

Histotripsy - Harnessing the Power of Acoustic Cavitation for Medicine

J. Brian Fowlkes, PhD

University of Michigan
Department of Radiology
Department of Biomedical Engineering



1

Disclosures

Histosonics – Founder and Scientific Advisor with financial interest.



2

Acknowledgements

- The Histotripsy Team
 - University of Michigan (Zhen Xu, Charles Cain, Tim Hall, Brian Fowlkes, Cliff Cho, Mishal Lala, Aditya Pandey, Gabe Owens, Jiaqi Shi, Lili Zhao)
 - University of Wisconsin (Fred Lee, Tim Ziemlewicz, Paul Laeseke)
 - HistoSonics
- Funding
 - NIH (R01 EB008998, R01 CA 211217, R01 NS108042, R01 DK 091267, R01 HL141967, R01 EB 028309)
 - Focused Ultrasound Foundation
 - Office of Naval Research (Dr. Timothy Bentley under grant N000141712058)
 - American Cancer Society (RSG-13-101-01-CCE)
 - The Hartwell Foundation



First Histotripsy Summit,
9/27/2019, Ann Arbor



3

Histotripsy

Definition: Non-invasive, non-thermal, mechanical (cavitation) tissue ablation

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



4

Histotripsy \neq **HIFU**

Histotripsy

- Very high intensity
- Pulsed energy
- Mechanical effect
- Cellular fractionation

HIFU

- High intensity
- “Continuous” energy
- Thermal effect
- Coagulation necrosis



5

What is Cavitation?

- Rapid formation and collapse of vapor/gas bubbles in a liquid.



