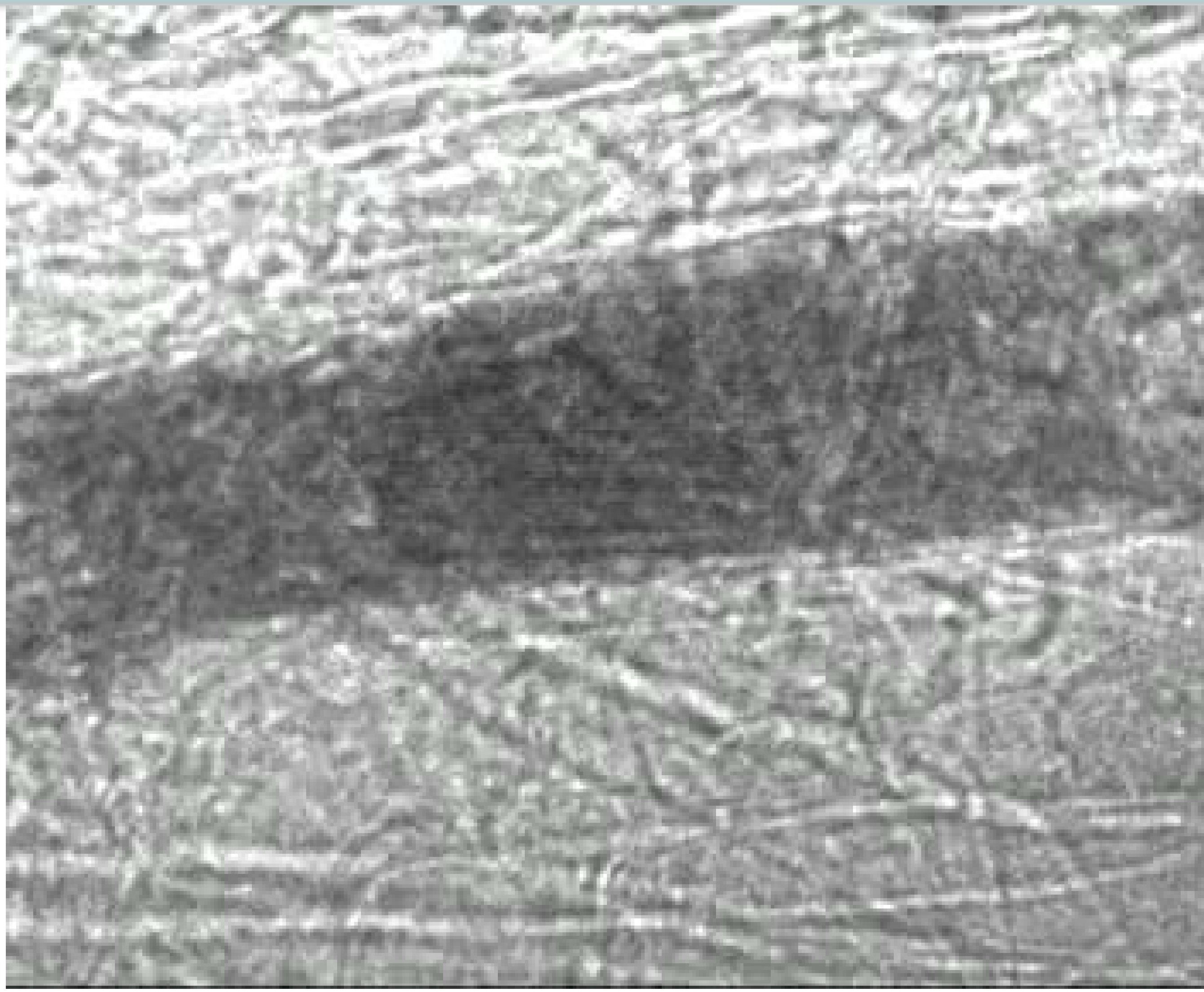


Vessel Distends and Invaginates



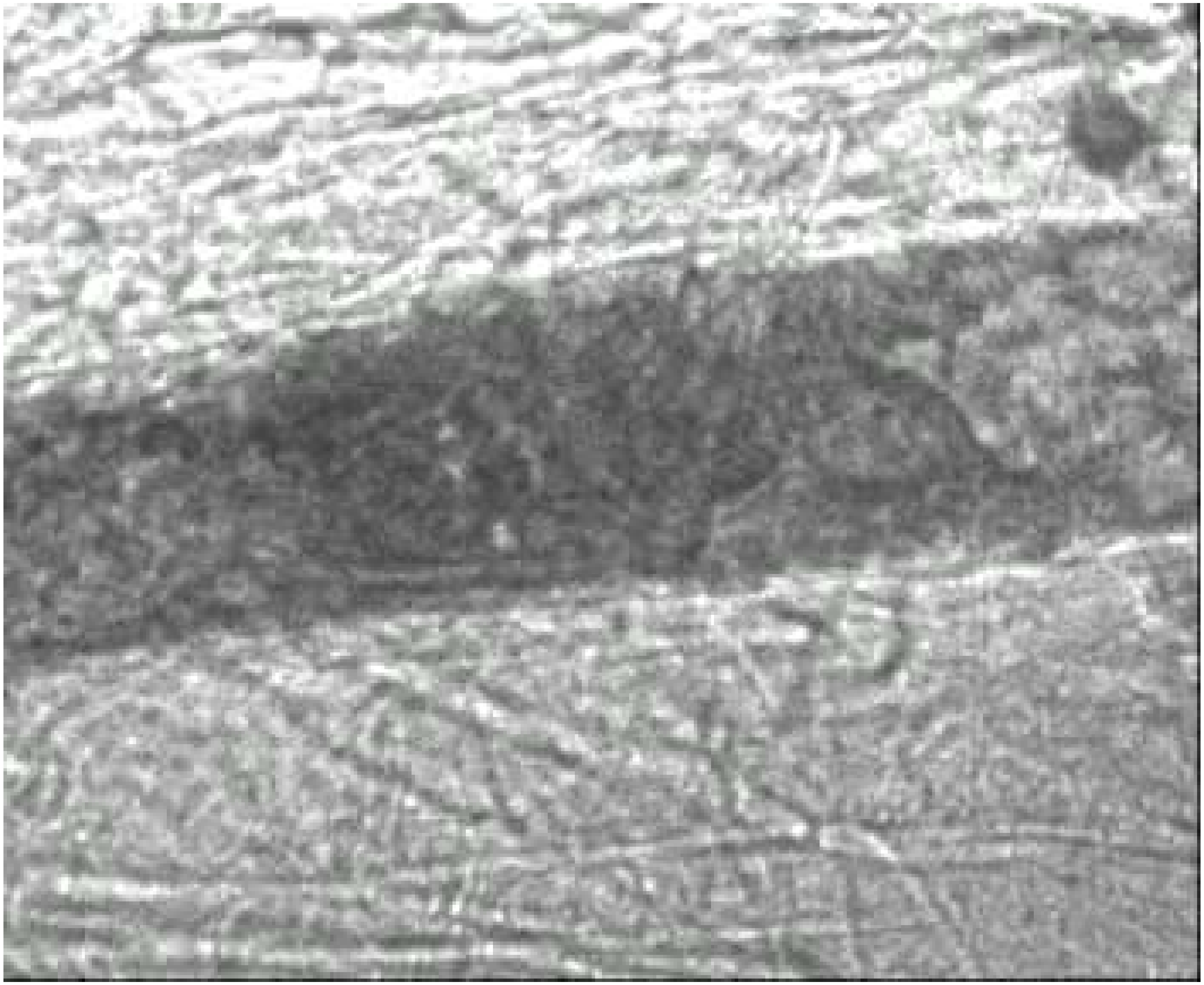
Vessel diameter = 20 μm; P^- = 1 MPa

Vessel Invagination



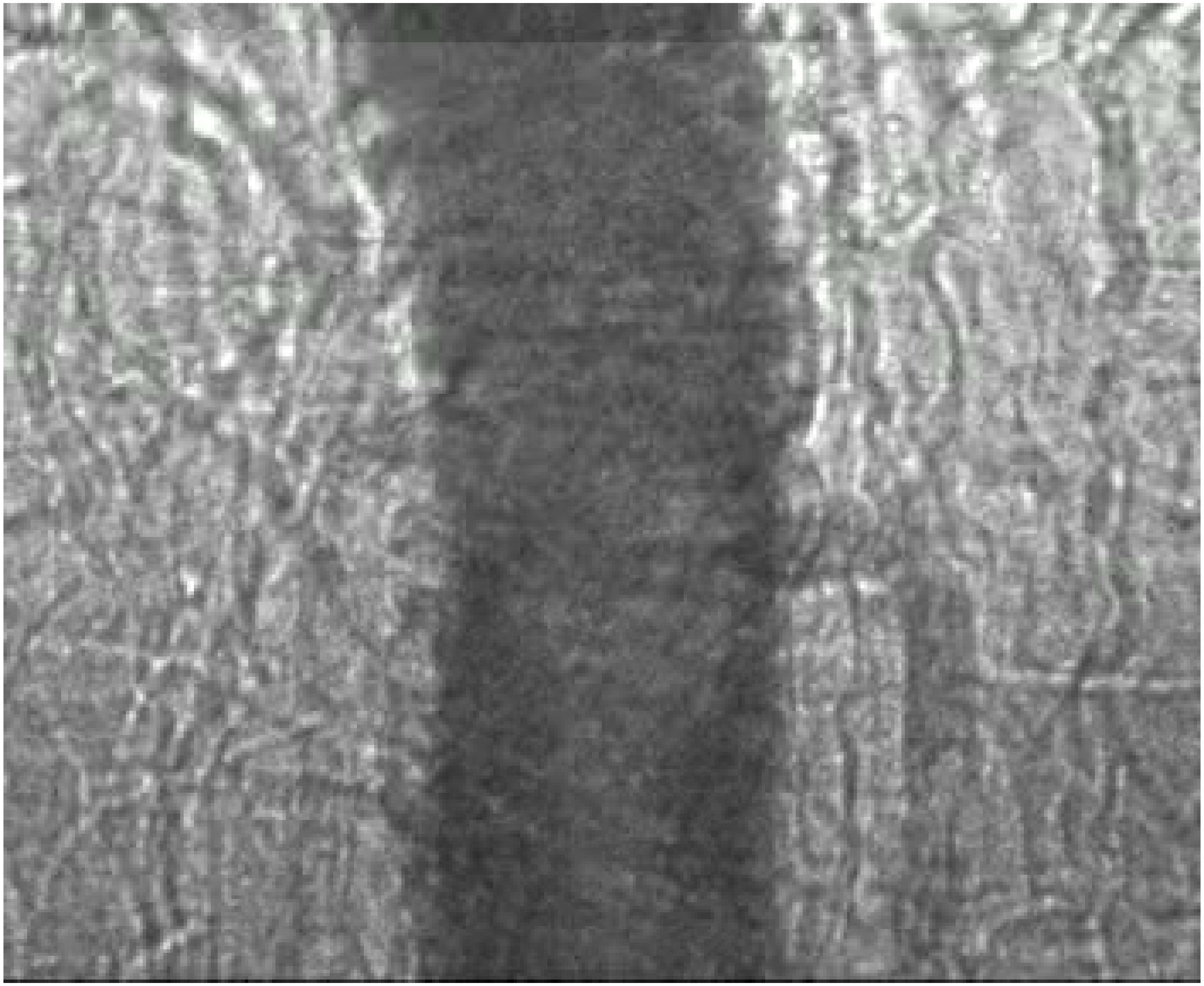
Vessel diameter = 46 μm; P^- = 7 MPa

Another Vessel Invagination Example



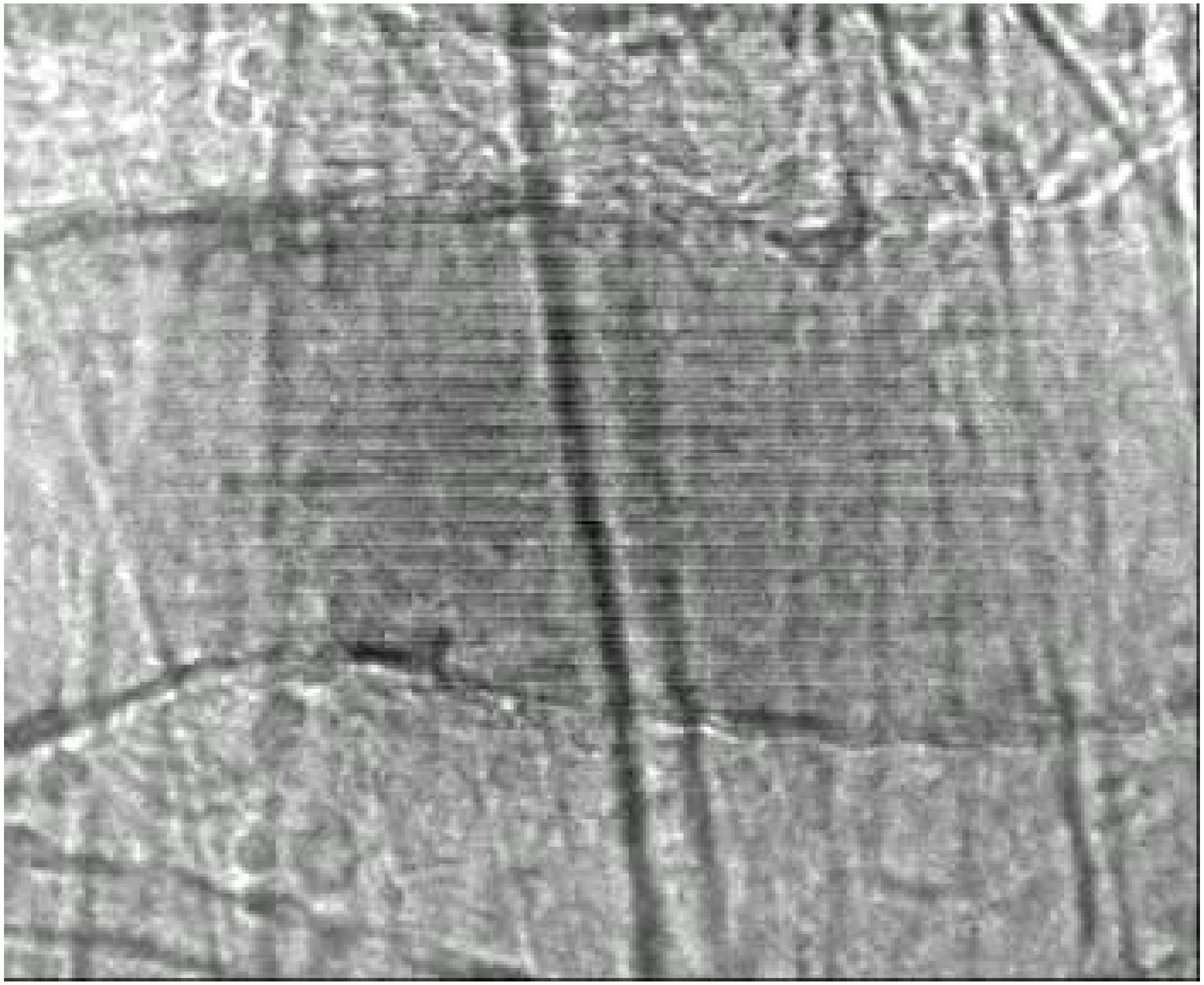
Vessel diameter = 22 μm; P^- = 4 MPa

Close-up Vessel Invagination



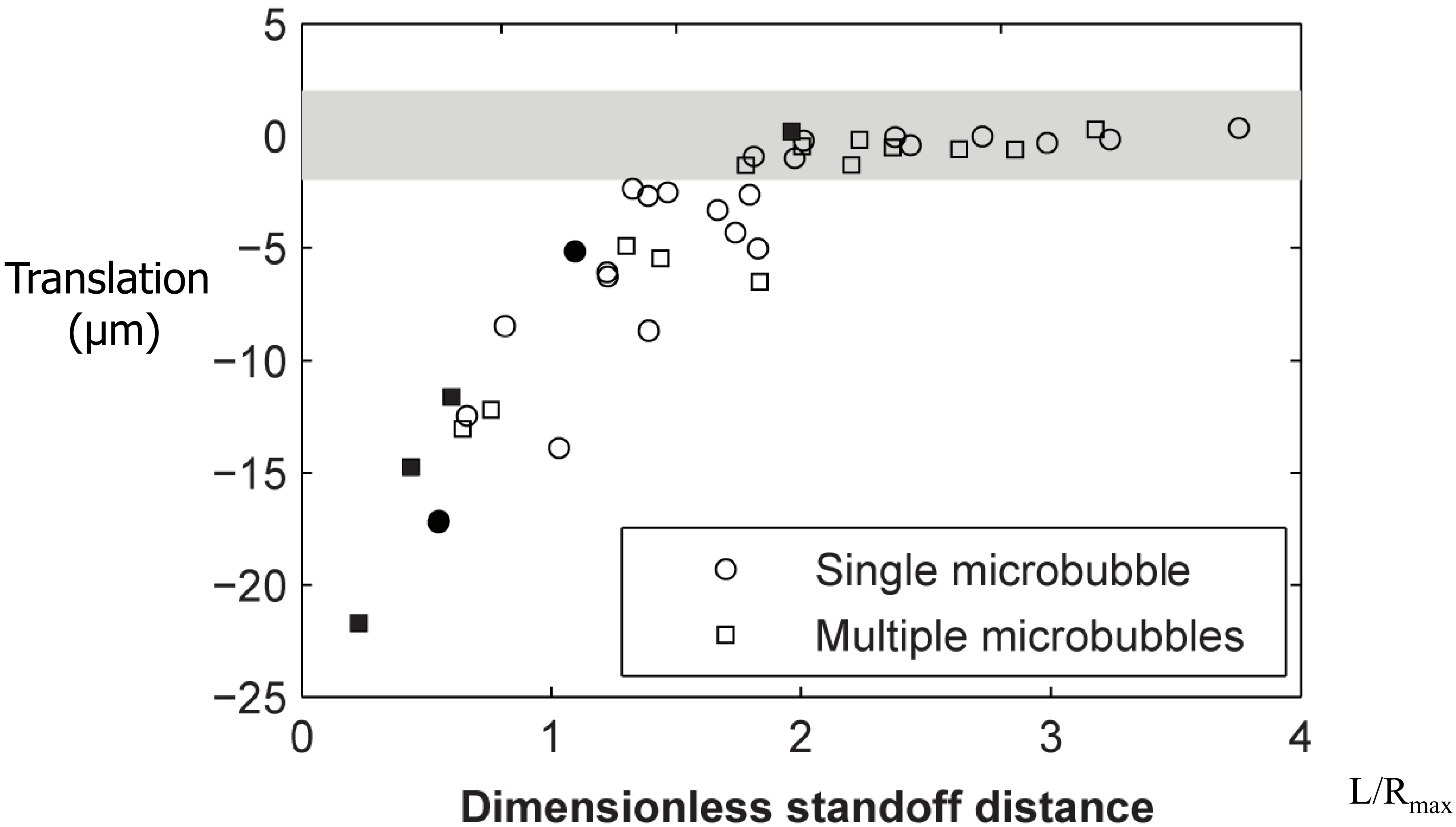
Vessel diameter = 35 μm; P^- = 4 MPa

Vessel Response Depends on Proximity of Bubble

