RECENT ADVANCES IN BOILING HISTOTRIPSY

MECHANICAL ABLATION: APPLICATIONS AND DEVICES

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CIMU

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
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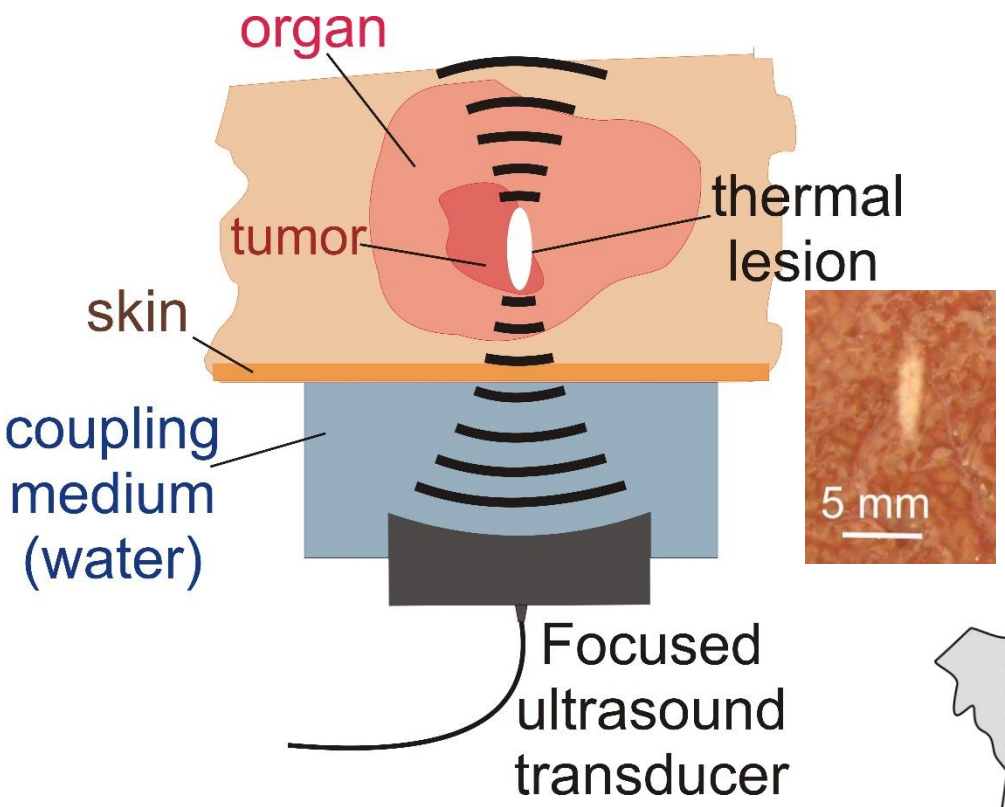
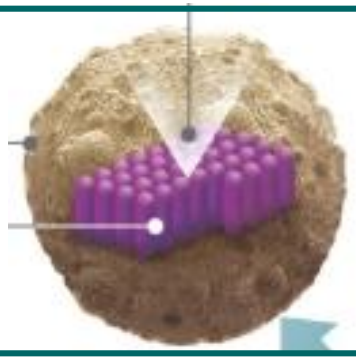
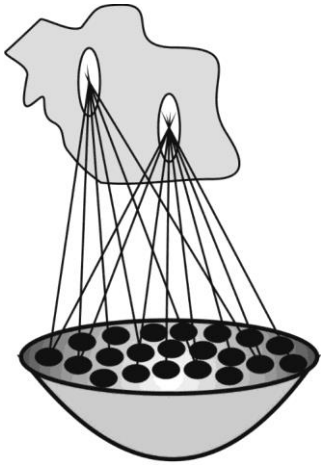
  - Soft tissue ablation (benign and malignant tumors)
  - Liquefaction and disinfection of abscesses
  - Liquefaction of soft tissue hematomas for needle aspiration

HIGH INTENSITY FOCUSED ULTRASOUND (HIFU) FOR THERMAL ABLATION



HIFU focus is scanned through the volume to be ablated





HIFU array transducer

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

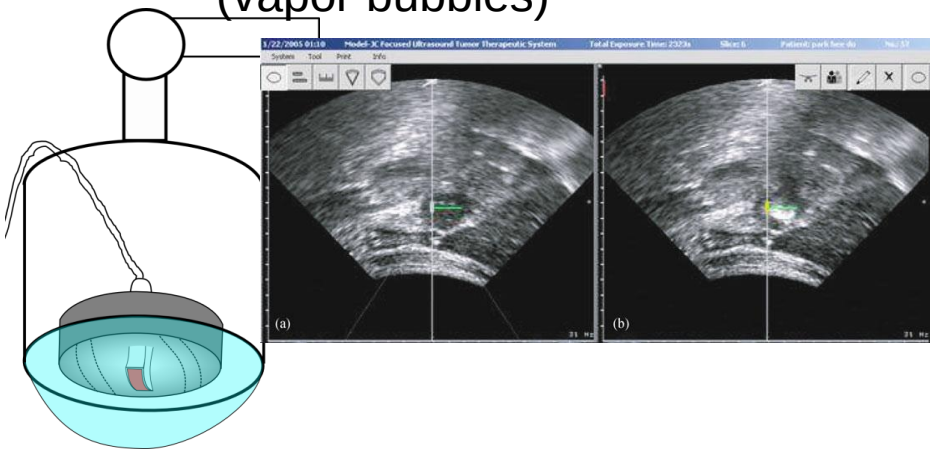
…

SUCCESSES AND CHALLENGES IN HIFU ABLATION

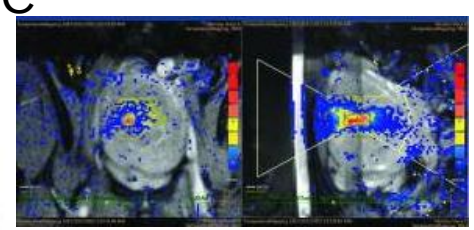
Advantages

- 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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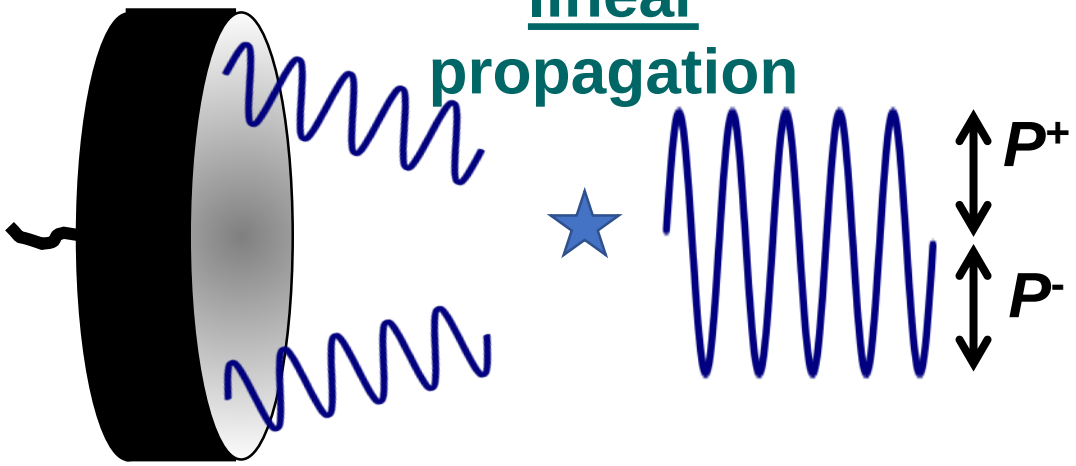
THE IMPORTANCE OF NONLINEAR PROPAGATION EFFECTS IN THERMAL HIFU