Wikimedia Commons



6

Tremendous Energy



Wikimedia Commons

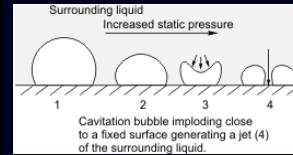


Erik Axdaht - Wikimedia Commons

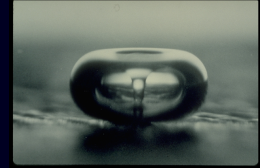


7

Locally Concentrated



Wikimedia Commons

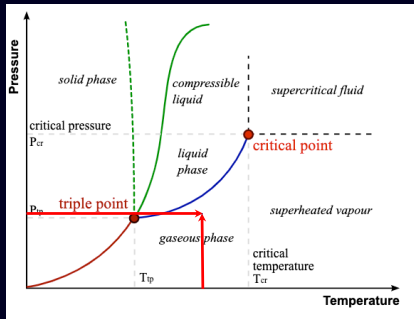


Courtesy of L. Crum



8

Boiling at Room Temperature



Wikimedia Commons



9



Wikimedia Commons

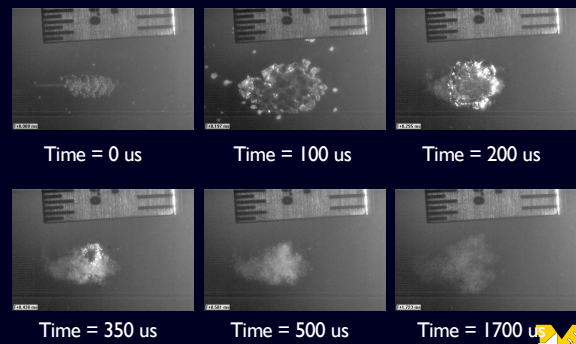


10

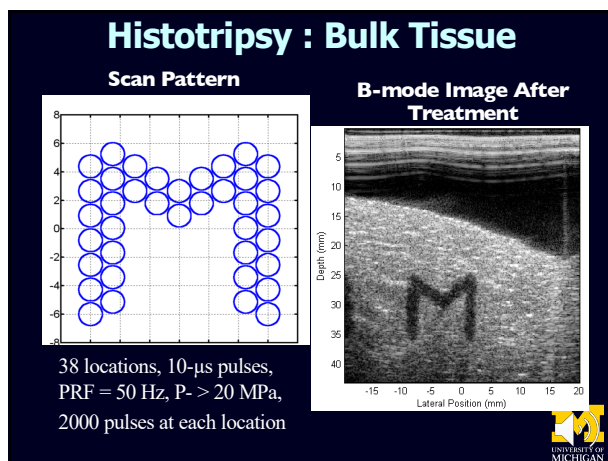


11

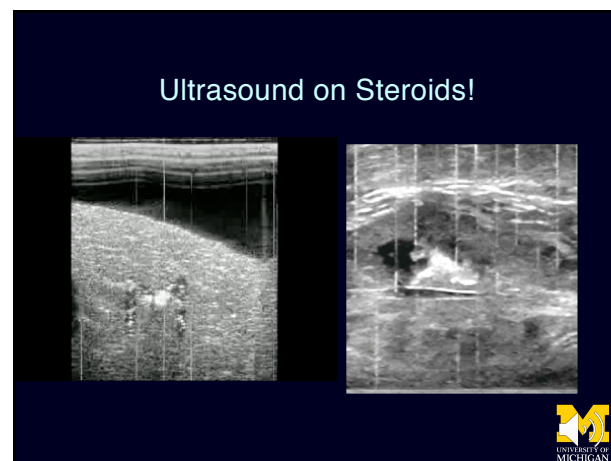
Non-prenucleated single pulse



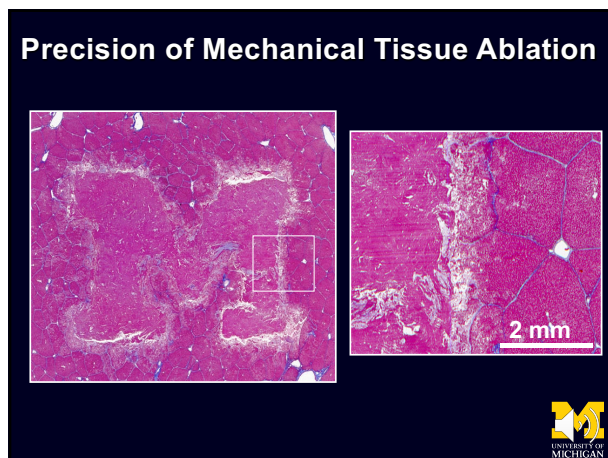
12



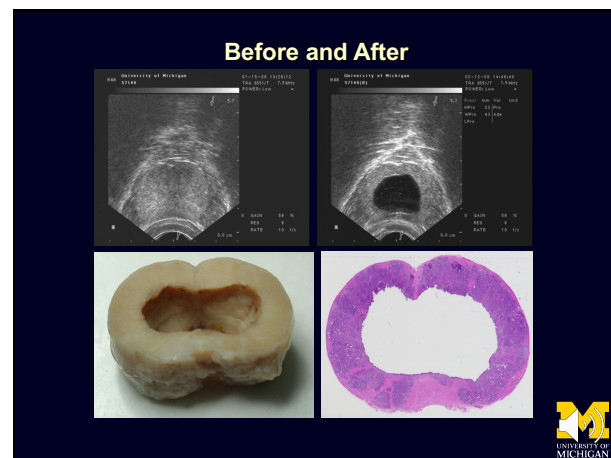
13



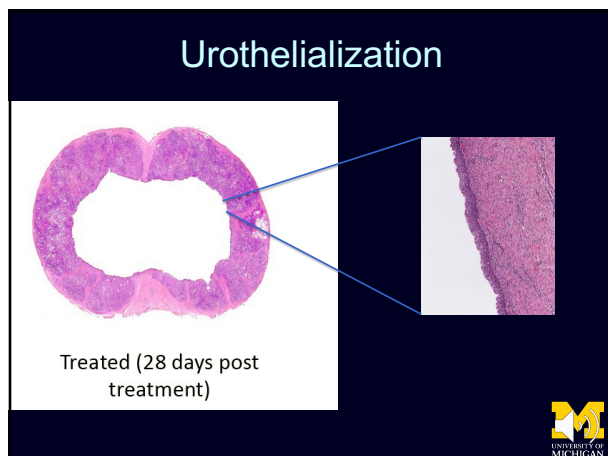
14



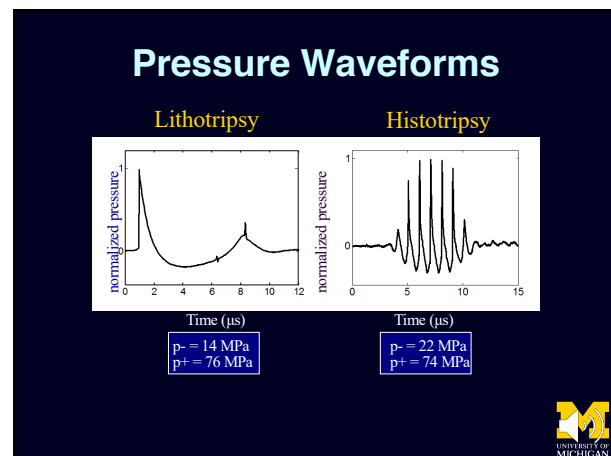
15



16



17



18

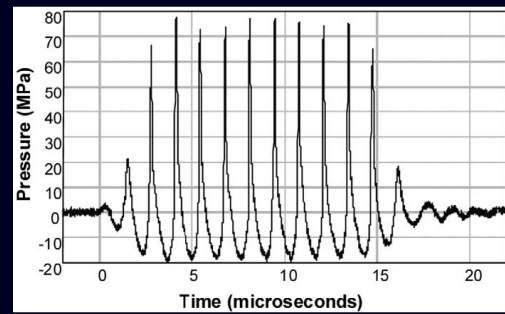
Initiation of Histotripsy

- Cavitation-cloud
 - Shock Scattering
 - Intrinsic Threshold
- Boiling
 - Boiling
 - And ?



19

Shock Scattering for Histotripsy



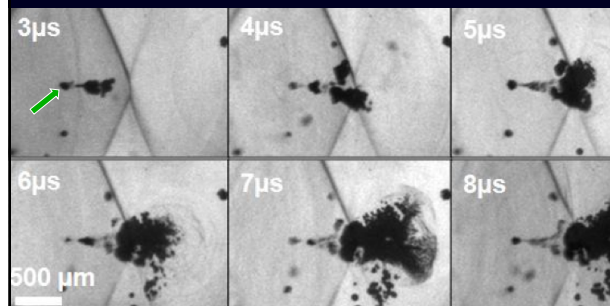
20

High Speed Imaging



21

Bubble Cloud Evolution

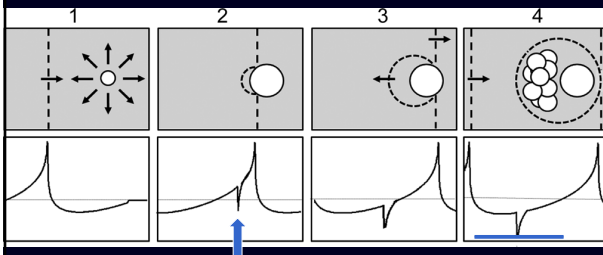


Maxwell et al. J Acoust Soc Am, 130(4): 1888-98, 2011.