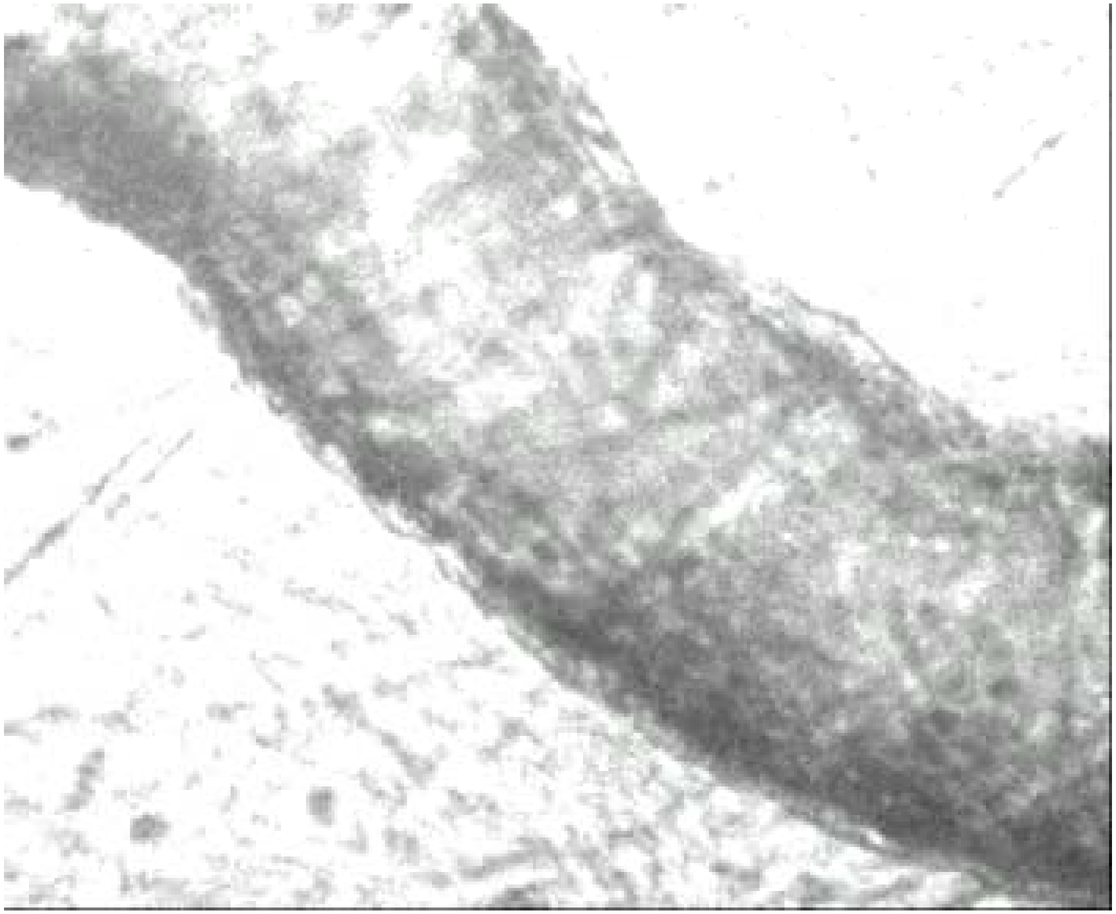


- Vessel diameter = 71 µm;
- Peak negative pressure = 4.3 MPa;
- Vessel dilation = 5 µm ; invagination = 10 µm

Pooled Data


Translation (μm)
5
0
−5
−10
−15
−20
−25
0
1
2
3
4
Single microbubble
Multiple microbubbles
Dimensionless standoff distance
L/R max

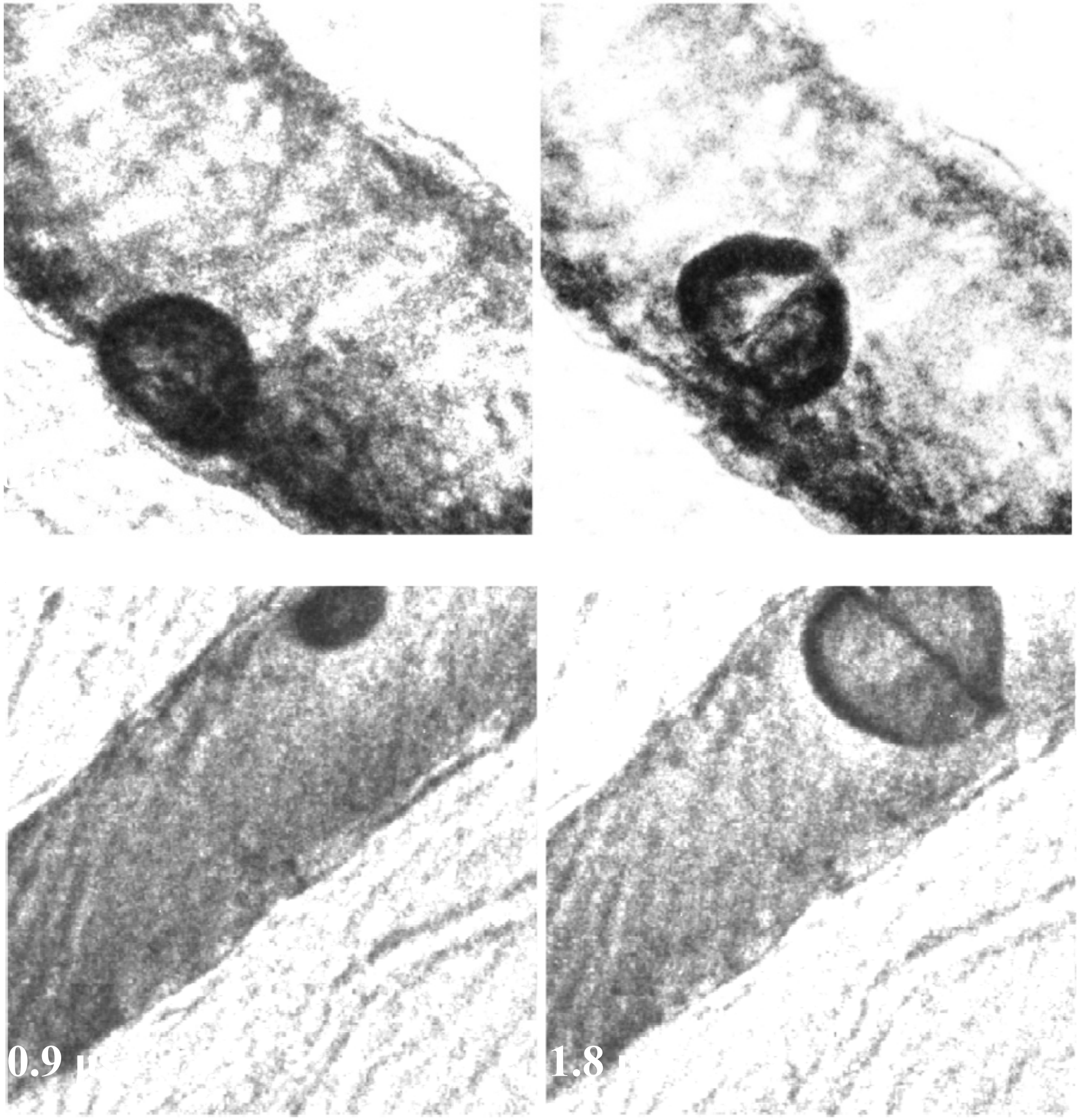
Microbubble Jetting



- Vessel diameter = 77 µm;
- Interframe time = 600 ns
- Peak negative pressure = 4.3 MPa;
- Vessel dilation = 1 µm; invagination = 7 µm