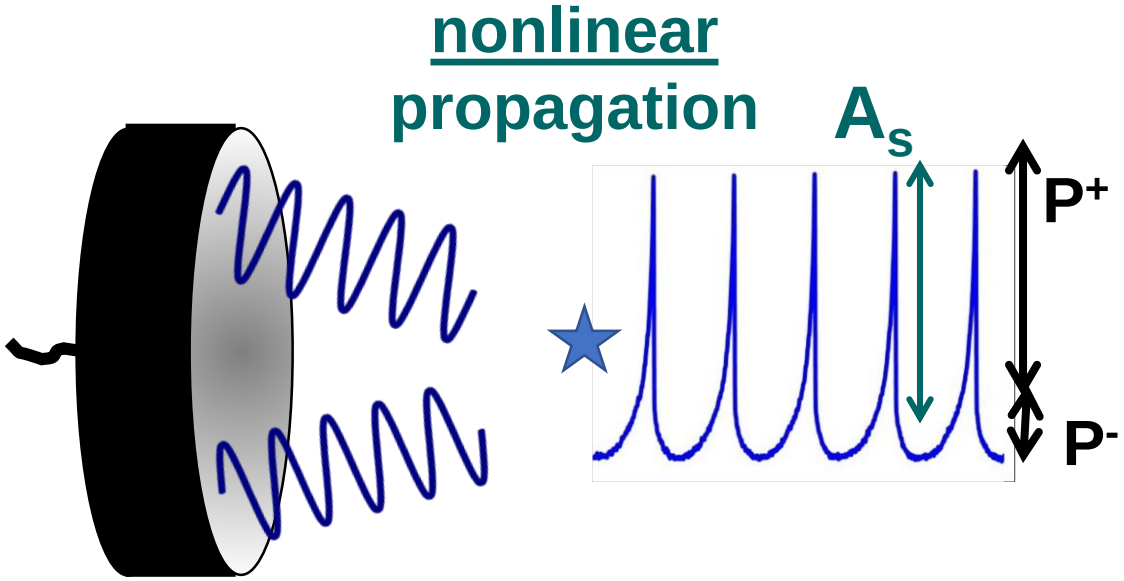


Linear heating:

$$\delta T = \frac{\alpha p^2}{\rho^2 c_0 c_v}\,\delta t$$

f = 1.2 MHz
$p^+ = p^- = 5.5$ MPa

δT = 10 °/s



Shock wave heating:

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

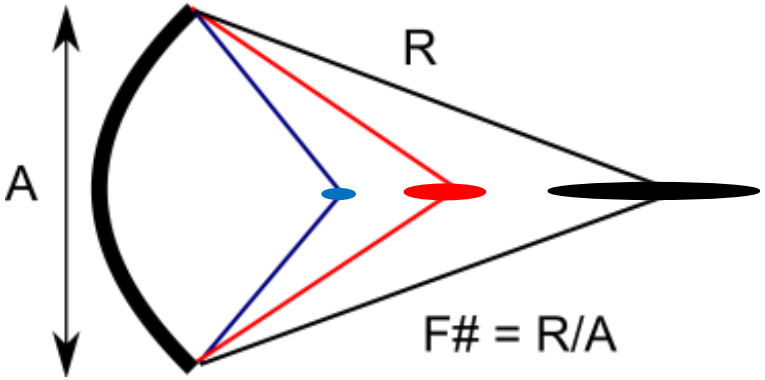
f = 1.2 MHz
A_s = 25 MPa
p^- = 5 MPa

δT = 100°

in 0.2 seconds!

DEPENDENCE OF SHOCK FORMATION ON HIFU TRANSDUCER PARAMETERS

In less focused transducers, shocks form at lower acoustic power, and have lower amplitude

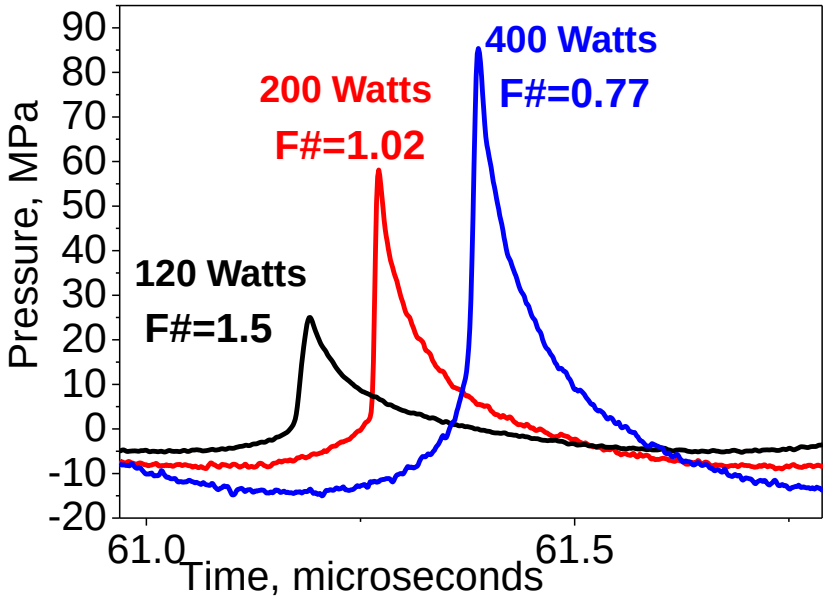


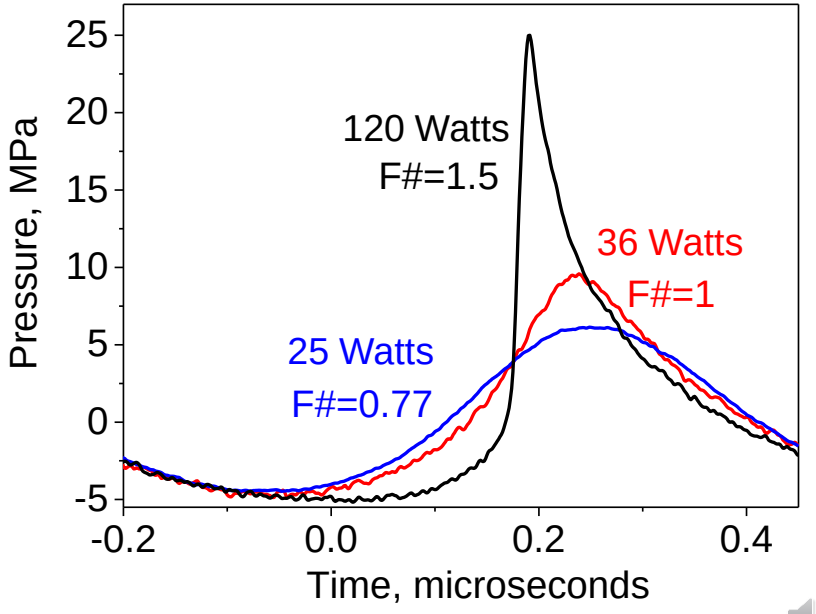
Example:

f = 1.5 MHz

A = 75 mm

F# = 0.77, 1 and 1.5





Khokhlova et al. JASA 2018

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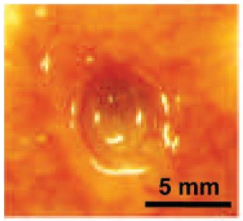
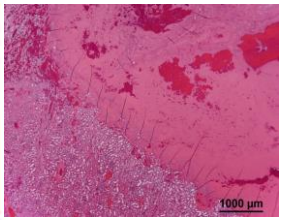
THE HISTOTRIPSY SPECTRUM

histo- tissue [G. *histos*] **-tripsy** to crush [G. *tripsis*]

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





Low duty cycle <2%

Pulse duration

1-2 µs	5-25 µs	500-800 µs	1-30 ms
Microtripsy 2014, UMich	Shock-scattering histotripsy 2004, UMich	Hybrid histotripsy	Boiling Histotripsy 2008, UW