22

Conceptually Speaking



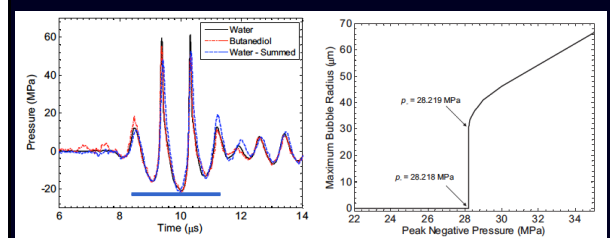
NOTE: Ultrasound propagating from the LEFT.

Maxwell et al. J. Acoust. Soc. Am., 130(4), 1888-98, 2011



23

What about short pulses?

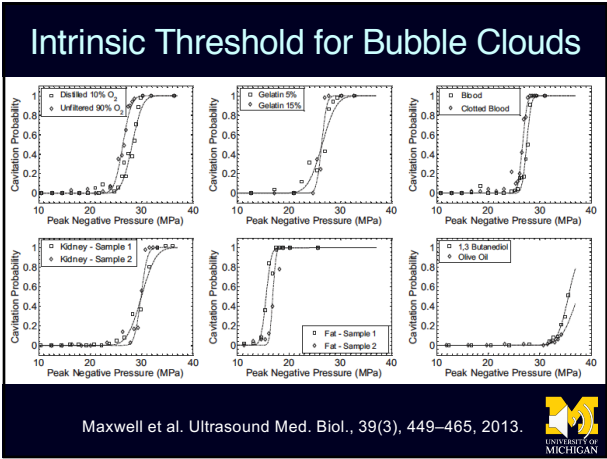


2.5 nm radius bubble

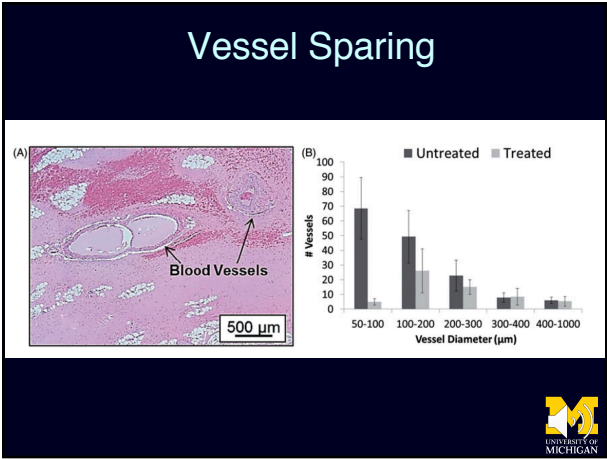
Maxwell, et al. Ultrasound in Med. & Biol., 39(3), 449-465, 2013