Microbubble Always Jets *Away* from Nearest Wall

Expansion | Re-expansion

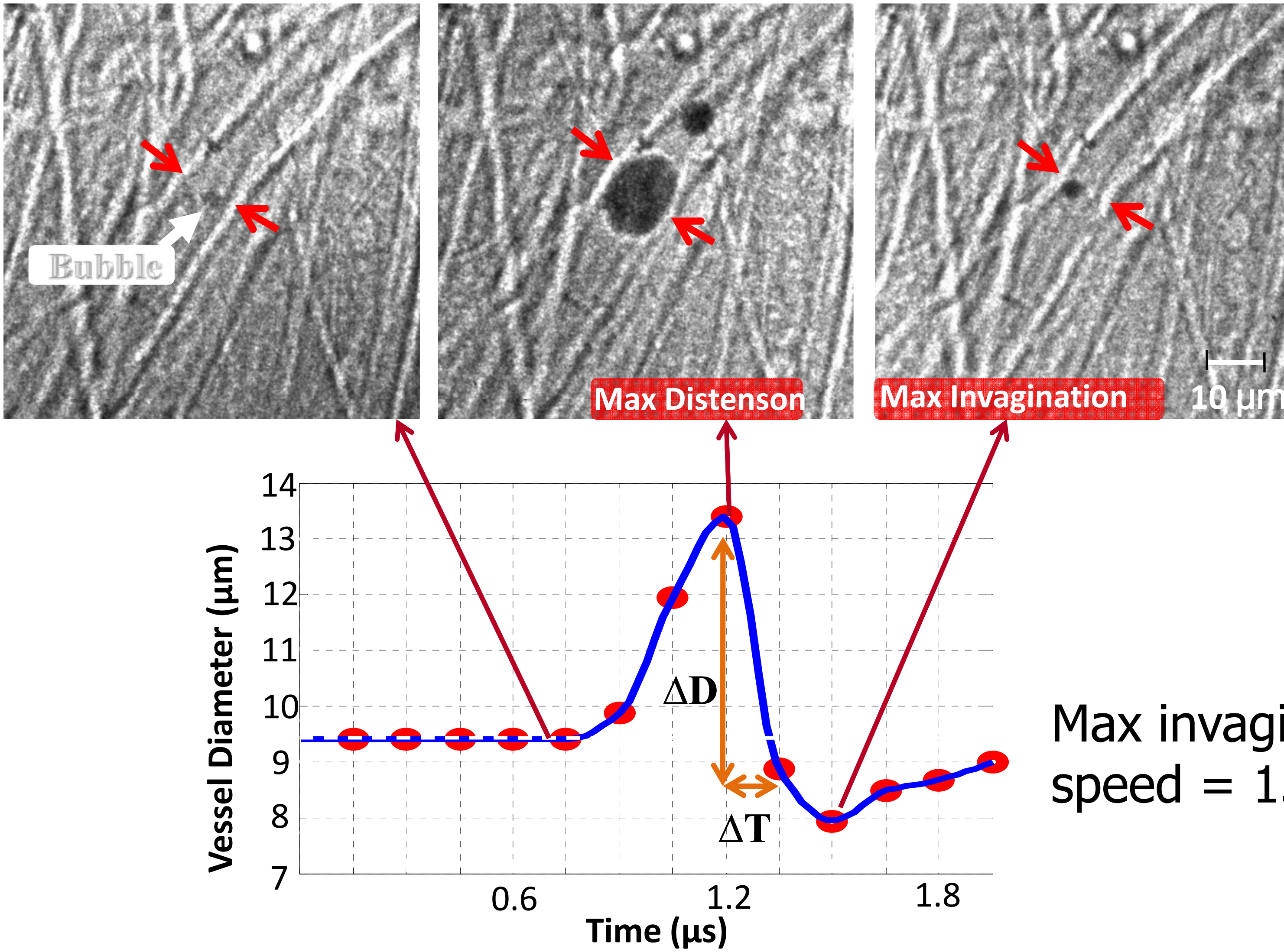


P^-: 4.3 MPa
Vessel = 77 μm
Jet velocity = 27 m/s

P^- = 3.1 MPa
Vessel = 46 μm
Jet velocity = 42 m/s

Water hammer ≈ 50 MPa.

Quantitative Measurements

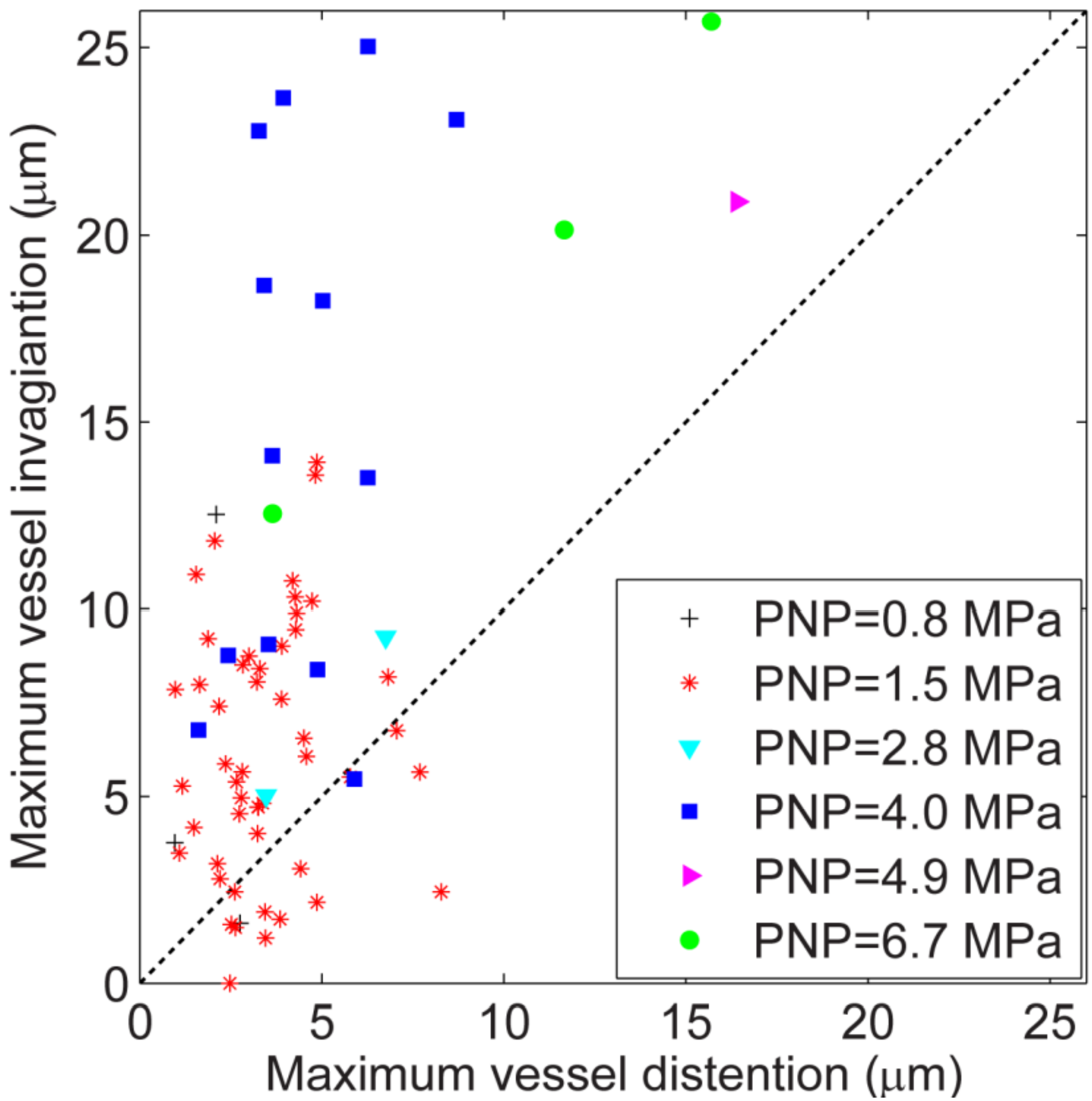


Max invagination speed = 15 m/s

Tissue response time scale on order of μs:
Not an evoked response, a mechanical response

Invagination vs. Distension

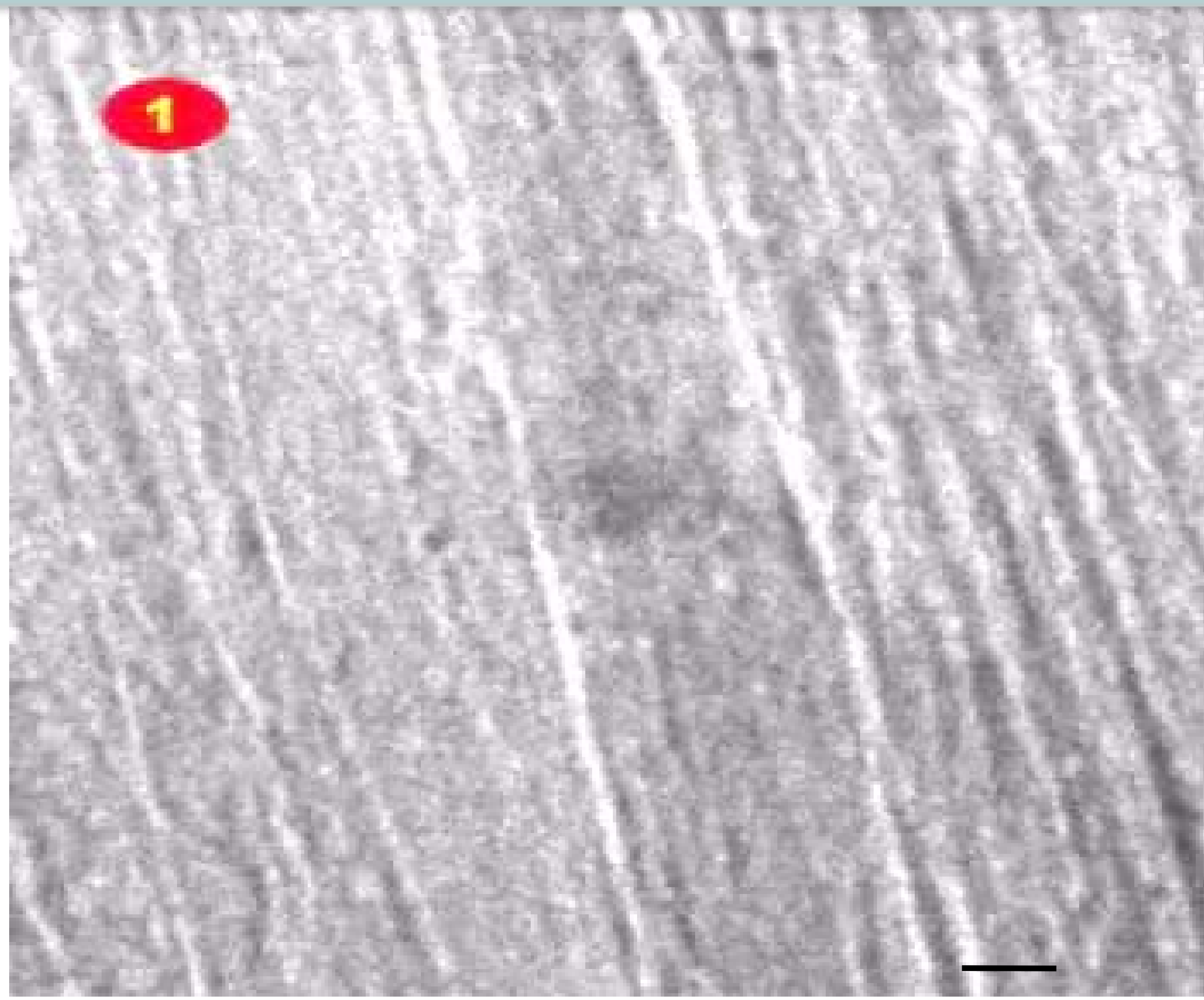
Vessel sizes: 10 - 80 μm
Pressures: 0.8 – 6.7 MPa