Peak negative pressure

>27-30	15-25 MPa	~18 MPa	10-15 MPa

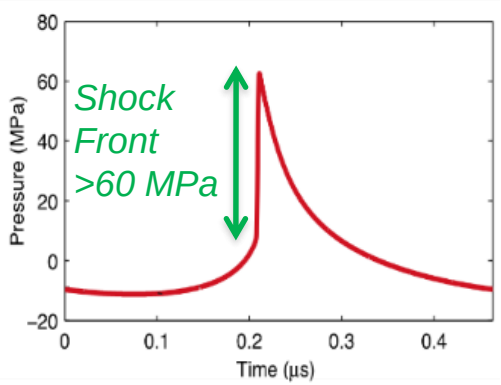
Eranki et al., IJH 2018
Guan et al., UMB 2016

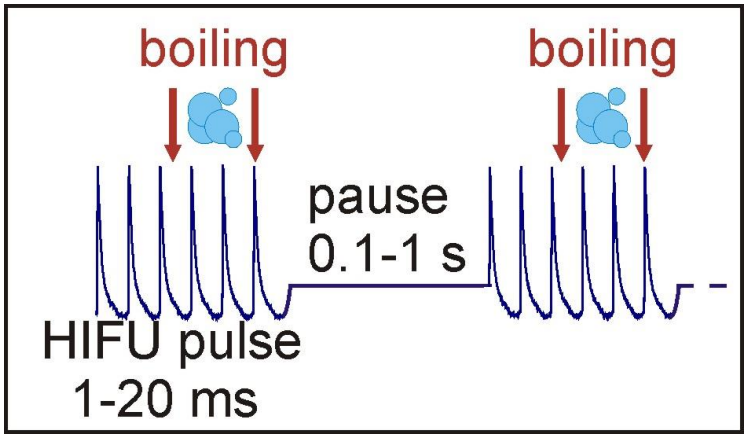
Optimal F-number

0.5 - 0.7	0.8 – 1.4

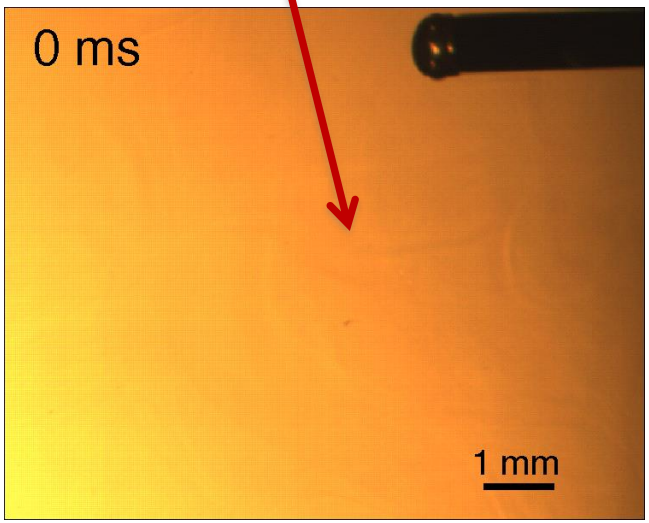
BOILING HISTOTRIPSY BUBBLE BEHAVIOR

Focal HIFU waveform





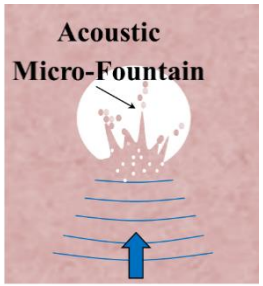
100°C can be reached in several milliseconds!



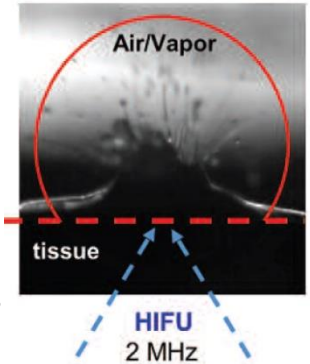
Canney et al., UMB 2010

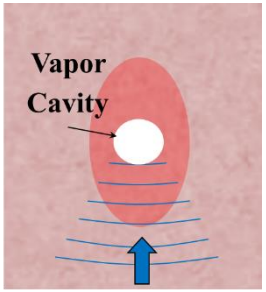
Interaction of shocks with vapor cavity

Mechanism 1



Simon et al. Phys Med Biol 2012





Mechanism 2

Pahk et al. Ultrasound Med Biol 2017

Secondary boiling bubble

Prefocal cavitation cloud

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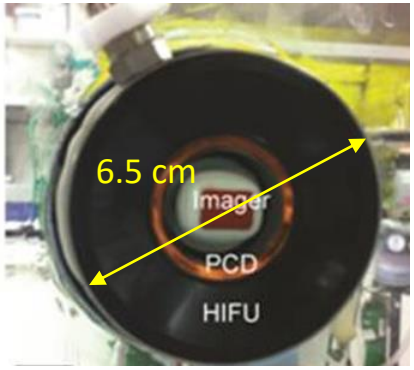
INSTRUMENTATION FOR BOILING HISTOTRIPSY

Required shock amplitude
50-100 MPa

⇨

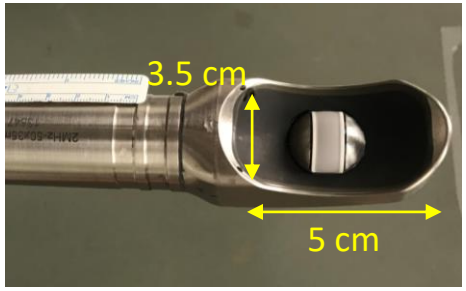
Transducer F#: 0.75 – 1.4 (90°- 40° angle)
Frequency: 1-3 MHz
Peak acoustic power: 300 – 4000 Watts

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



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

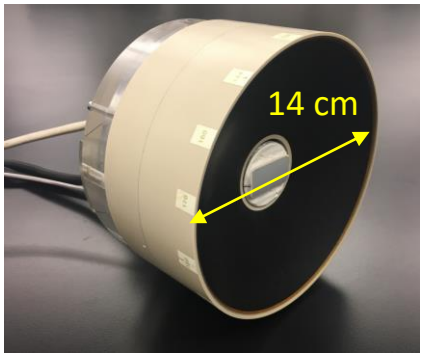
Custom-built endorectal system (BH of canine prostate)

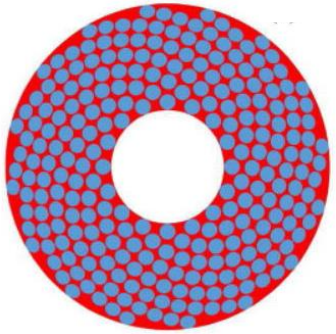


Effective F# = 1
Frequency: 2 MHz
Power: 250-400 W

Similar to EDAP Ablatherm

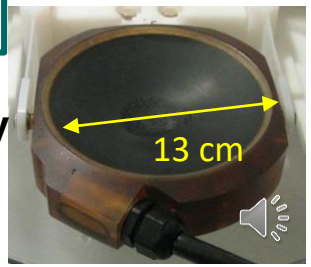
Custom-built 256-element spiral array (BH of porcine liver, kidney)