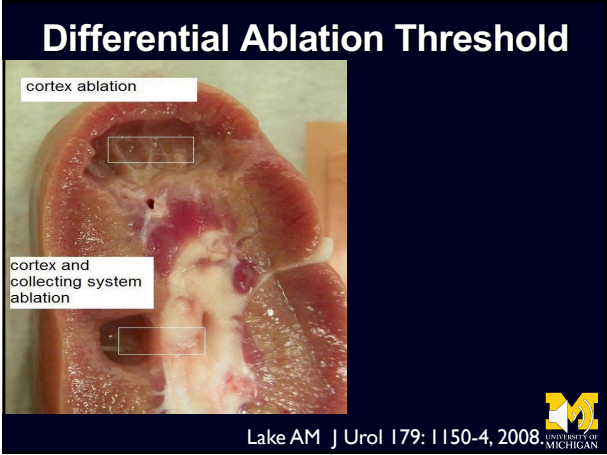
24



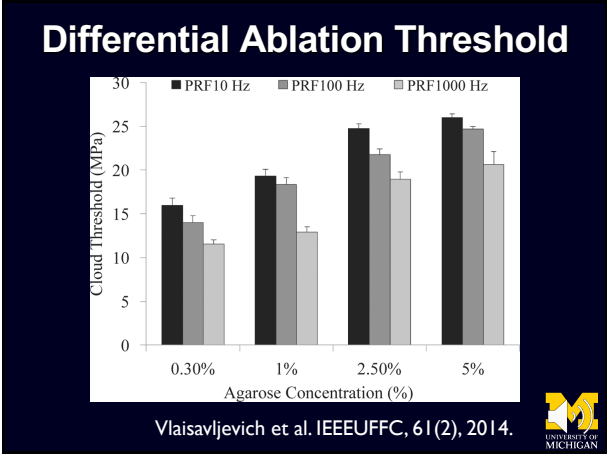
25



26



27



28

Differential Ablation Threshold

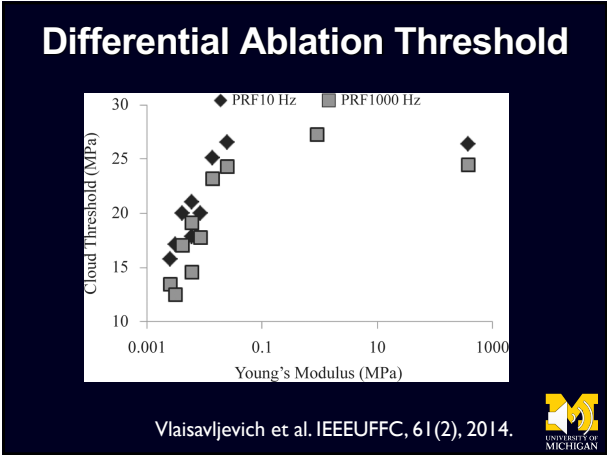
TABLE II. CAVITATION CLOUD INITIATION THRESHOLD IN EX VIVO PORCINE TISSUE.

Tissue	Threshold (MPa) PRF 100	Threshold (MPa) PRF 1000	Young's modulus (MPa)
Lung	1.578 ± 0.89	13.42 ± 1.08	0.0026
Fat	17.13 ± 1.41	13.26 ± 1.55	0.0032
Kidney	17.84 ± 1.48	14.56 ± 0.95	0.0061
Liver	19.97 ± 0.77	17.75 ± 1.07	0.0087
Heart	20.03 ± 0.36	17.06 ± 1.28	0.0042
Muscle	21.01 ± 0.48	19.12 ± 0.57	0.0062
Skin	25.10 ± 0.69	23.21 ± 1.01	0.014
Tongue	26.54 ± 0.88	24.27 ± 0.44	0.025
Tendon	26.41 ± 0.52	24.47 ± 0.49	380
Cartilage	no cloud	27.28 ± 0.85	0.90
Bone	no cloud	no cloud	18600

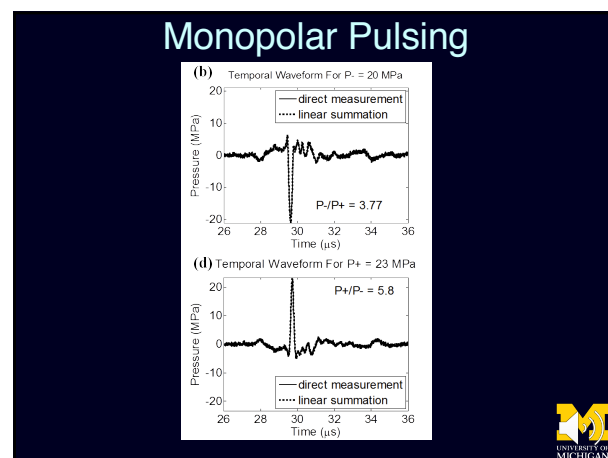
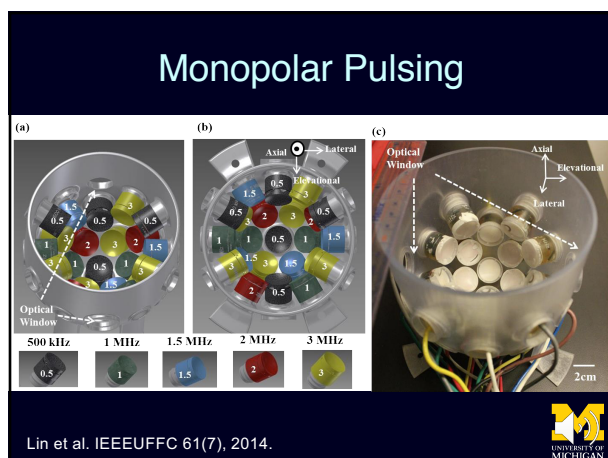
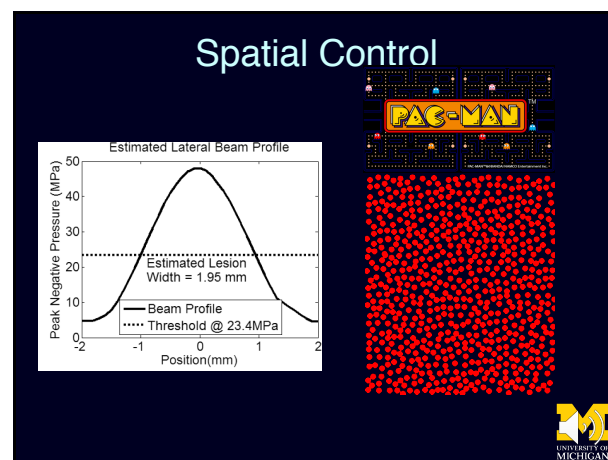
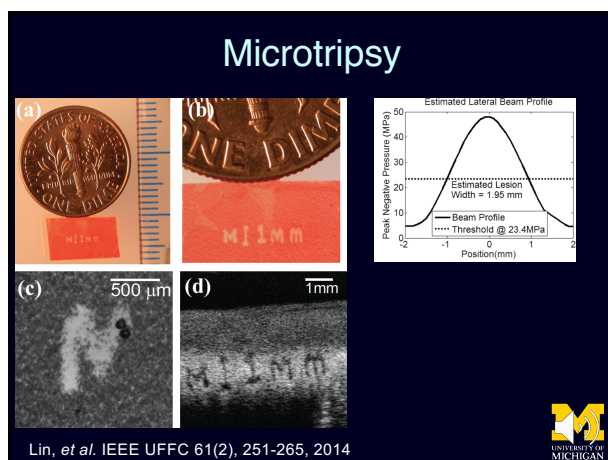
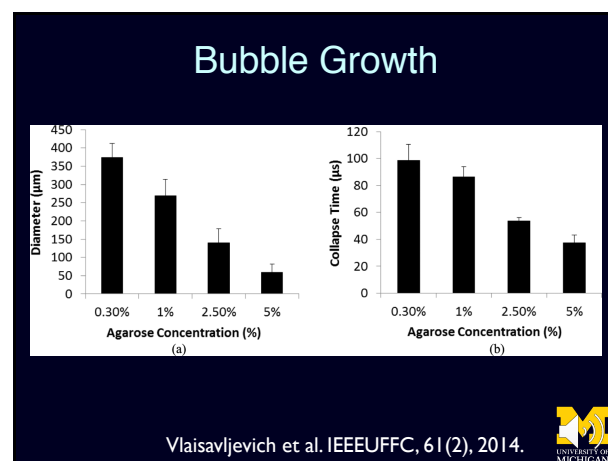
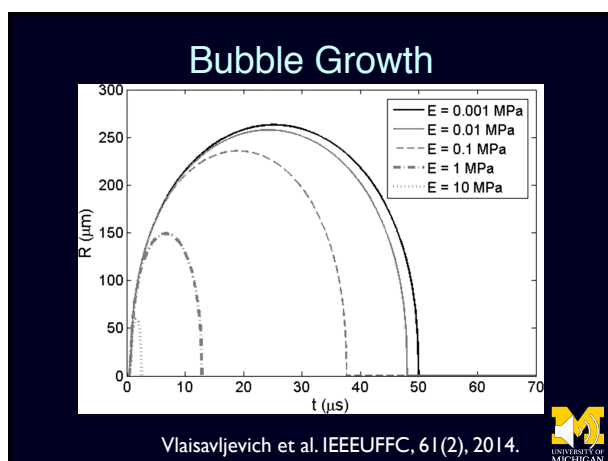
Table shows cavitation initiation threshold for porcine tissue treated at pulse repetition frequencies (PRFs) of 100 and 1000 Hz with corresponding Young's modulus (tension) values from literature [28]–[37].