Example of Small Vessel at High Pressure

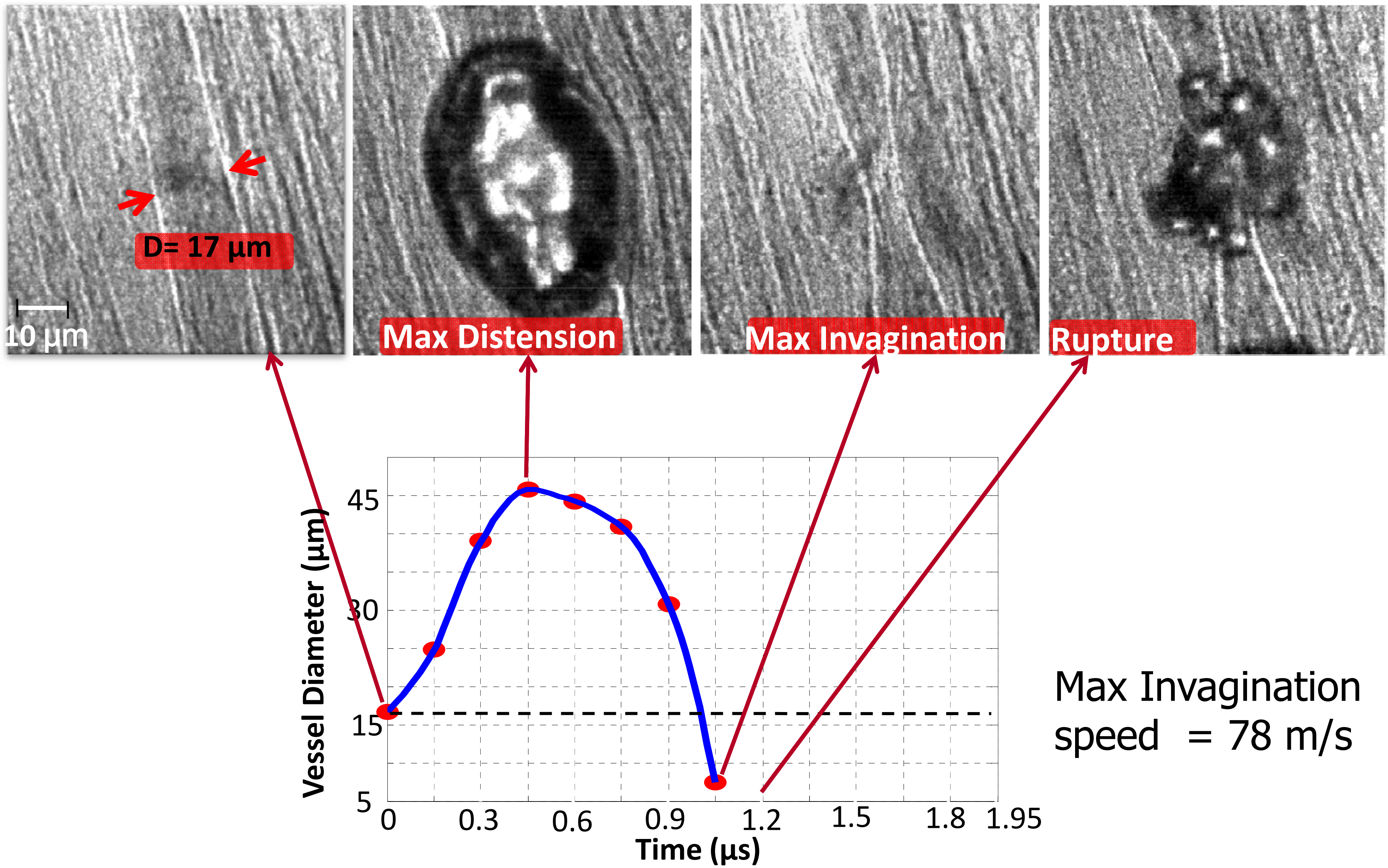
Vessel Size = 17 µm
P⁻ = 7 MPa

Vessel walls are highlighted.



After a single pulse, microbubble fragments extravasate into the interstitiam

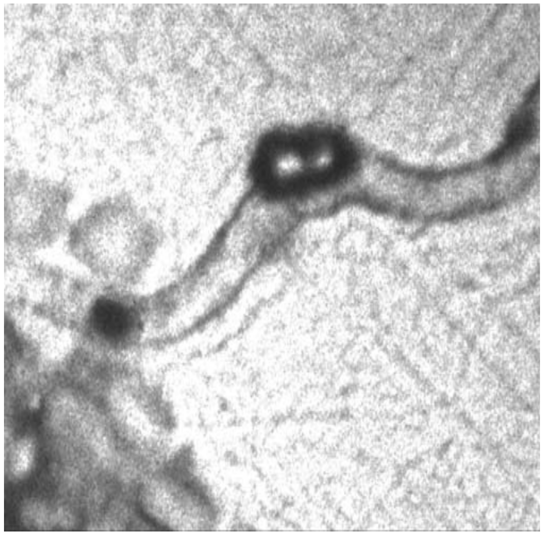
Quantitative Measurements



Max Invagination speed = 78 m/s

Rupture of a 50-µm Vessel

Before

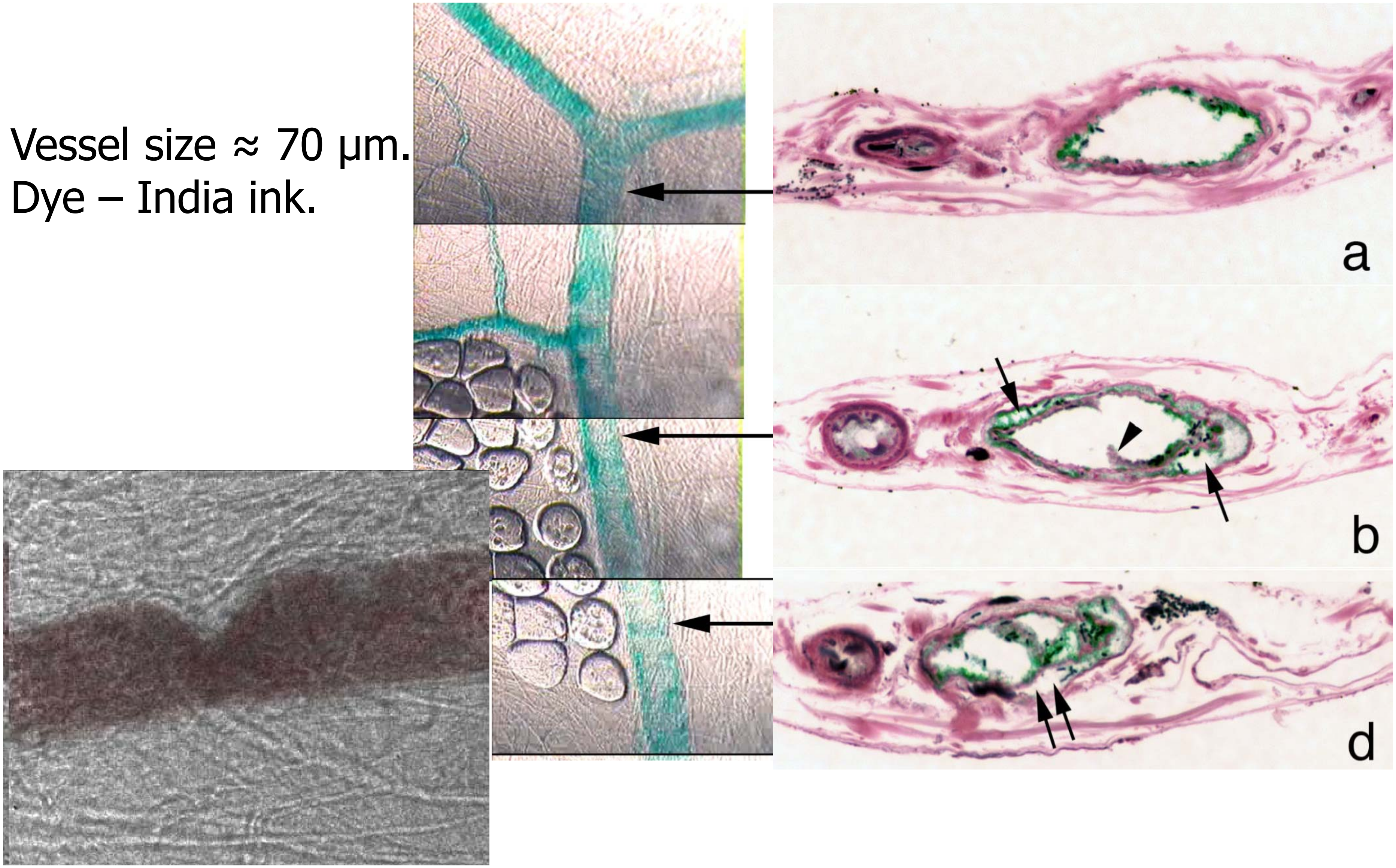


During

After

An Example of Microvessel Damage

- Vessel size ≈ 70 μm.
- Dye – India ink.



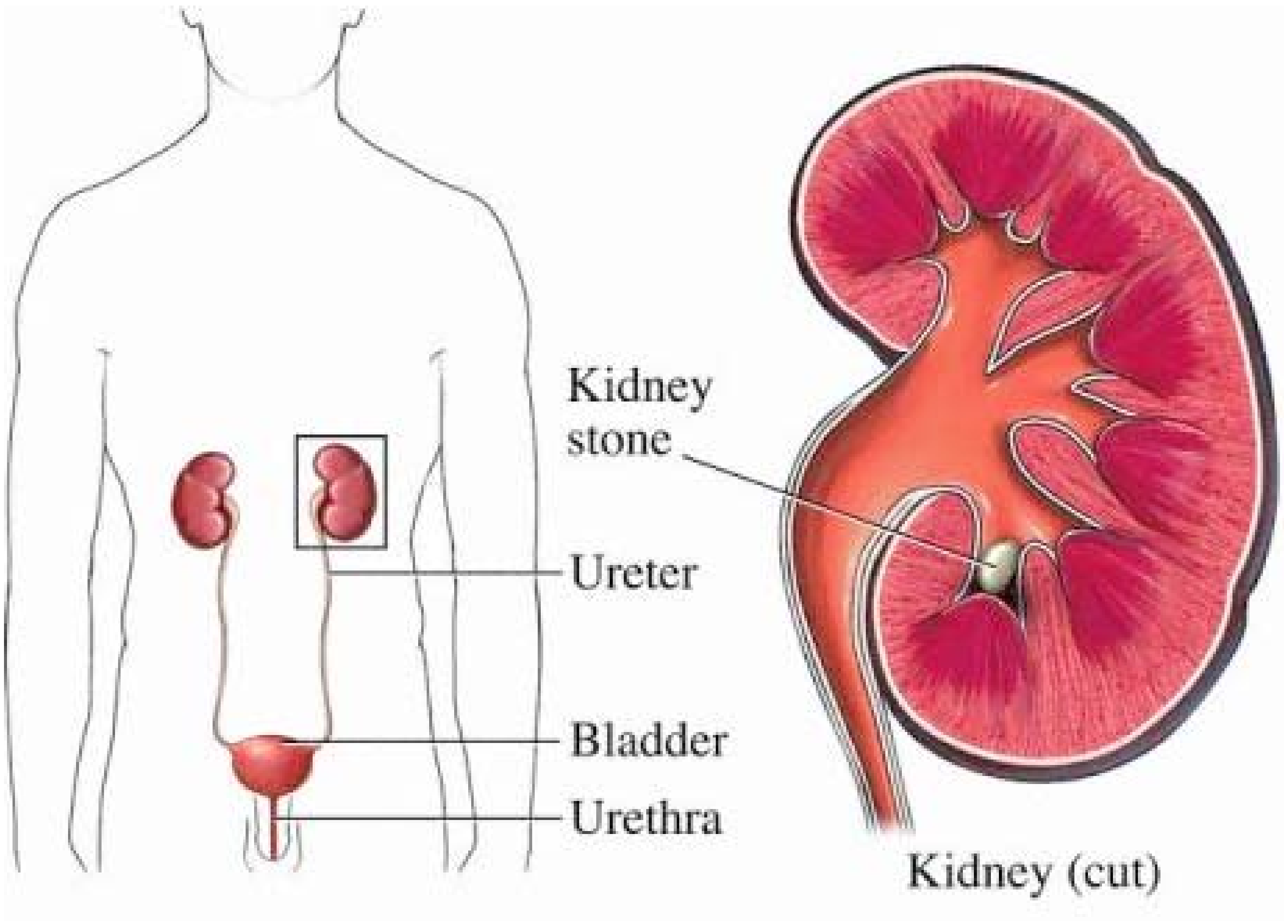
Mechanisms for Vascular Bioeffects from Bubbles