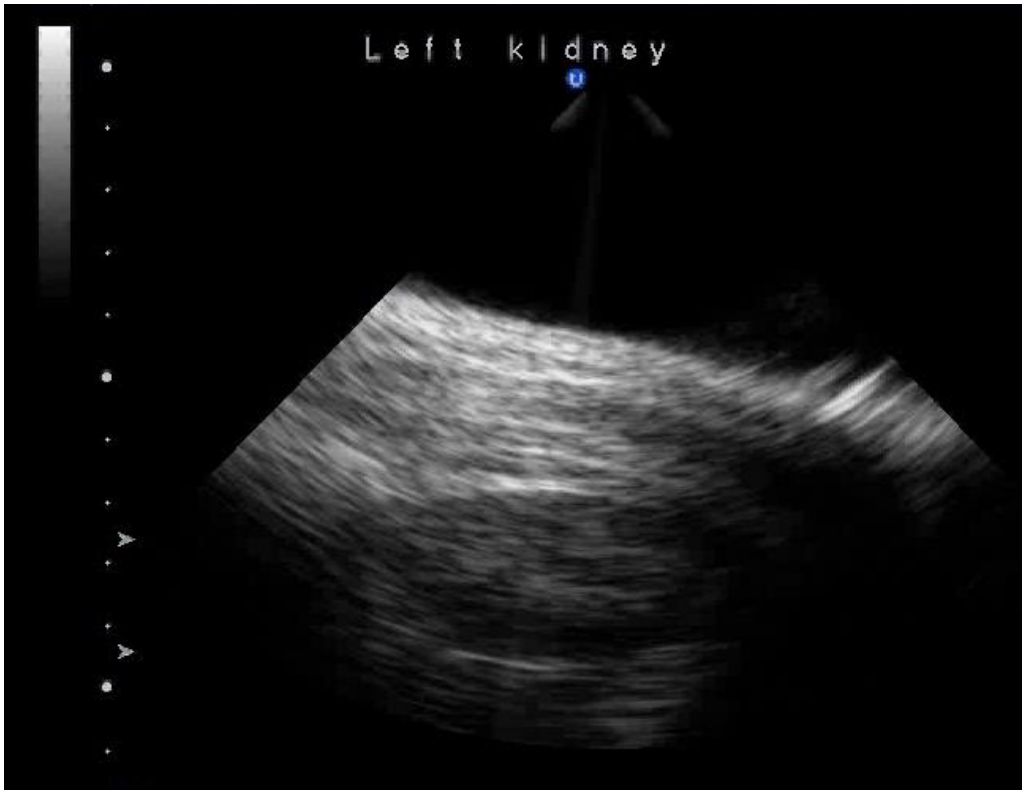
F# = 0.8 - 0.9
Frequency: 1.5 MHz
Power: 600-2,300 W

Similar to HIFU array in Phillips Sonalleve

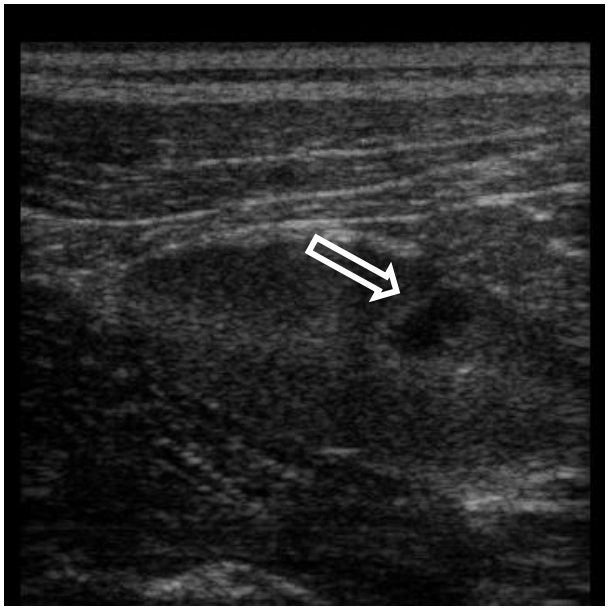


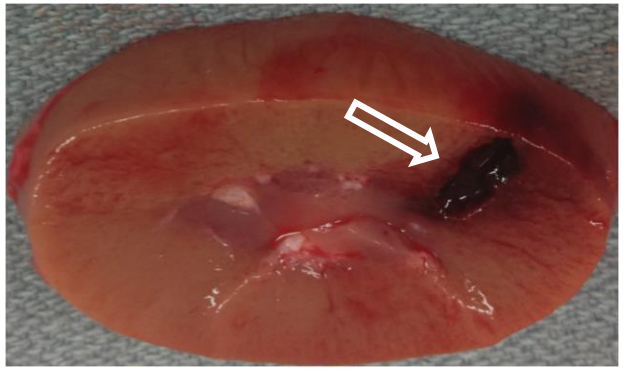
B-MODE ULTRASOUND GUIDANCE IN HISTOTRIPSY

In vivo porcine kidney



Post-treatment





Hyperechoic region corresponds to vapor bubbles

Khokhlova et al. Scientific Reports 2019

QUANTITATIVE MEASURES OF BH ABLATION COMPLETENESS

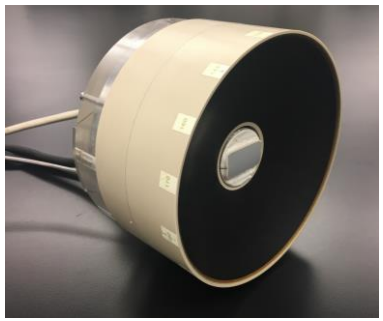
Observation: Each BH pulse causes motion of tissue debris and residual bubbles due to acoustic radiation force and acoustic streaming

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

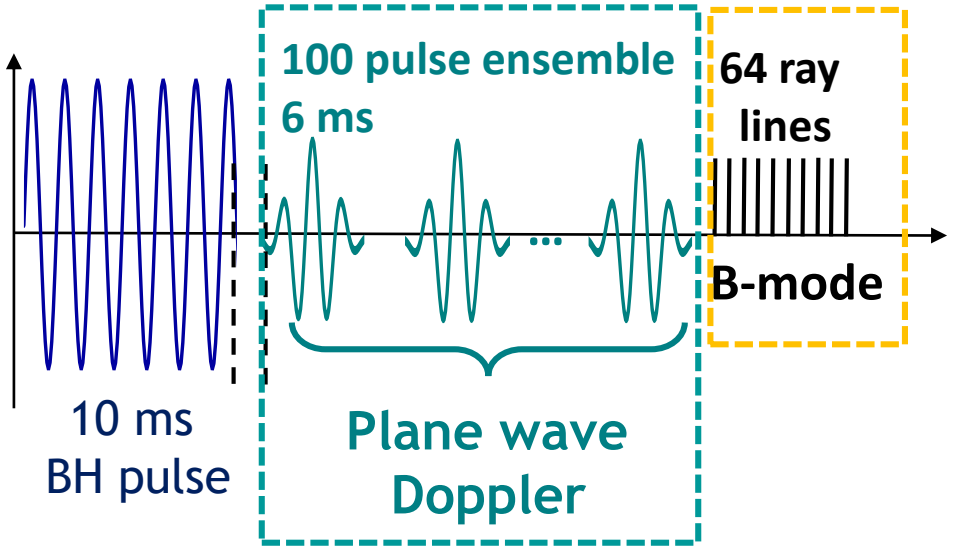
Proof of principle experiments in ex vivo bovine myocardium