Vlaisavljevich et al. *IEEEUFFC*, 61(2), 2014.

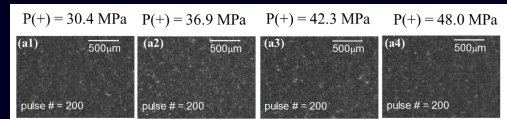
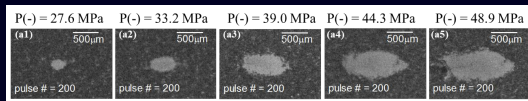
29



30

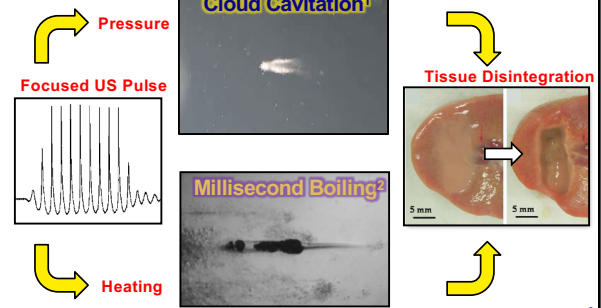


Monopolar Pulsing



37

Different mechanisms – similar result – exciting field



¹ Parsons *et al.* Ultrasound Med Biol. 2006;32:115-129

² Canney *et al.* Ultrasound Med Biol. 2010;36:250-67

³ Khokhlova, Fowlkes *et al.* Int. J. Hyperthermia, 2015, Feb 24:1-18.

newer clinical applications³



38

Rapid heating of tissue mimicking gel due to absorption at the shocks

160 W acoustic power

$I_p = 12000 \text{ W/cm}^2$

(in situ, linear deration)

Time-to-boil:

Predicted nonlinearly: 7 ms

Predicted linearly: 380 ms

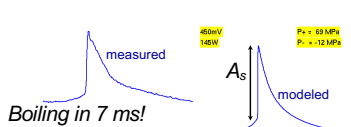
Nonlinear predictions

$$\frac{dT}{dt} = \frac{q_v}{c_v} = \frac{\epsilon f A_s^3}{6c_0^4 \rho_0^2 c_v}$$

($A_s = 68 \text{ MPa}$)

$$\Delta T(7 \text{ ms}) = 80^\circ \text{C}$$

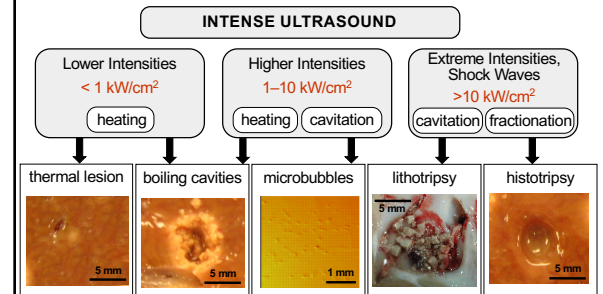
Boiling in 7 ms!



