RECENT ADVANCES IN BOILING HISTOTRIPSY
MECHANICAL ABLATION: APPLICATIONS AND DEVICES

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OUTLINE

- Thermal ablation with High Intensity Focused Ultrasound (HIFU): successes and challenges
- Nonlinear propagation effects in HIFU
- Histotripsy methods of HIFU-based mechanical ablation and boiling histotripsy (BH)
- Instrumentation for BH and methods for ultrasound imaging guidance
- Clinical applications of BH and associated bioeffects:
  - Soft tissue ablation (benign and malignant tumors)
  - Liquefaction and disinfection of abscesses
  - Liquefaction of soft tissue hematomas for needle aspiration
HIGH INTENSITY FOCUSED ULTRASOUND (HIFU) FOR THERMAL ABLATION

Benign neoplasms
- Uterine fibroids
- Thyroid nodules
- Benign prostate hyperplasia
- Benign breast nodules

Cancer tumors
- Tumors in the liver, kidney, pancreas, breast, prostate, bone metastases, brain...

Essential tremor

Skin tightening and body shaping

HIFU focus is scanned through the volume to be ablated
SUCCESSES AND CHALLENGES IN HIFU ABLATION

**Advantages**
- Treatments are completely noninvasive
- Can be repeated, well tolerated
- The shape of ablated volume tailored to the target (unlike for example RF)

**Ultrasound-guided HIFU**
based on echogenicity changes (vapor bubbles)

**MR-guided HIFU:**
based on temperature mapping, reaching 65°C

**Challenges**
- Near-field heating of the intervening tissues: ribs, skin, muscle, fat
- Heat sink effect in well vascularized targets: incompleteness of ablation (ultrasound-guided)
- Cost, lengthy procedure (MR-guided)
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THE IMPORTANCE OF NONLINEAR PROPAGATION EFFECTS IN THERMAL HIFU

**Linear heating:**

\[ \delta T = \frac{\alpha p^2}{\rho^2 c_0 c_v} \delta t \]

- \( f = 1.2 \text{ MHz} \)
- \( p^+ = p^- = 5.5 \text{ MPa} \)
- \( \Delta T = 10 ^\circ \text{s} \)

**Shock wave heating:**

\[ \delta T = \frac{\beta f_0 A_s^3}{6 \rho^2 c_0^4 c_v} \delta t \]

- \( f = 1.2 \text{ MHz} \)
- \( A_s = 25 \text{ MPa} \)
- \( p^- = 5 \text{ MPa} \)
- \( \Delta T = 100 ^\circ \text{s} \) in 0.2 seconds!
In less focused transducers, shocks form at lower acoustic power, and have lower amplitude.

Example:
\( f = 1.5 \text{ MHz} \)
\( A = 75 \text{ mm} \)
\( F\# = 0.77, 1 \text{ and } 1.5 \)
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**THE HISTOTRIPSY SPECTRUM**

Histotripsy – a regime of pulsed HIFU, mediated by bubbles that leads to **mechanical** ablation of tissue

<table>
<thead>
<tr>
<th>Pulse duration</th>
<th>Low duty cycle &lt;2%</th>
<th>1-30 ms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-2 µs</td>
<td>Microtripsy</td>
<td></td>
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<tr>
<td>Shock-scattering histotripsy</td>
<td></td>
<td></td>
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<tr>
<td>Hybrid histotripsy</td>
<td></td>
<td></td>
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<tr>
<td>5-25 µs</td>
<td>Boiling Histotripsy</td>
<td></td>
</tr>
<tr>
<td>500-800 µs</td>
<td></td>
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<table>
<thead>
<tr>
<th>Peak negative pressure</th>
<th></th>
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<tbody>
<tr>
<td>&gt;27-30</td>
<td>15-25 MPa</td>
</tr>
</tbody>
</table>

Optimal F-number

| 0.5 - 0.7 | 0.8 – 1.4 |  |

© University of Michigan, 2004

Histotripsy – *a regime of pulsed HIFU, mediated by bubbles that leads to mechanical ablation of tissue.*

Histotripsy: a regime of pulsed HIFU, mediated by bubbles that leads to mechanical ablation of tissue.
BOILING HISTOTRIPSY BUBBLE BEHAVIOR

Focal HIFU waveform

Pressure (MPa)

Time (μs)

Shock Front >60 MPa

Interaction of shocks with vapor cavity

100°C can be reached in several milliseconds!

