Therapeutic Ultrasound and the Contribution of Bubbles

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Nonlinear Acoustic Pulses

HIFU or Histotripsy

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

Shock wave therapy

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

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

Focused Ultrasound

Unfocused Ultrasound Clamp

18 W/cm² Intensity; 25% DF; 120 S pulse duration; 11 Min treatment; 8532 J
Example of Cavitation: Lithotripsy or Histotripsy

Pig kidney
Histotripsy

Histotripsy: Cavitation or Boiling?

Depends on pulse length

Exposure: 150 msec
Power: 160 W
12000 W/cm² (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”**

**HI FU 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

Data courtesy Joo Ha Hwang

Power – 1.37 W/cm²
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 agents perfusion in renal cortex and out to parenchyma in a mouse model.
13 MHz transducer, color Doppler.
Image courtesy of Visualsonics
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

Steric stabilizer

Phospholipid Shell
  DPPE
  DPPA
  DPPC

Hydrophobic bonds

~1µm

Octafluoropropane


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

Targeting thrombosis: From E. Chung, University of Leicester, UK.
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: 1 MHz
- Cycle #: 1
- $P^\pm$: 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

Ultrasound Pressure Waveform

Time (μs)

High-speed Camera Timing

Frame #

50 ns
150 – 300 ns
Vessel Response to Bubble Oscillations
Vessel Distends and Invaginates

Vessel diameter = 20 µm; $P^- = 1$ MPa
Vessel diameter = 46 µm; P⁻ = 7 MPa
Another Vessel Invagination Example

Vessel diameter = 22 µm; $P^-$ = 4 MPa
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
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 $\mu$m
Jet velocity = 27 m/s

$P = 3.1$ MPa
Vessel = 46 $\mu$m
Jet velocity = 42 m/s

Water hammer $\approx 50$ MPa.
Tissue response time scale on order of µs: Not an evoked response, a mechanical response

Max invagination speed = 15 m/s
Invagination vs. Distension

Vessel sizes: 10 - 80 \( \mu \text{m} \)
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 interstitium
Quantitative Measurements

Diameter: $D = 17 \, \mu m$

Max Distension

Max Invagination

Rupture

Max Invagination speed = 78 m/s

Graph showing vessel diameter over time.
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

- Microstreaming
- Jetting
  - SHEAR
  - POKING
  - INVAGINATION
- Expansion
  - DISTENSION
- Compression
  - INVAGINATION
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

- water filled cavity
- 8 mm stone
- ultrasound source
Proof of Concept in Pig
B-Mode Imaging of Rolling Stone
Endoscopic Imaging of Rolling Stone
THANK YOU!

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Cavitation Rheology:
Characterizing tissue viscoelastic properties
Cavitation Rheology

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

$P_{NP} = 1.5 \text{ MPa}$, vessel diameter = 30 µm
A Voigt model was used to fit the experimental data to get the relaxation time constant from the best-fit curve.

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

\[ \tau = \frac{\eta}{E} \]

\( \tau \): relaxation time constant
Model fitting

\[ D = D_{\text{max}} \exp\left(-\frac{(t - t_0)}{\tau}\right) \]

Relaxation time constant:
\[ \tau = \frac{\eta}{k} = 15 \mu s \]
No significant difference among the three groups
Results Depend on Initial Strain

- Relaxation time constant vs. Syringe pump speed

\[ \tau = \frac{\eta}{E} \Rightarrow \text{elasticity} \uparrow \]
Example from Dog Arteries

Modulus increases with internal pressure (strain)

Incremental Elastic Modulus

Pressure (mmHg)

From: Bergel, J. Physiol. (1961)
Analysis of > 40 Experiments

- Correlation coefficient vs. relaxation time constant

Criteria:
1. $D_{\text{max}} > 3 \ \mu\text{m}$
2. Have $\geq 4$ data points for curve fitting

- Strong fit of the model to the data
- The mean of $\tau$ is $\sim 10 \ \mu\text{s}$, suggesting $//E = \sim 10 \ \mu\text{s}$

Problem: 3 orders of magnitude different from literature!
Viscosity and Modulus vs. Strain Rate in Pig Kidney

\[ \tau = \frac{\eta}{E} \]

Maximum circumferential strain rate is at the order of $\sim 100$ kHz.

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

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

$$= 170 \text{ kHz}$$

<table>
<thead>
<tr>
<th>Strain rate</th>
<th>20 Hz (measurement)</th>
<th>100 kHz (extrapolation)</th>
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</thead>
<tbody>
<tr>
<td>Viscosity (Pa s)</td>
<td>100</td>
<td>0.1</td>
</tr>
<tr>
<td>Elasticity (kPa)</td>
<td>10</td>
<td>100</td>
</tr>
<tr>
<td>Time constant</td>
<td>10 ms</td>
<td>1 $\mu$s</td>
</tr>
</tbody>
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*J. B. Freund, JASA, 2008, 123: 2867-2874*