M. Canney, *et al.* Shock-induced heating and millisecond boiling in gels and tissue due to high intensity focused ultrasound, *UMB*, 2010, 36(2), 250-267.

39

Characteristic intensity levels of therapeutic ultrasound and corresponding bioeffects



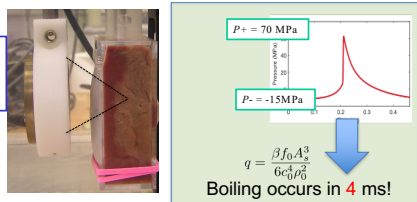
Maxwell A. *et al.* Disintegration of tissue using high intensity focused ultrasound: Two approaches that utilize shock waves. *Acoustics today*, 2012, 8(4), 24-36.



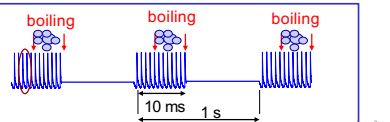
40

Shock wave heating in excised liver

HIFU source
• $f_0 = 2 \text{ MHz}$
• I_L up to 15 kW/cm^2



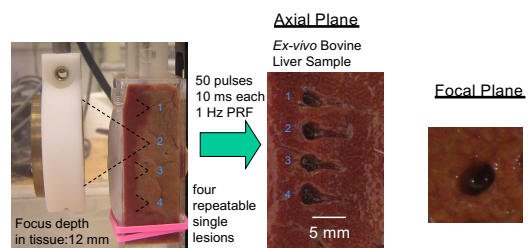
Protocol:
• 10 ms pulse
• 1 Hz PRF
• 1% duty cycle
• 50 seconds



41

Tissue fractionation

induced by 10 ms pulses, 1 Hz prf, 50 seconds

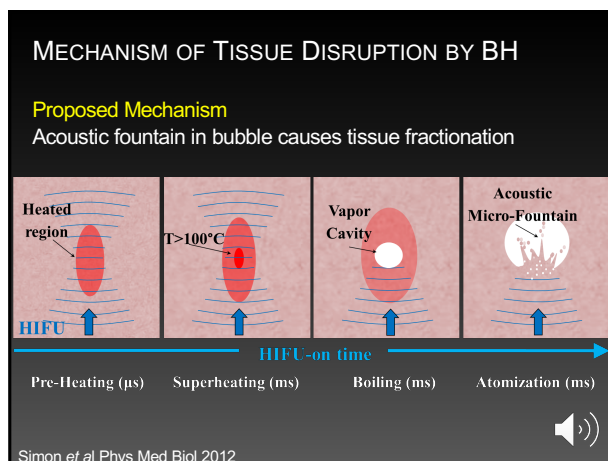


Tissue damage observed included repeatable "holes" in tissue filled with disintegrated tissue

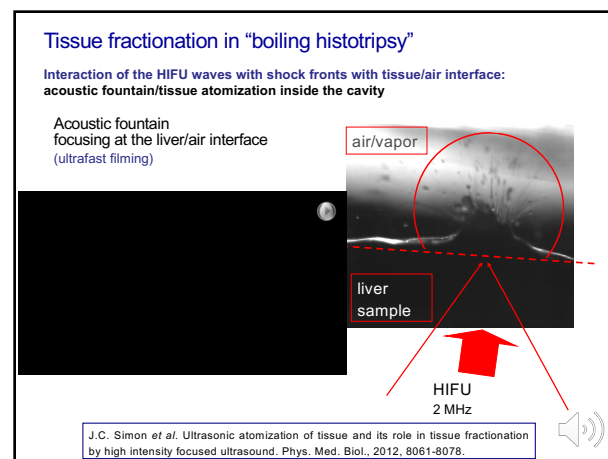
T.D. Khokhlova, *et al.* Controlled tissue emulsification produced by high intensity focused ultrasound waves and millisecond boiling. *JASA*, 2011, 130(5), 3498-3510.