256-element HIFU array



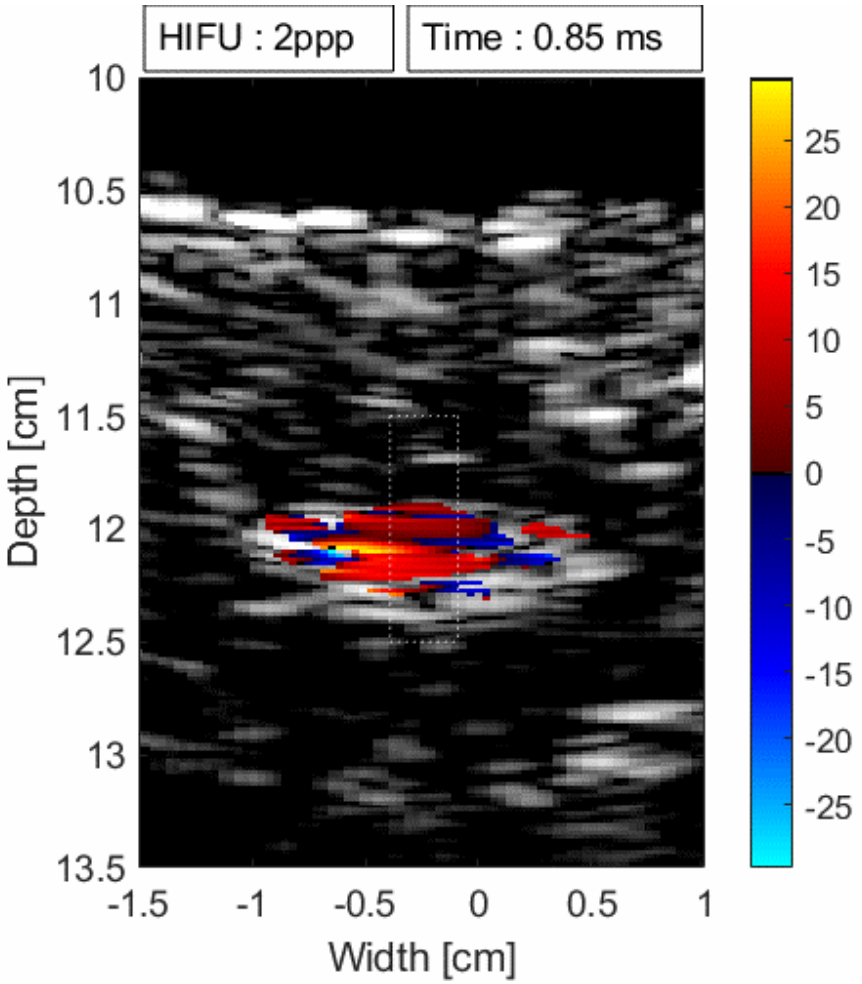
ATL P6-3 imaging probe

Both driven by Verasonics V1 system

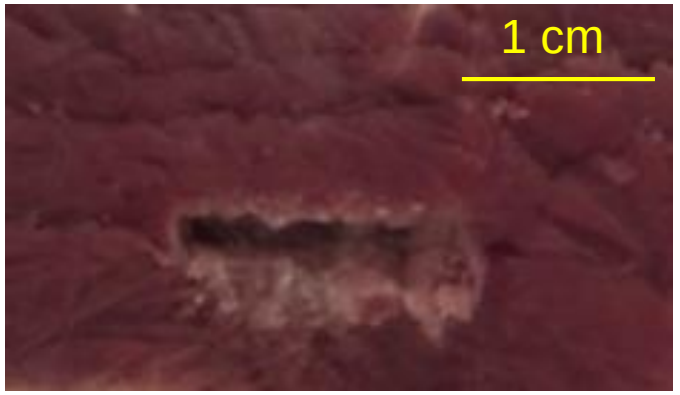


QUANTITATIVE MEASURES OF BH ABLATION COMPLETENESS

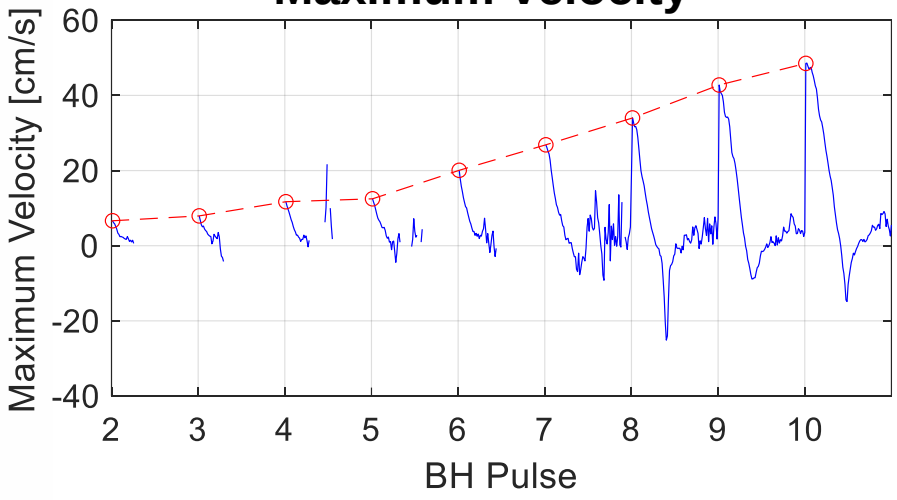
Color Doppler during BH treatment



Volumetric BH lesion (10 pulses per point)