Rolling Stones (Mike Bailey, PI)

Goal is to pass kidney stones

Problems: Large stones can block the ureter

Small stones in lower pole not easily 'flushed'

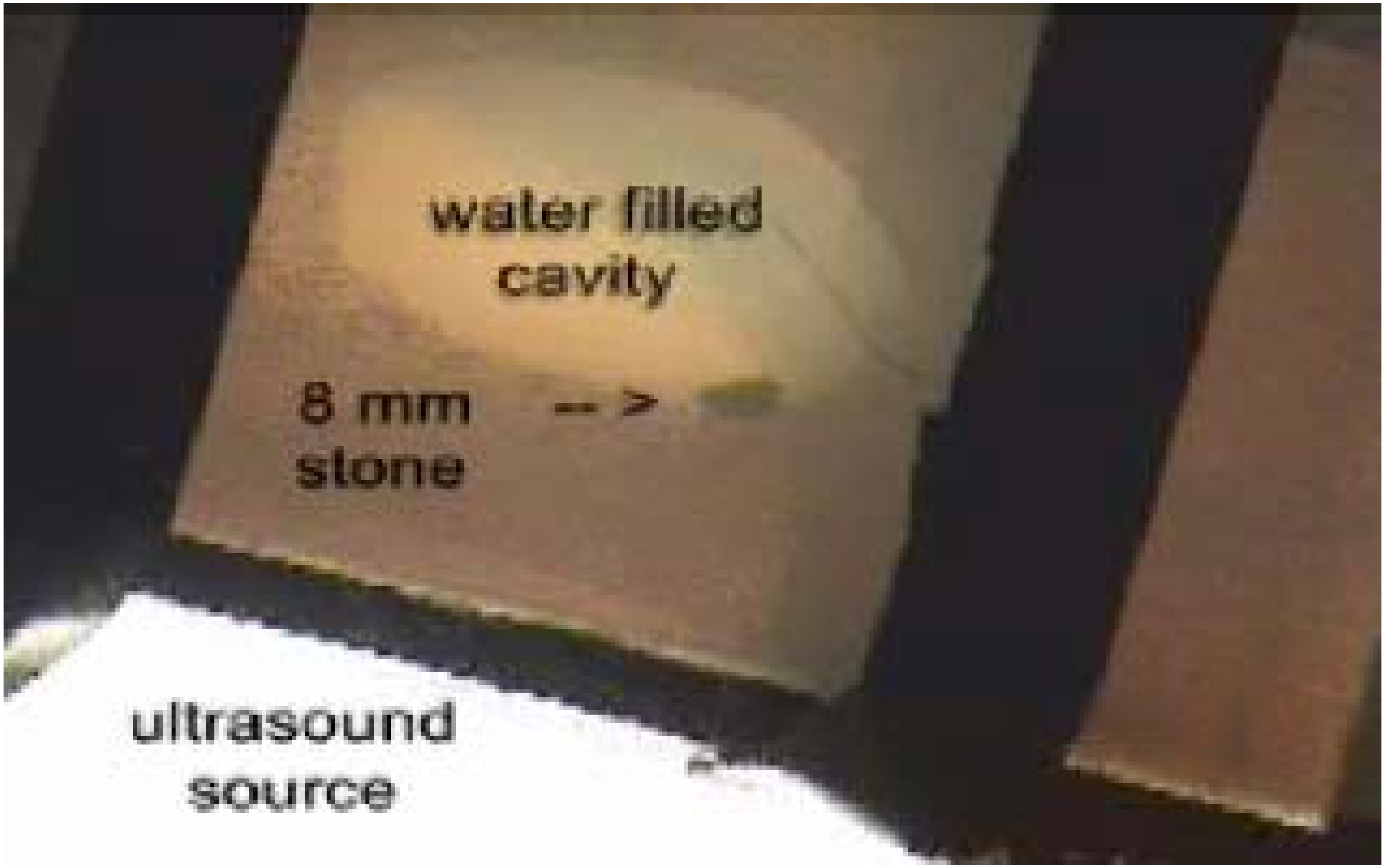


Hardware

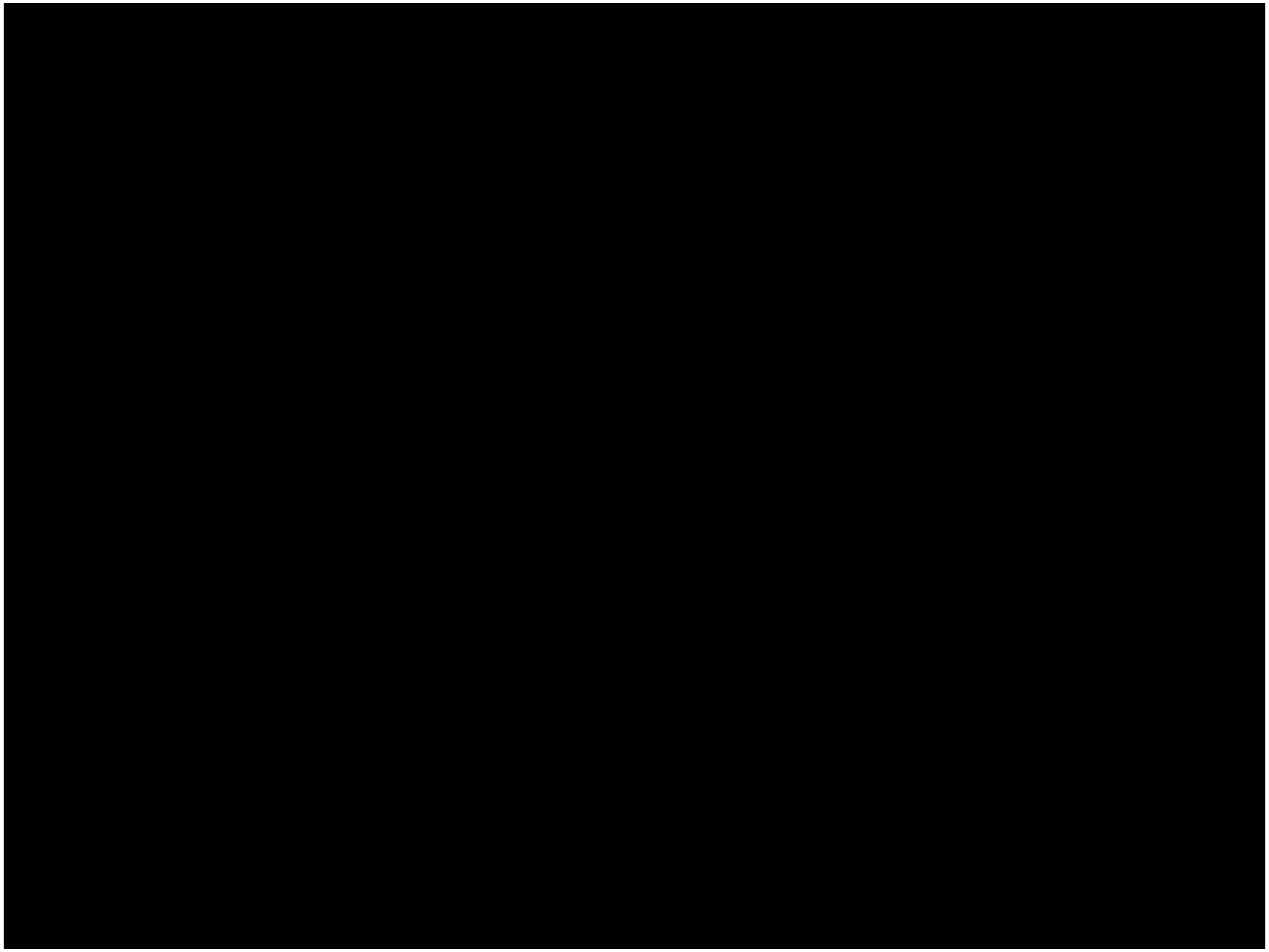
Clinical Diagnostic Scanheads (HDI P4-1, C5-2)