Mechanism 1

Mechanism 2

Canney et al., UMB 2010

Pahk et al. Ultrasound Med Biol 2017

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INSTRUMENTATION FOR BOILING HISTOTRIPSY

Required shock amplitude 50-100 MPa

Transducer

F#: 0.75 – 1.4 (90° - 40° angle)
Frequency: 1-3 MHz
Peak acoustic power: 300 – 4000 Watts

Alpinion VIFU2000 small animal system
(BH in mice, rats)

F# = 0.75
Frequency: 1.5 MHz
Power: 400-500 W

Custom-built endorectal system
(BH of canine prostate)

Effective F# = 1
Frequency: 2 MHz
Power: 250-400 W

Similar to EDAP Ablatherm

Custom-built 256-element spiral array
(BH of porcine liver, kidney)

F# = 0.8 - 0.9
Frequency: 1.5 MHz
Power: 600-2,300 W

Similar to HIFU array
in Phillips Sonalleve

6.5 cm

5 cm

3.5 cm

14 cm

13 cm
**In vivo** porcine kidney

**Post-treatment**

Hyperechoic region corresponds to vapor bubbles

*Khokhlova et al. Scientific Reports 2019*
**Observation:** Each BH pulse causes motion of tissue debris and residual bubbles due to acoustic radiation force and acoustic streaming.

**Hypothesis:** Streaming debris and bubble remnants will move faster and more freely as tissue is fully liquefied.

**Potential solution for BH:** Ultrafast color Doppler ultrasound imaging to measure debris velocity after each BH pulse.

**Proof of principle experiments in ex vivo bovine myocardium**

- 256-element HIFU array
- ATL P6-3 imaging probe
- Both driven by Verasonics V1 system

**Diagram:**
- Plane wave Doppler
- 100 pulse ensemble
- 6 ms
- 64 ray lines
- B-mode
QUANTITATIVE MEASURES OF BH ABLATION COMPLETENESS

Color Doppler during BH treatment

Volumetric BH lesion
(10 pulses per point)

Maximum Velocity

Song et al. International Symposium on Therapeutic Ultrasound, 2021
Aberration of HIFU beam by soft tissues, primarily fat (sound speed ~1420 m/s vs 1560 m/s in tissues) HIFU focus is shifted and broadened, shock front is split

Aberration correction approach (borrowed from US imaging)
- Use HIFU array in pulse/echo mode, receive echoes from soft tissue at the focus
- Use cross-correlation approaches to align phases of the echoes
- Apply corresponding delays to the HIFU transducer elements
- Repeat iteratively until the amplitude of echoes from the focus is maximized

Thomas et al. IEEE-UFFC 2020
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TISSUE EFFECTS OF HISTOTRIPSY

- Cells and organelles are mechanically disintegrated into protein suspension
- Boundary between treated and intact tissue is very sharp (~10-20 microns)

Example: boiling histotripsy lesion in the *in vivo* porcine kidney cortex

![H&E histology](image1)
![TEM](image2)

- Tissue selectivity: connective tissue structures more resistant than cells

Example: *in vivo* porcine liver (vessels >200 µm preserved)

- Kidney collecting system

HEALING RESPONSE IN A RAT KIDNEY CANCER MODEL

Naturally occurring RCC model – Eker rat
25-50% of the tumor liquefied by BH

B-mode ultrasound

Day 7

Day 14

Hypoechoic cavity peaks on day 7
- disappears by day 14
- correlates with contraction grossly
Kidney appears healed by day 56

Eker rat

Day 7

Day 14

Day 56

Wild-type rat

Day 7

Day 14

Day 56
BH alone is unlikely to trigger a clinically significant anti-tumor immune response, but can boost response to immunotherapy.
HISTOTRIPSY FOR LIQUEFACTION OF LARGE HEMATOMAS

Hematoma – a collection of blood outside of blood vessels caused by trauma or post-surgical bleeds

Health effects:
- pain
- compartment syndrome
- organ failure
- risk of infection

Clinical management:
- Surgery
- Indwelling drain (ineffective)

Approach: liquefy hematoma with boiling histotripsy, drain the liquid with fine needle

Liquefaction rate up to 1.3 cc/minute

1Khokhlova et al. UMB 2016
**HISTOTRIPSY FOR LIQUEFACTION OF LARGE HEMATOMAS**

**Alternative approach:** liquefy hematoma with BH while continuously draining the liquid

- Faster liquefaction rate (up to 5 mL/minute)
- No need to move the HIFU focus around the volume (hematoma collapses on itself)

**B-mode US imaging during treatment**

Treatment of large acute pelvic hematoma in a pig *in vivo*
Abscess - walled-off collection of infected fluids containing viscous pus and bacteria. Often treated with percutaneous drainage for up to several weeks.

Porcine subcutaneous abscess model:
- Bimicrobial inoculation (E.coli+B.fragilis)
- Abscesses mature in 2-4 weeks

BH used to liquefy a large part of abscess volume within 20 minutes.

Efficient bacterial kill requires longer treatment time or combination with cavitation histotripsy (3.3 log kill achieved).

Matula et al. UMB 2021
SUMMARY

- Boiling histotripsy is a pulsed HIFU-based mechanical ablation method
- Can be implemented with existing clinical and preclinical HIFU systems
- B-mode ultrasound provides qualitative real-time and post treatment guidance
- Color Doppler ultrasound may provide quantitative feedback on ablation completeness
- Differential threshold for damage depending on tissue type, connective structures spared
- Liquefied tissue reabsorbs quickly without fibrosis, stimulates anti-tumor immune response
- Promising treatment modality for hematoma and abscess liquefaction
ACKNOWLEDGEMENTS

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