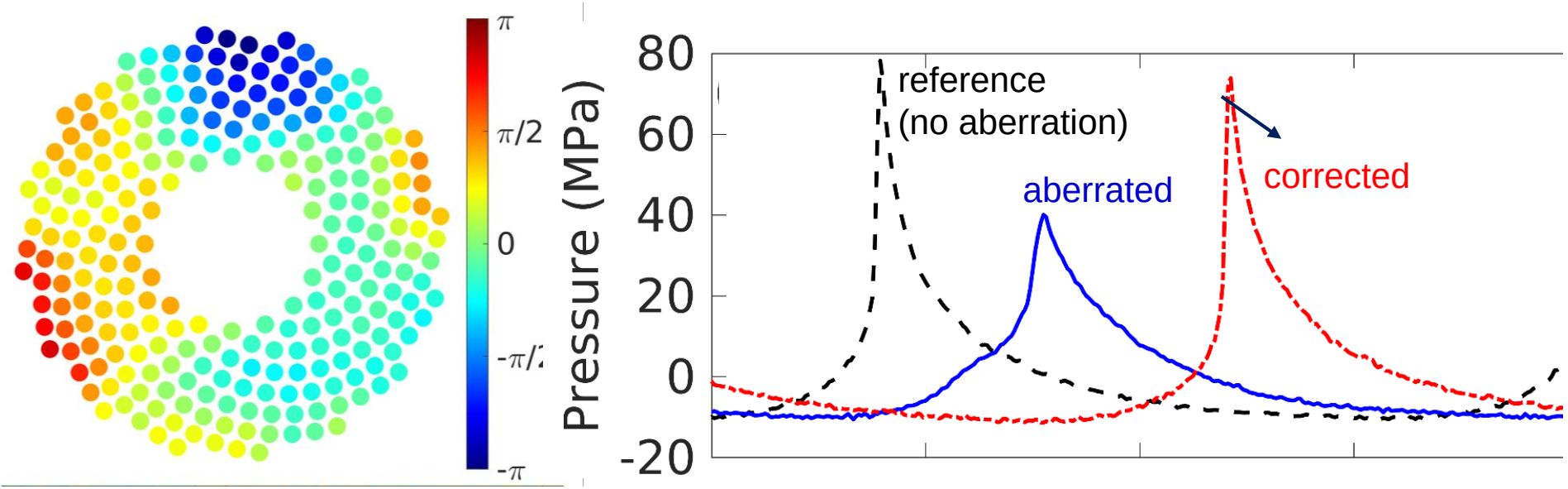
Maximum Velocity



Song et al. International Symposium on Therapeutic Ultrasound, 2021

CORRECTION OF SOFT TISSUE-INDUCED ABERRATION

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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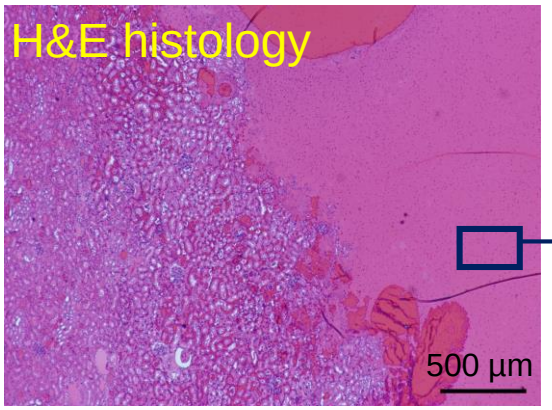
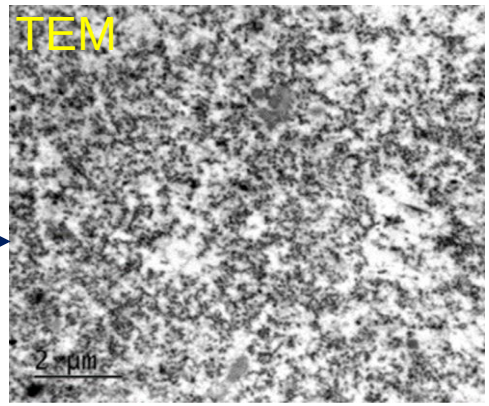
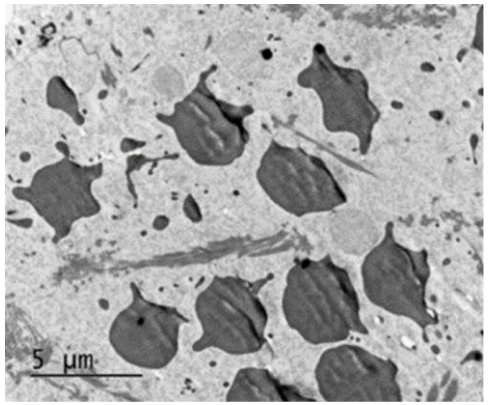
TISSUE EFFECTS OF HISTOTRIPSY

- 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

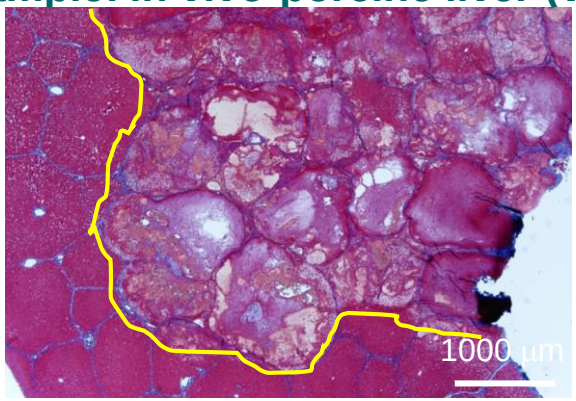


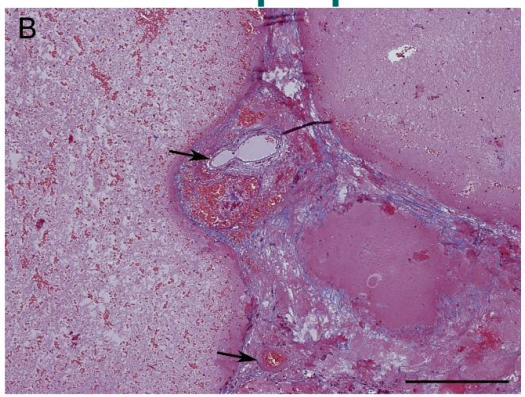




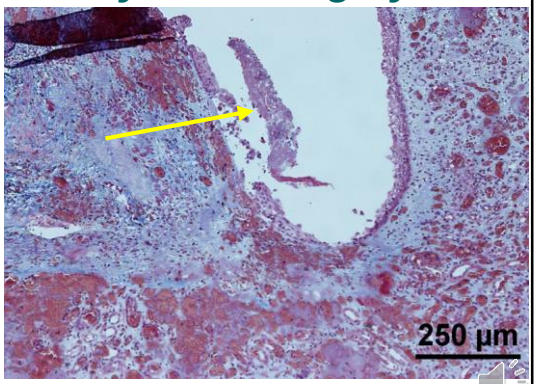
- Tissue selectivity: connective tissue structures more resistant than cells

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





Kidney collecting system

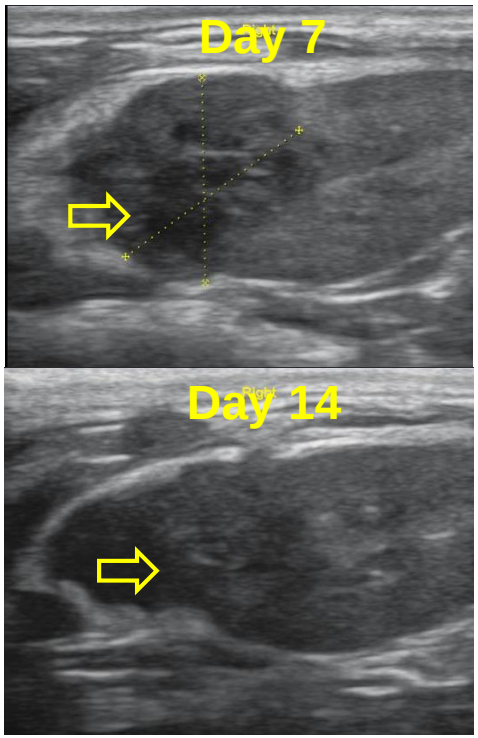


Khokhlova et al. Sci. Rep. 2019

HEALING RESPONSE IN A RAT KIDNEY CANCER MODEL

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

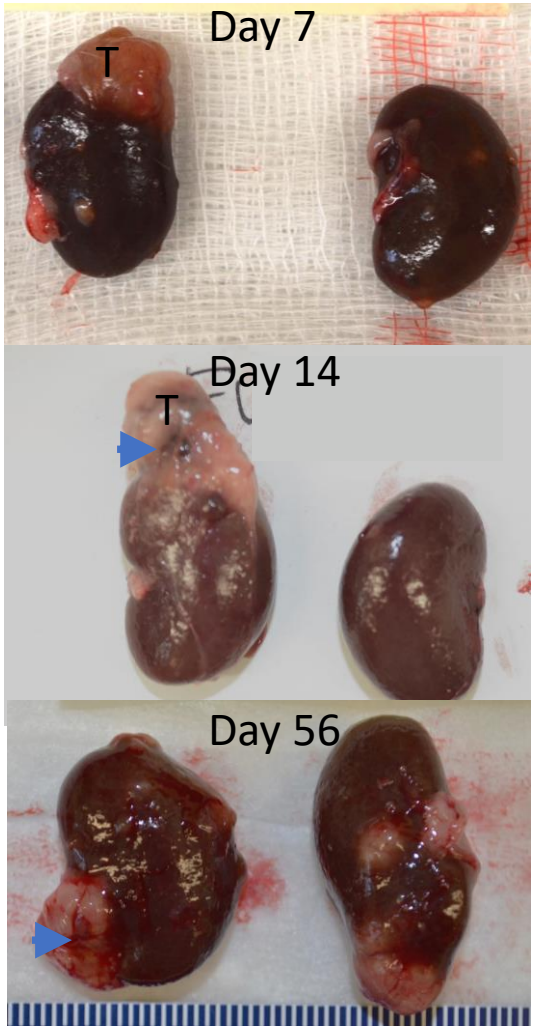
B-mode ultrasound



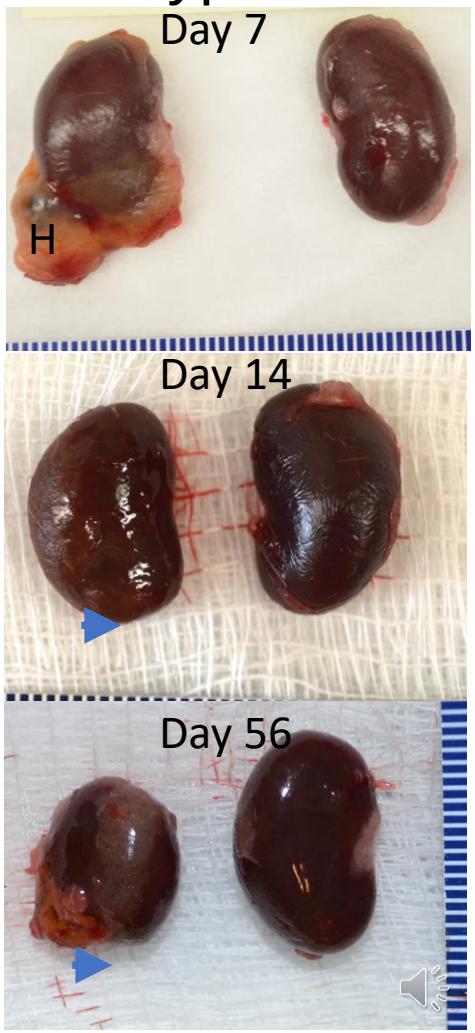
Hypoechoic cavity peaks on day 7
- disappears by day 14
- correlates with contraction grossly