Verasonics Ultrasound Engine

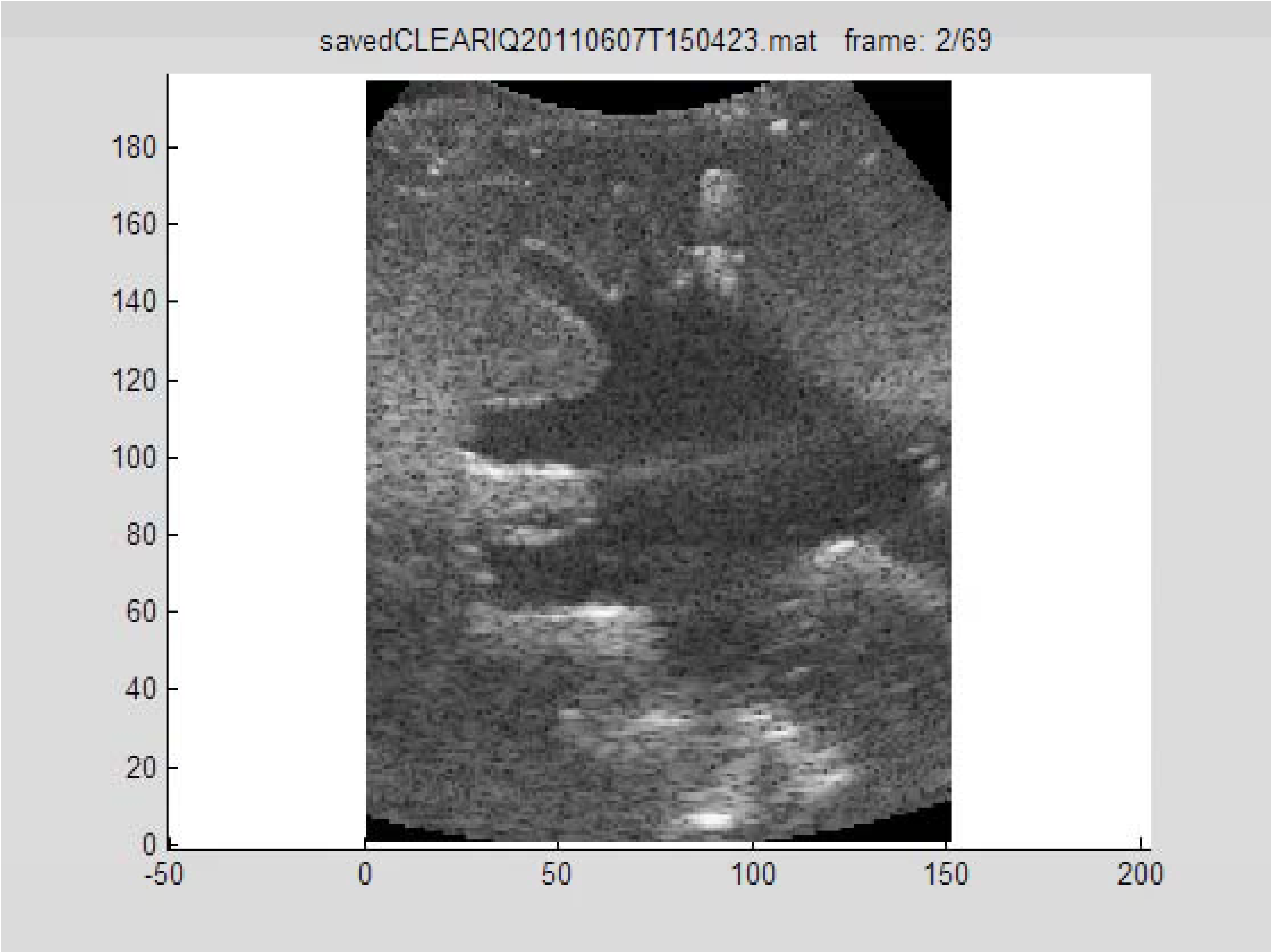
Proof of Concept in Gel



Proof of Concept in Pig

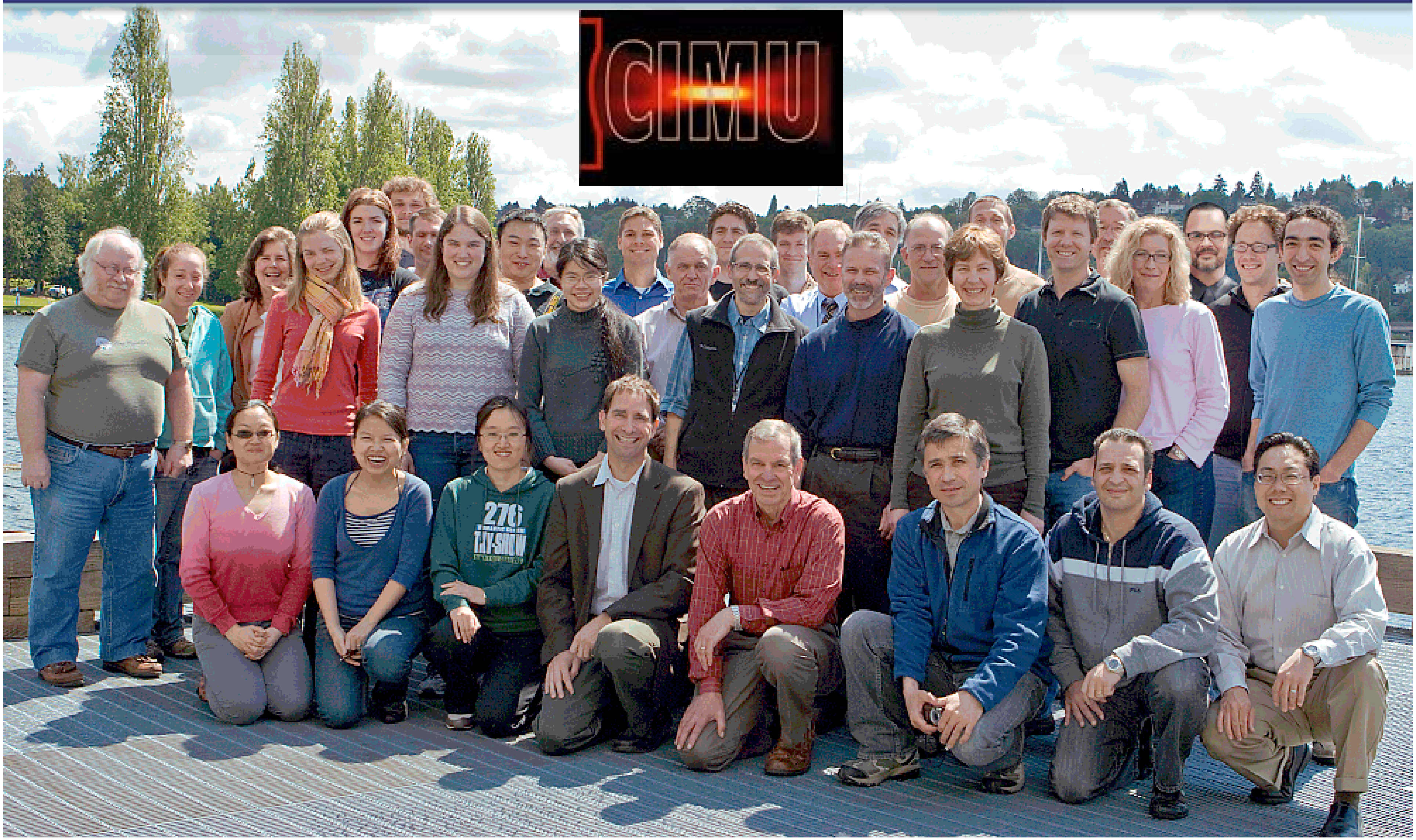


B-Mode Imaging of Rolling Stone



Endoscopic Imaging of Rolling Stone

THANK YOU!



Funding by NIH NIBIB, NIAMS, and NIDDKD

Cavitation Rheology:
Characterizing tissue viscoelastic properties

Cavitation Rheology

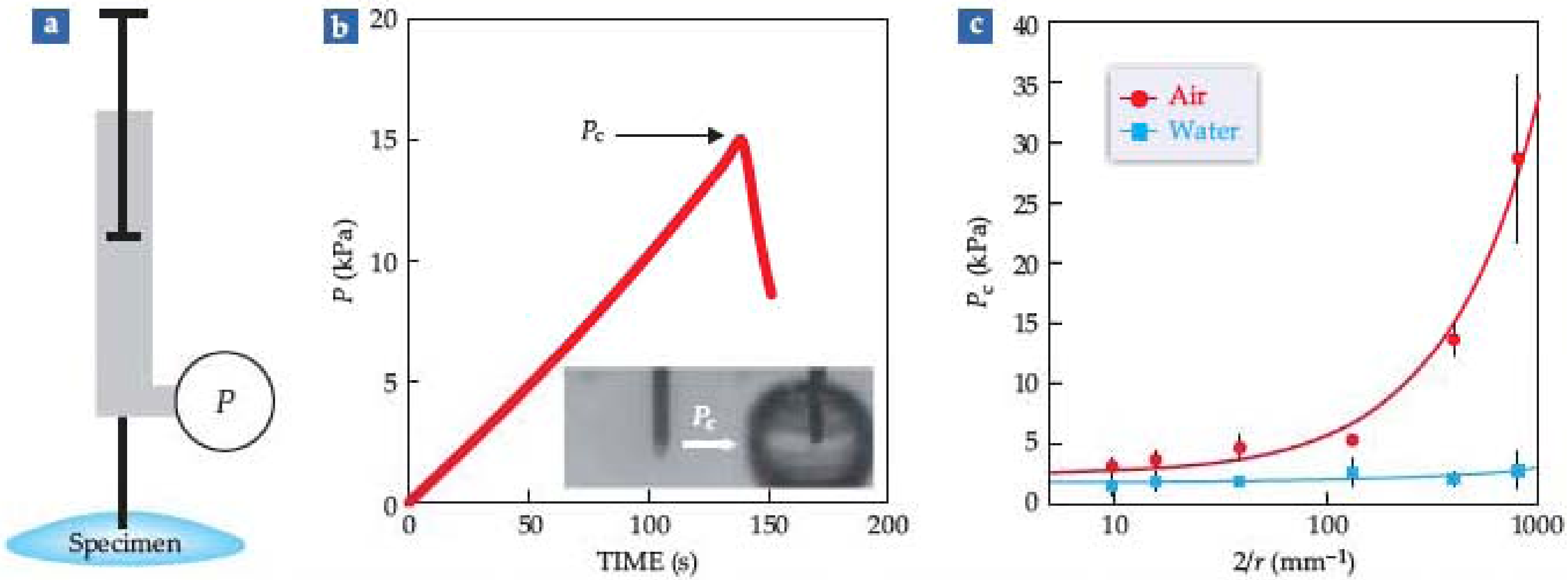


Image courtesy of A. Crosby and J. McManus, Phys. Today Feb 2011

a) Air-filled syringe generates pressure inside material

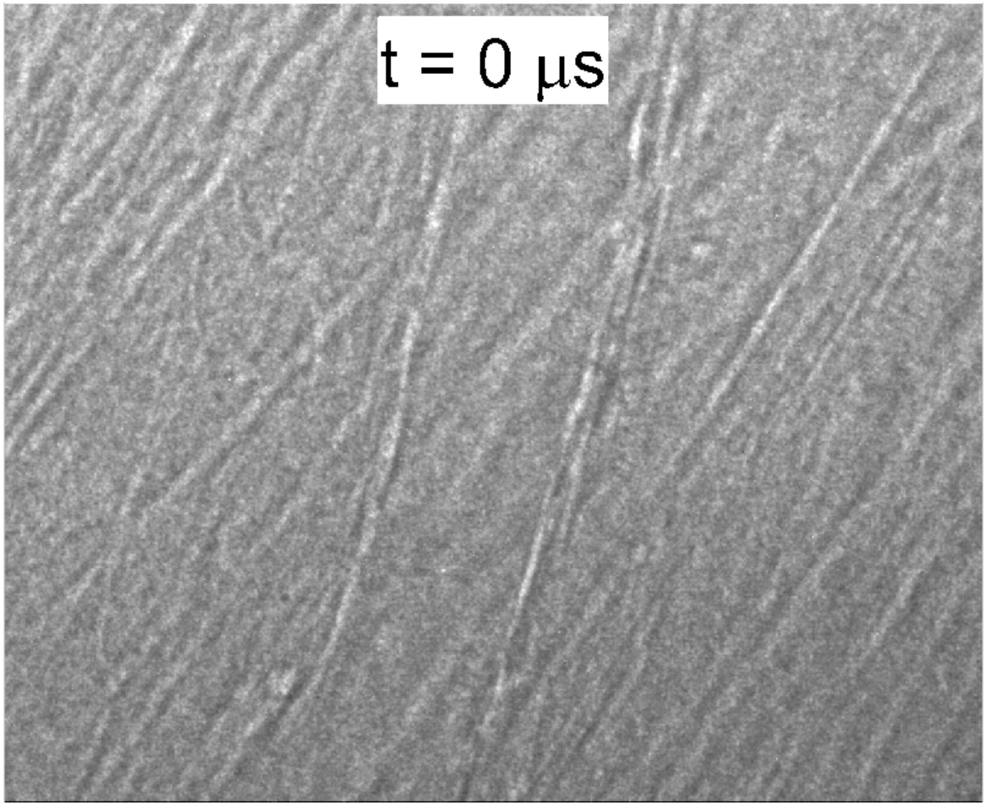
b) At Critical pressure, bubble expands quickly

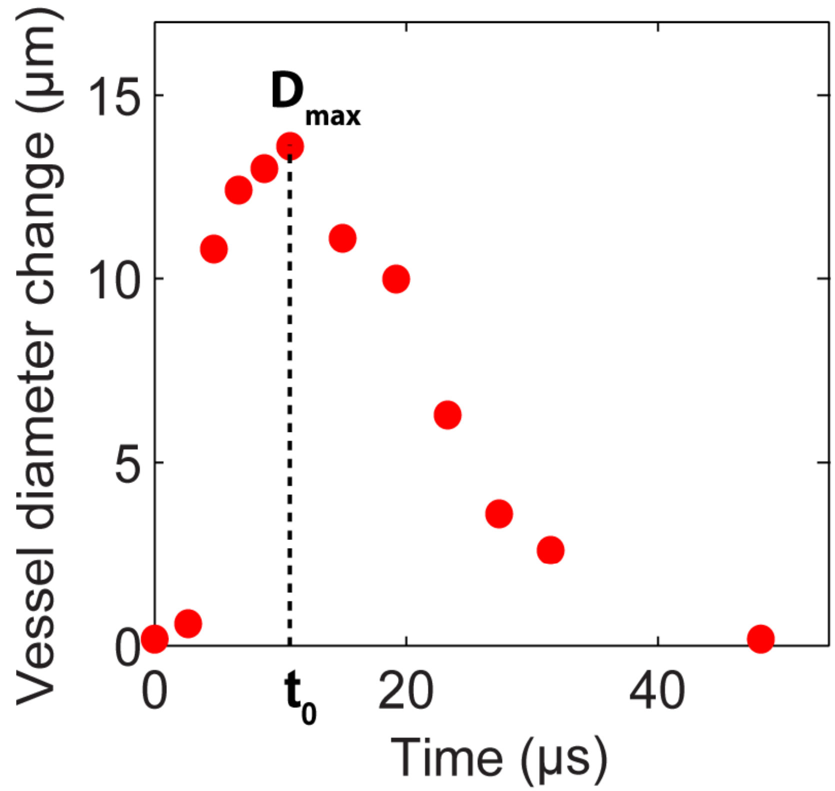
c) Critical pressure is related to elastic modulus

Caveat: Surface tension can also play a role (and be determined)

$$P_c = \frac{5}{6}E + \frac{2\gamma}{r}$$

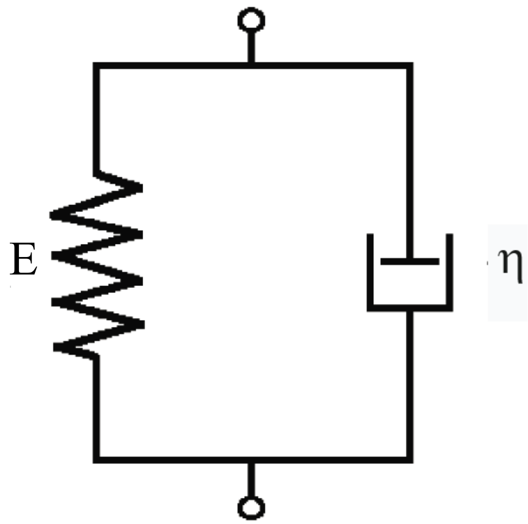
Relaxation Example





Modeling (linear) Viscoelastic Material

- A Voigt model was used to fit the experimental data to get the relaxation time constant from the best-fit curve.