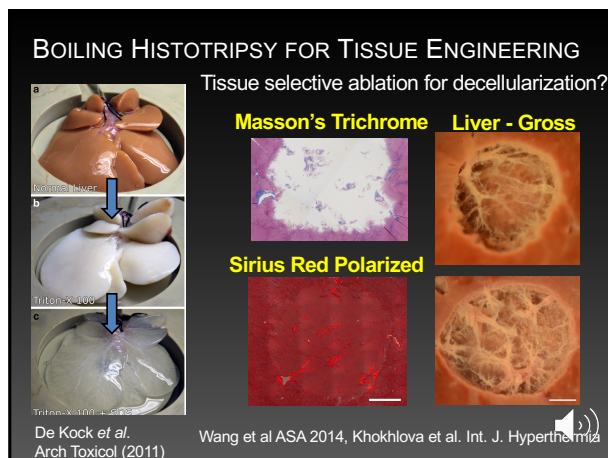
42



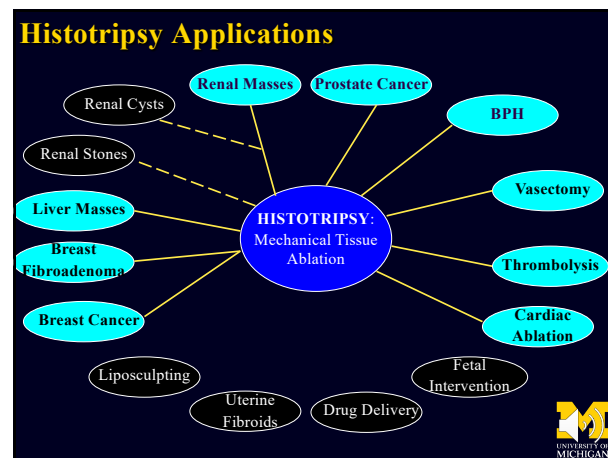
43



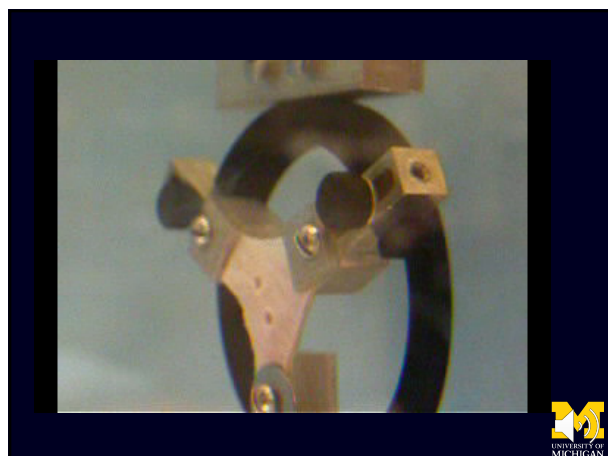
44



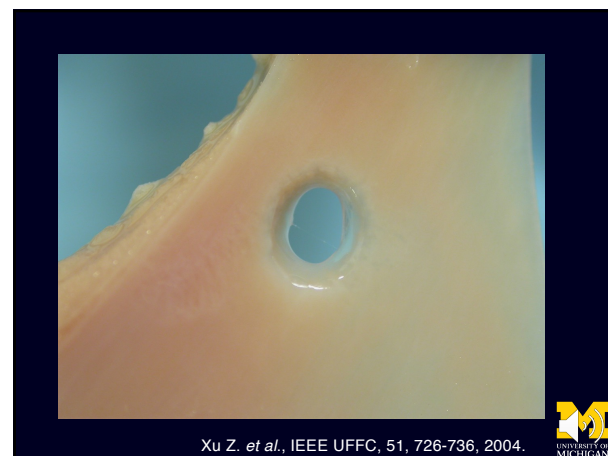
45



46



47



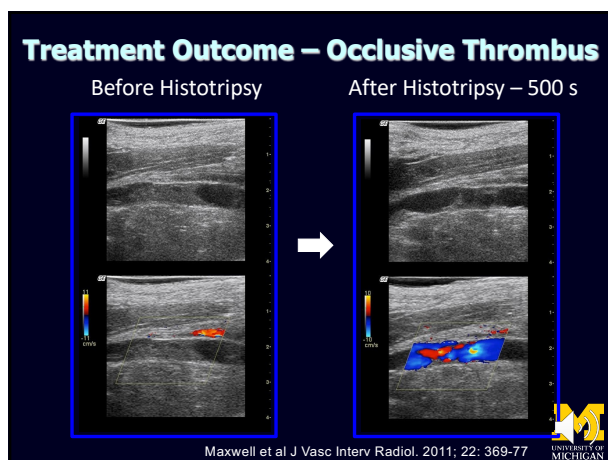
48



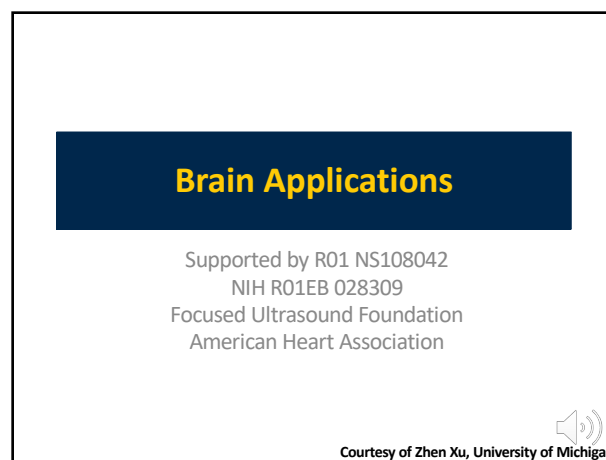
49



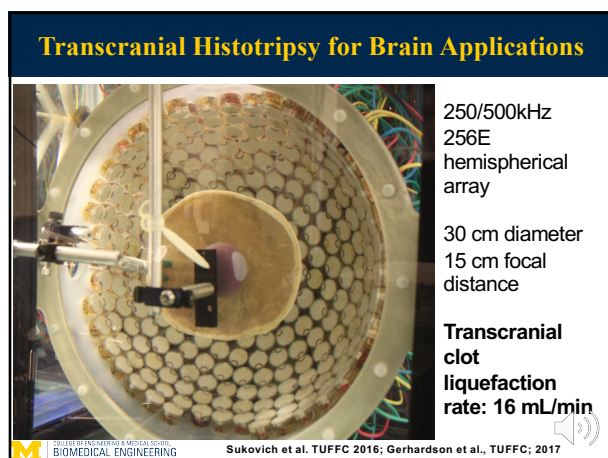
50



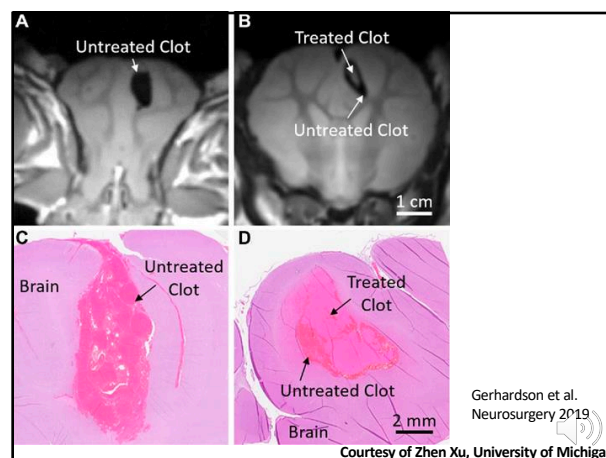
51



52



53



54

Transcranial Histotripsy

- Capability to
 - ablate a volume
 - ablate near skull surface
 - Without overheating skull

Gerhardson et al., UMB, 43(10):2302-17

55

Transcranial Histotripsy – In Vivo Safety

Courtesy of Zhen Xu, University of Michigan

Sukovich et al., J. Neurosurgery, 2018

56

Acoustic Cavitation Emission (ACE) : Transcranial focal pressure measurement

Aberration Correction Method	Pressure		-3dB Width [x × y × z] (mm)	Estimated Steering Diameter* (mm)
	Est'd Peak (MPa)	% Increase Over None		
None	35	N/A	1.21 × 1.77 × 3.54	16
Hydrophone	70	100%	1.17 × 1.36 × 2.75	40
ACE	58	66%	1.20 × 1.58 × 3.05	30

Aberration correction through excised human skull improves the focal pressure >60%

Courtesy of Zhen Xu, University of Michigan

57

Liver Cancer

Supported by NIH R01 CA211217
American Cancer Society (RSG-13-101-01-CCE)
Forbes Institute
Focused Ultrasound Foundation

Courtesy of Zhen Xu, University of Michigan

58

Histotripsy Induces Systemic Immune Response

Qu et al. Journal for Immunotherapy of Cancer 2020;8:e000200.

Courtesy of Zhen Xu, University of Michigan

59

Histotripsy Induces Systemic Immune Response