Kidney appears healed by day 56

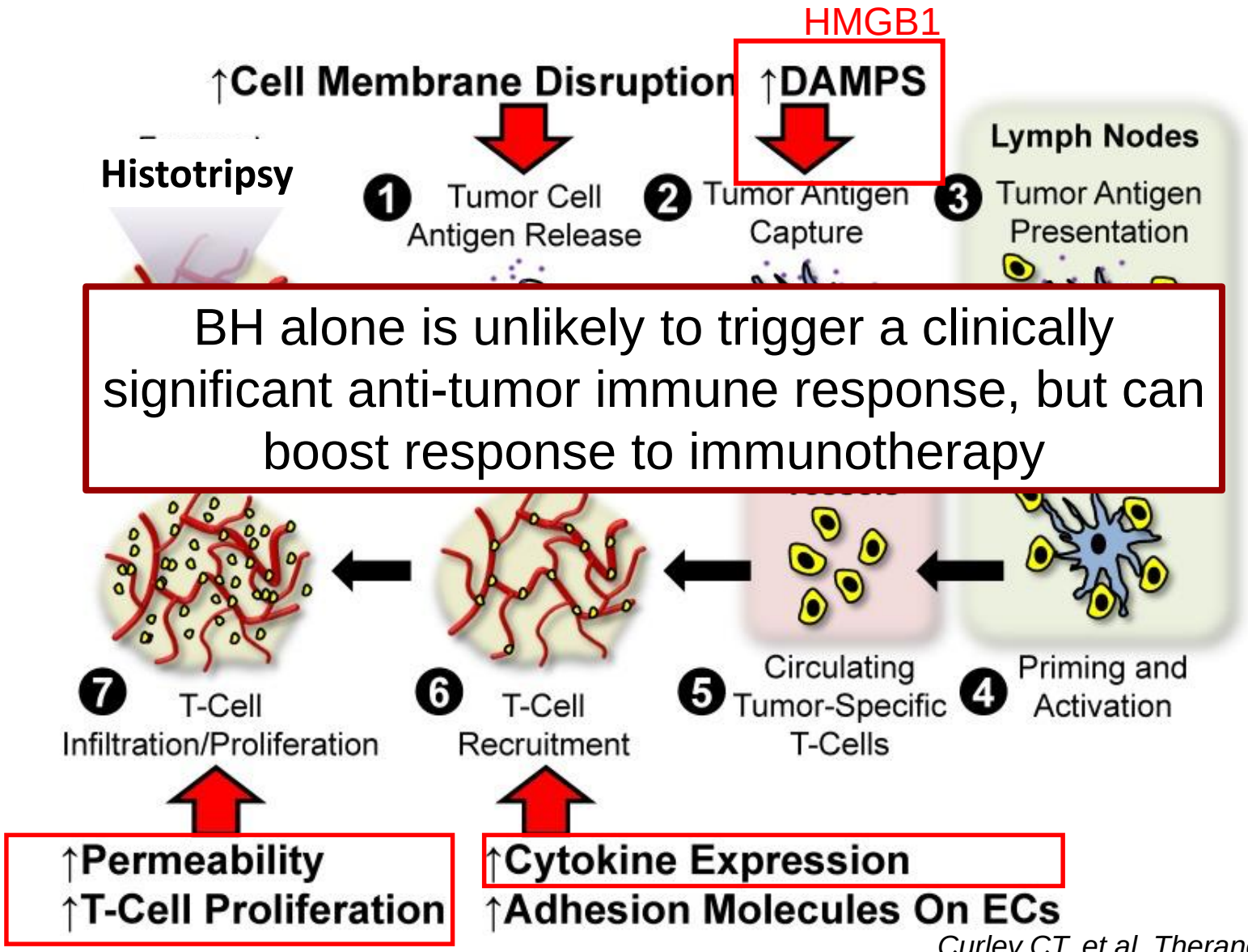
Eker rat



Wild-type rat



BOILING HISTOTRIPSY PROMOTES ANTITUMOR IMMUNE RESPONSE

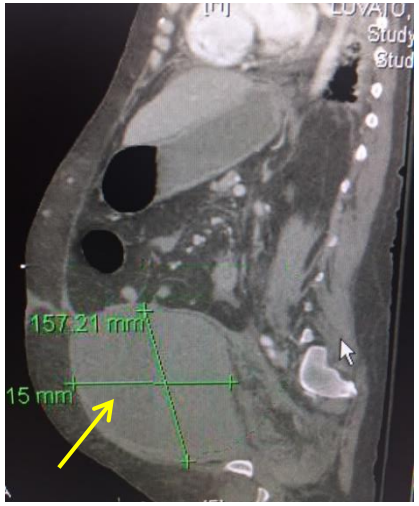


Curley CT, et al. Theranostics 2017
Schade et al. UMB 2016

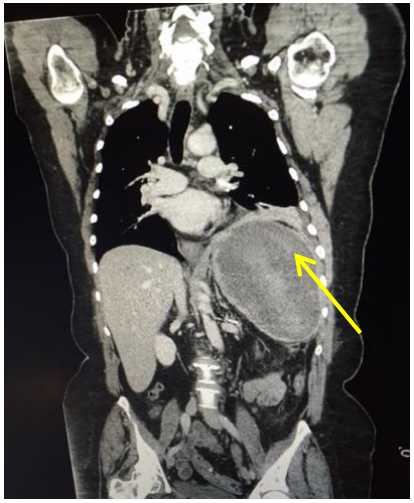
HISTOTRIPSY FOR LIQUEFACTION OF LARGE HEMATOMAS

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

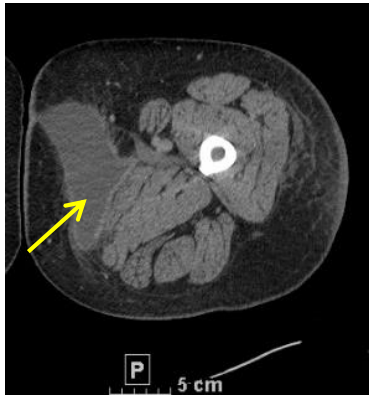
Pelvic hematoma



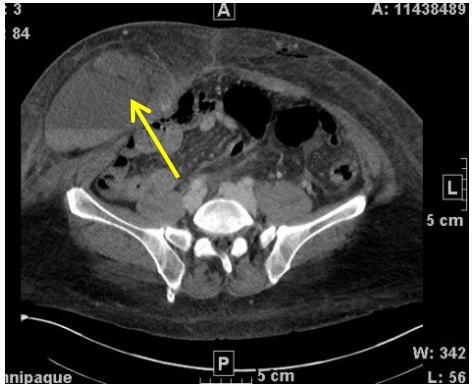
Splenic hematoma



Leg hematoma



Rectus sheath hematoma



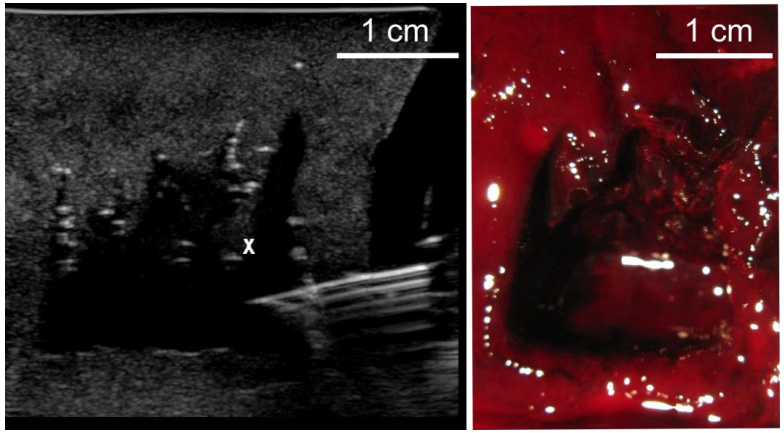
Health effects:

- 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[1]

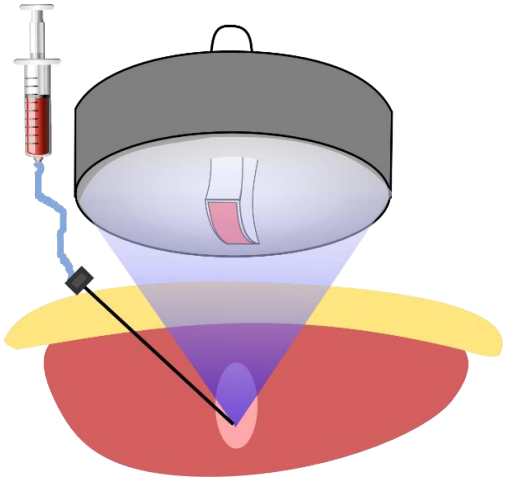


Liquefaction rate up to 1.3 cc/minute

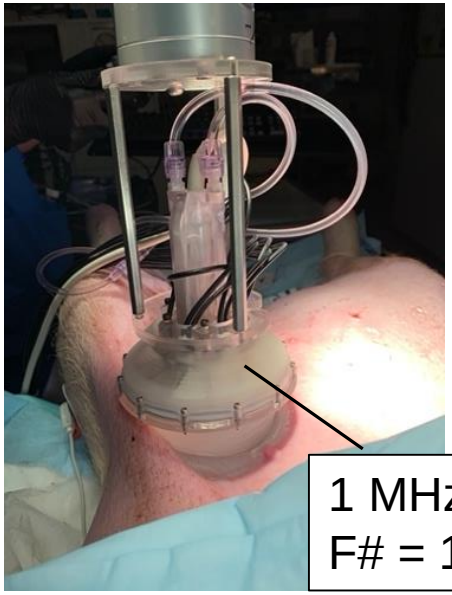
[1]*Khokhlova et al. UMB 2016*

HISTOTRIPSY FOR LIQUEFACTION OF LARGE HEMATOMAS

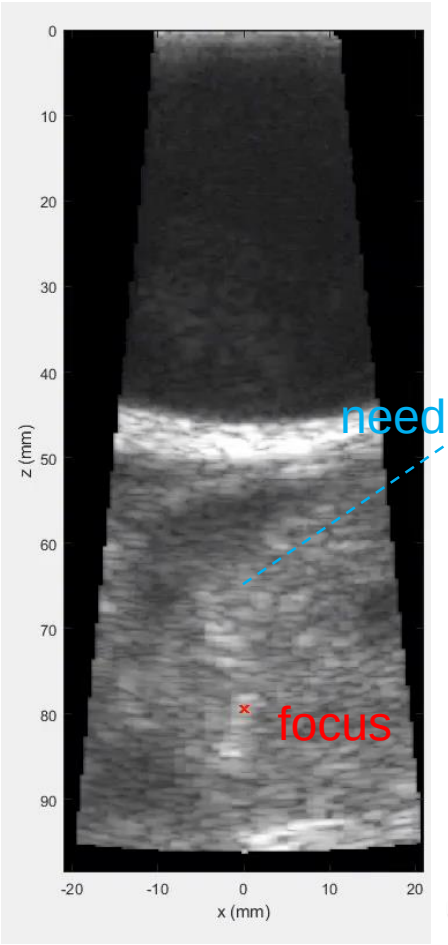
Alternative approach: liquefy hematoma with BH while continuously draining the liquid



Treatment of large acute pelvic hematoma in a pig *in vivo*



B-mode US imaging during treatment

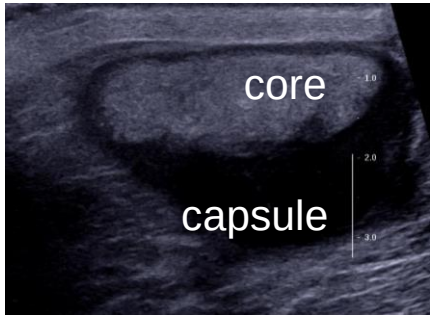


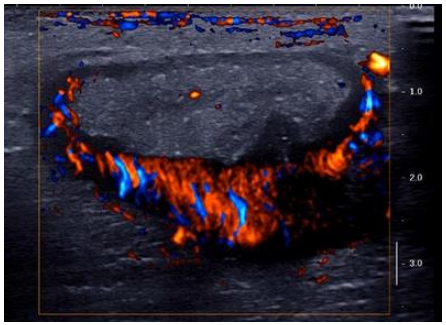
- Faster liquefaction rate (up to 5 mL/minute)
- No need to move the HIFU focus around the volume (hematoma collapses on itself)

BH FOR LIQUEFACTION AND DISINFECITON OF ABSCESSES

Abscess - walled-off collection of infected fluids containing viscous pus and bacteria
Often treated with percutaneous drainage for up to several weeks

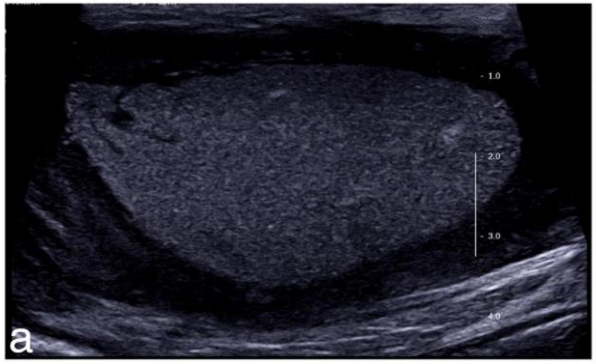
Porcine subcutaneous abscess model
- bimicrobial inoculation (E.coli+B.fragilis)
- abscesses mature in 2-4 weeks





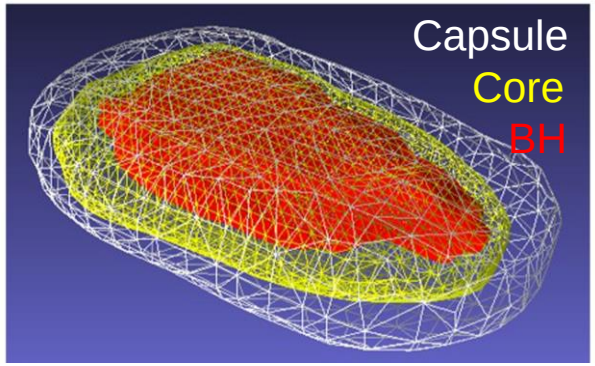
BH used to liquefy a large part of abscess volume within 20 minutes

B-mode before treatment



B-mode after treatment

3D ultrasound reconstruction



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

[1]*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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