Voigt model

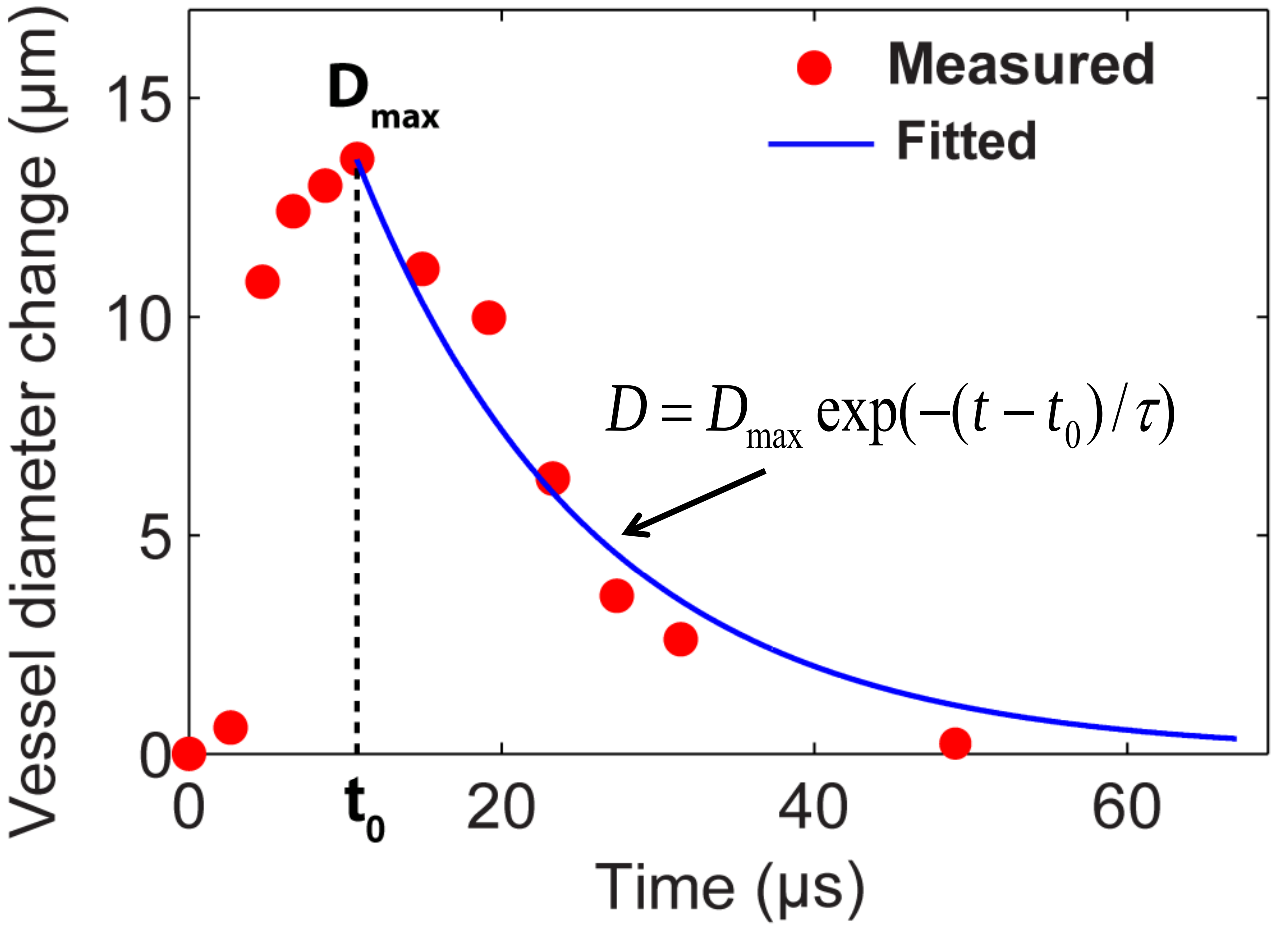
Maxwell model

$$D = D_{max} \exp[-t / \tau]$$

$$\tau = \eta / E$$

τ : relaxation time constant

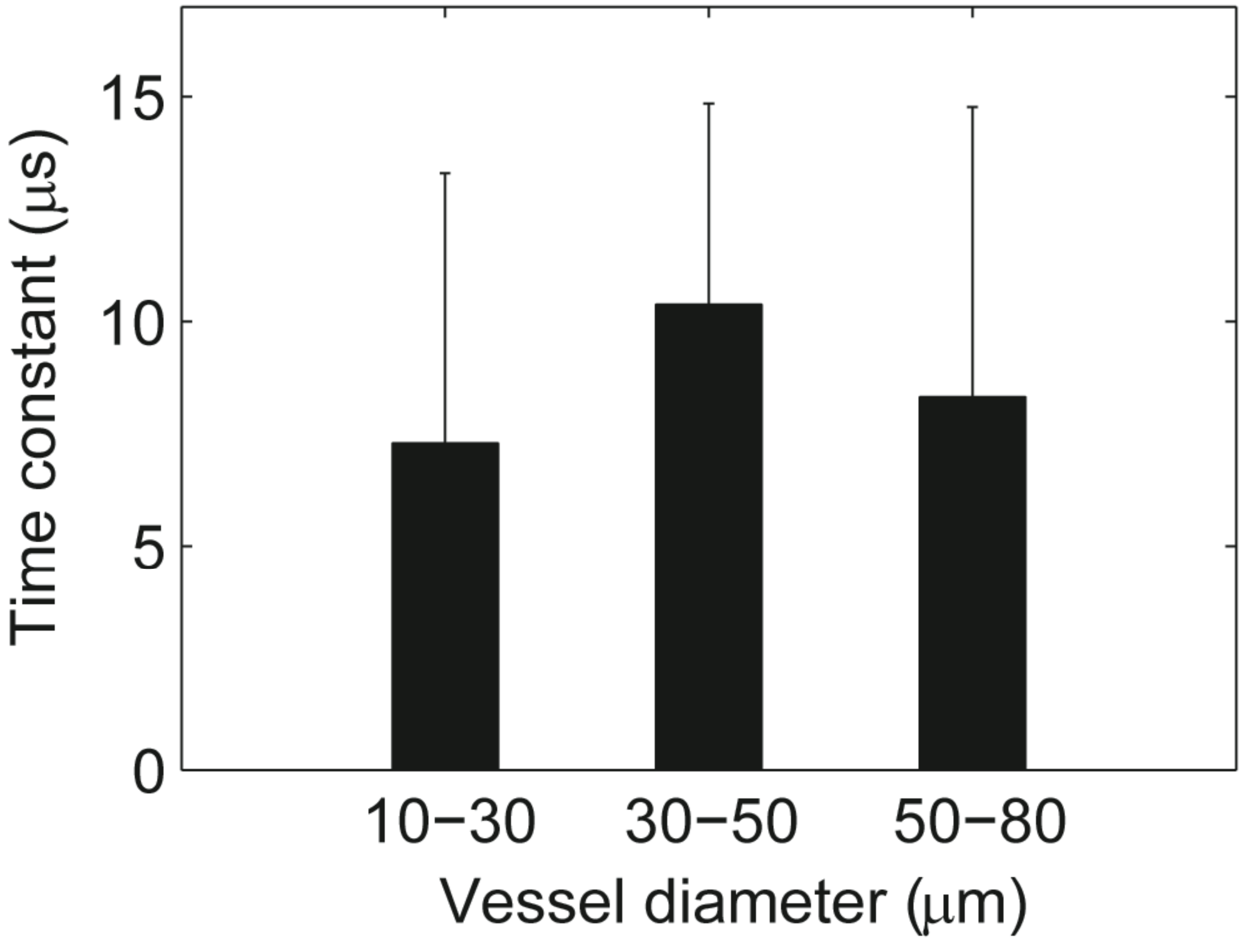
Model fitting



Relaxation time constant:

$$\tau = \eta / k = 15\mu s$$

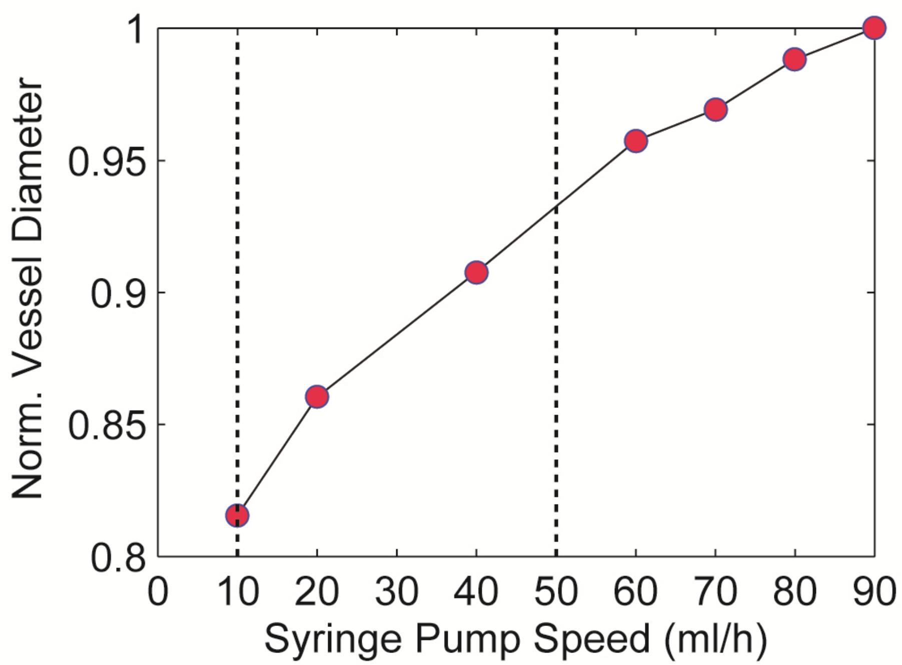
Relaxation Time Constant Vs. Vessel Size