Qu et al. Journal for Immunotherapy of Cancer 2020;8:e000200.

Courtesy of Zhen Xu, University of Michigan

60

Histotripsy Initial Human Trial

Purpose: To evaluate the safety and short-term efficacy of histotripsy for hepatic ablation in patients with primary or metastatic liver cancer

Joan Vidal Jove, Surgery, Barcelona University Hospital
Fred Lee, Tim Ziemlewicz, Radiology, University of Wisconsin
Jon Cannata, Ryan Miller, Alex Duryea, HistoSonics



61

Patient Population

- 8 patients
 - 5 Female/3 Male (mean 64 yrs (range 46-87))
- 11 tumors
 - 6 patients - 1 tumor
 - 1 patient - 2 tumors
 - 1 patient - 3 tumors
- Mean tumor size 1.3 cm (0.5-2.3 cm)

1° Tumor Type	Tumor Number
Colorectal	7
Gallbladder	2
HCC	1
Breast	1

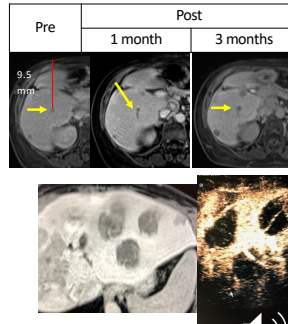


Courtesy of Zhen Xu, University of Michigan

62

Results

- Secondary Endpoints
 - Local tumor regression
 - 90 % (9/10)
 - Liver function
 - Transient 2-3x elevation of AST/ALT which normalized 1 week after histotripsy in all patients
 - Analgesic requirements
 - No analgesic requests
 - No reported pain
 - Abscopal effect
 - 2 in 8 patients biomarkers drop
 - In 1 patient, overall tumor burden reduced in 2 months



Courtesy of Zhen Xu, University of Michigan

63

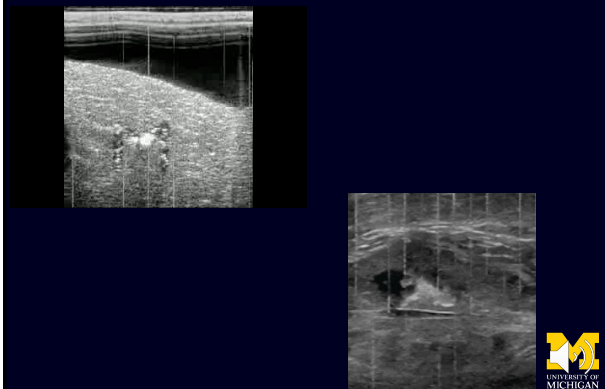
Conclusions

- Controlling acoustic cavitation and its associated effects is possible using ultrasound fields.
- Histotripsy provides a means for tissue disruption using a non-thermal mechanism.
- A wide variety of applications are envisioned histotripsy therapies.



64

Thanks for your attention!!!!



65