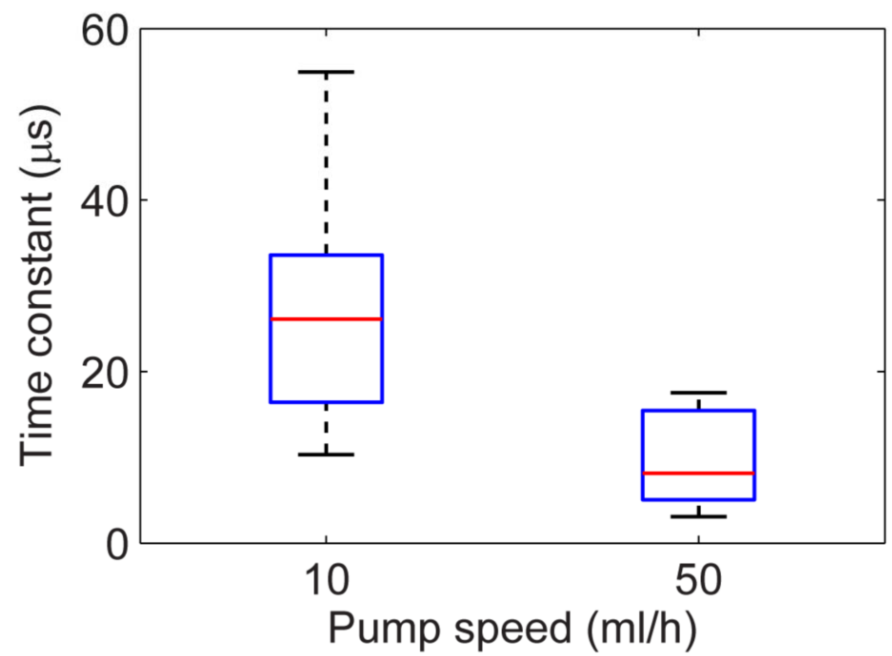


No significant difference among the three groups

Results Depend on Initial Strain

- Relaxation time constant vs. Syringe pump speed

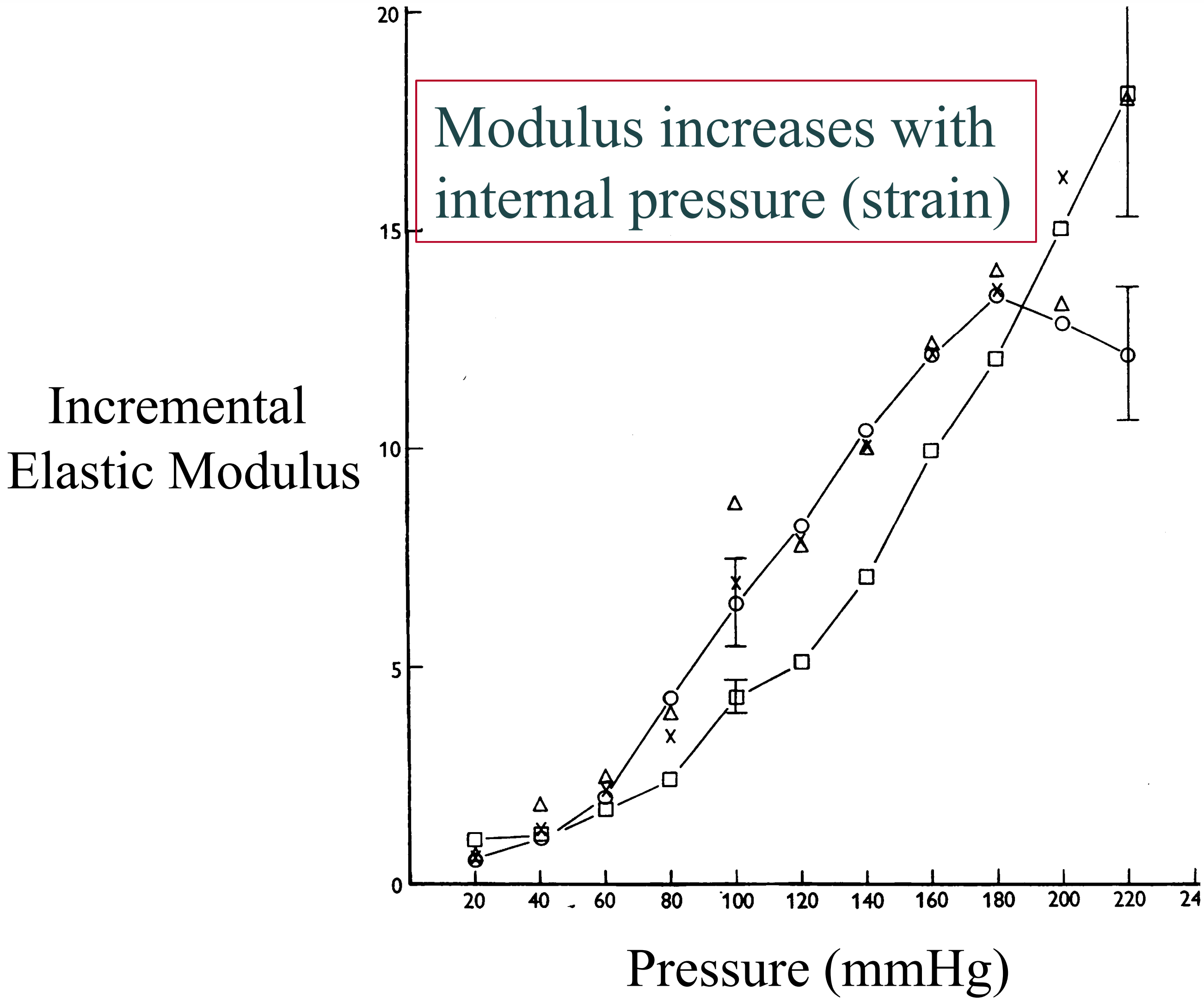




Significant difference

$$\tau = \eta / E \Rightarrow \text{elasticity} \uparrow$$

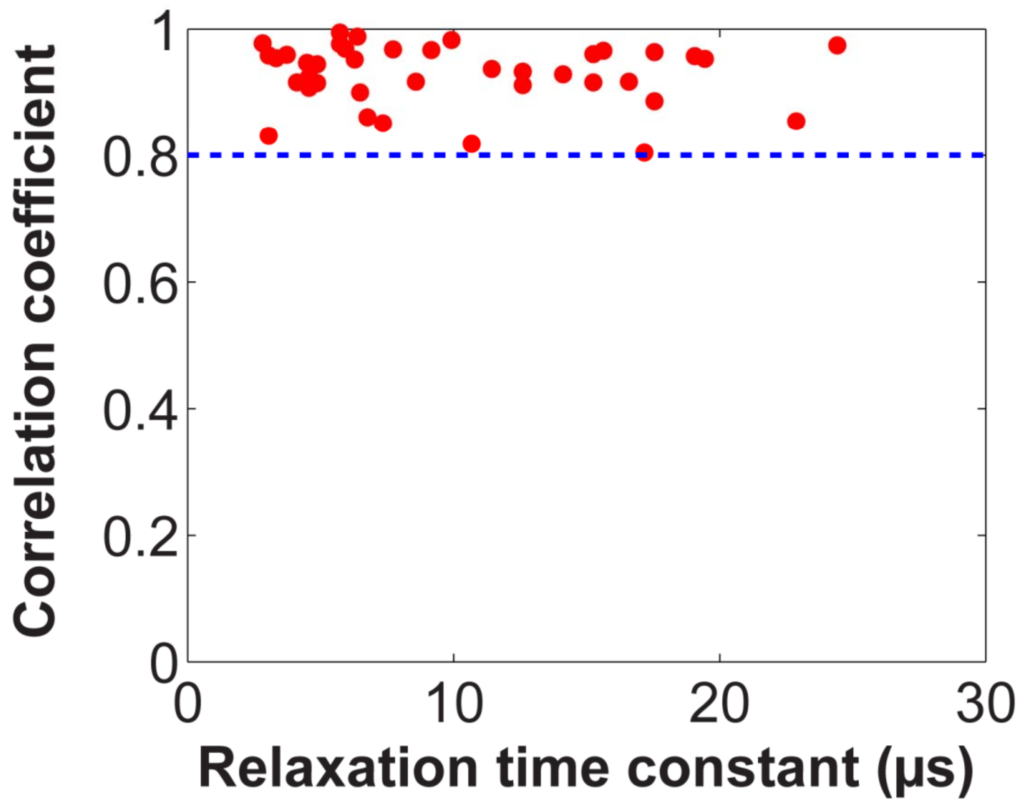
Example from Dog Arteries



From: Bergel, J. Physiol. (1961)

Analysis of > 40 Experiments

- Correlation coefficient vs. relaxation time constant



Criteria:

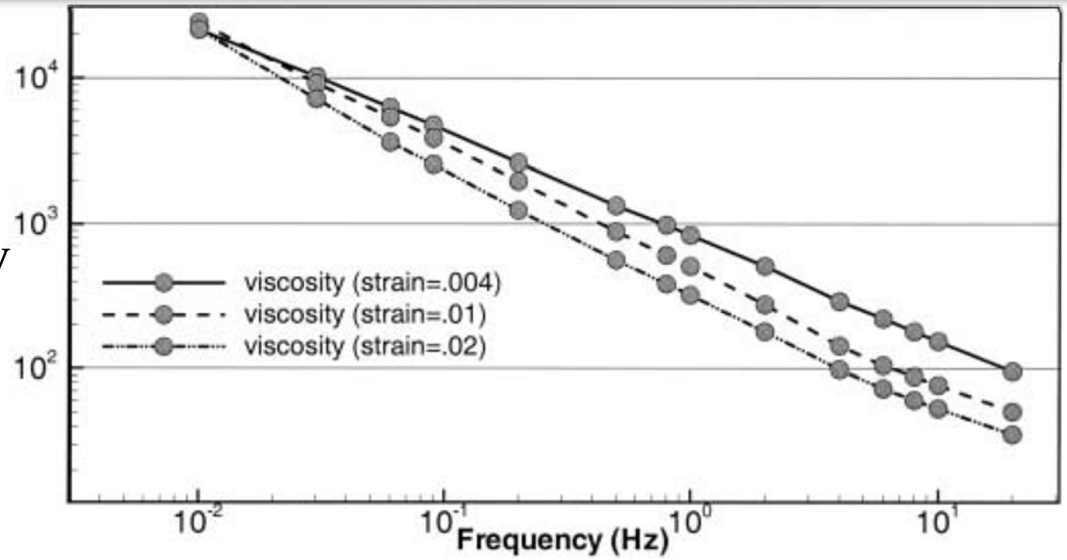
1. $D_{max} > 3$ µm
2. Have ≥ 4 data points for curve fitting

Problem: 3 orders of magnitude different from literature!

- Strong fit of the model to the data
- The mean of τ is ~ 10 µs, suggesting $//E = \sim 10$ µs

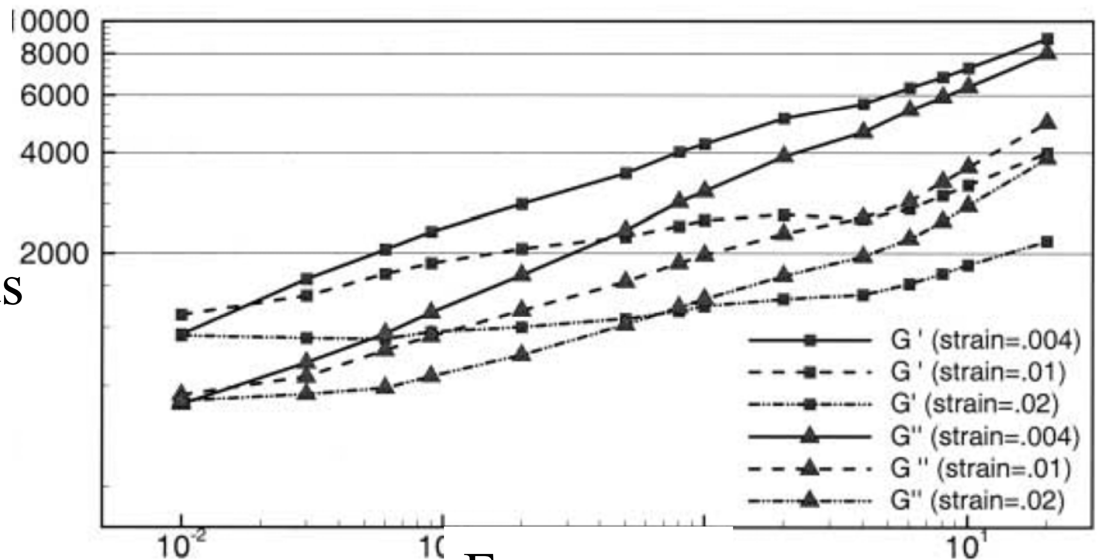
Viscosity and Modulus vs. Strain Rate in Pig Kidney

Viscosity



$$\tau = \eta / E$$

Shear Modulus

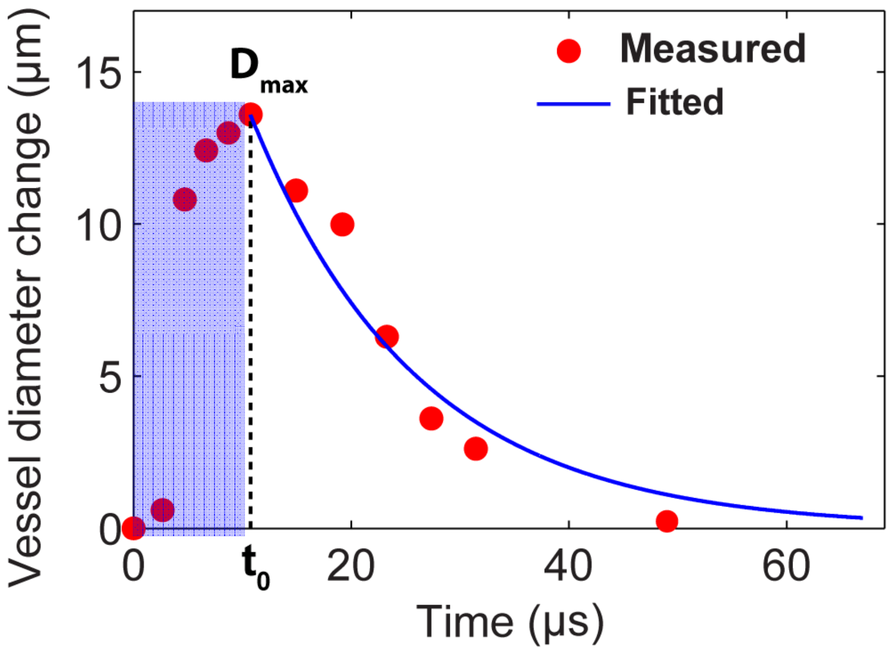


Frequency

Nasseri, *et al.*, Rheol. Acta. (2002)

Relaxation Time Vs. Strain Rate

- Maximum circumferential strain rate is at the order of ~100 kHz.



$$\dot{\varepsilon}_{max} = \left(\frac{d\varepsilon}{dt}\right)_{max} = \frac{1}{D_0}\left(\frac{dD}{dt}\right)_{max}$$

$$= 0.17 \times 10^6 \ s^{-1}$$

$$= 170 \ kHz$$

Strain rate	20 Hz (measurement)	100 kHz (extrapolation)
Viscosity (Pa s)	100	0.1
Elasticity (kPa)	10	100
Time constant	10 ms	1 µs

J. B. Freund, JASA, 2008, 123: 2867-2874