QUANTITATIVE CONTRAST-ENHANCED ULTRASOUND IMAGING FROM PRE-CLINICAL MODELS TO HUMAN TRIALS

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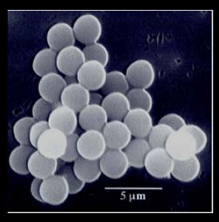
Disclosures

- Equipment loan from Canon Medical Systems
- Equipment loan from GE Medical Systems
- Equipment loan from Siemens Healthineers
- Contrast agent from GE Healthcare
- Contrast agent from Lantheus Medical Imaging
- Contrast agent from Bracco

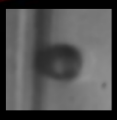
Ultrasound Contrast Agents

- Gas filled 1 to 10 μm bubbles
- Injected intravenously and transpulmonary
- Air or higher molecular weight gasses
- Bubbles are encapsulated for longevity
  - Albumin or polymer hard shell
  - Lipid or surfactant coated
- Up to 30 dB increase in SNR
- Signals mainly from vessels 20 - 40 μm

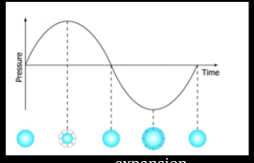


[www.escardio.org]

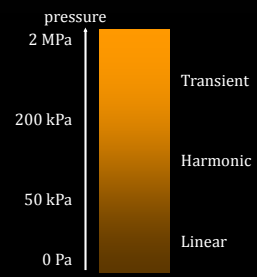
Microbubble Oscillations



compression

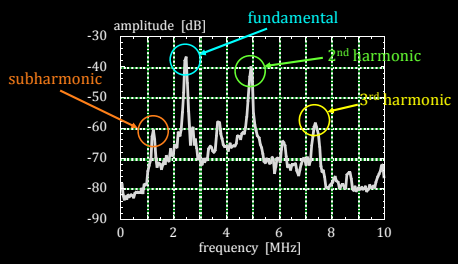


expansion



[Kotopoullis et al. J. Acoust.Soc. Am. 2016; www.levermed.com]

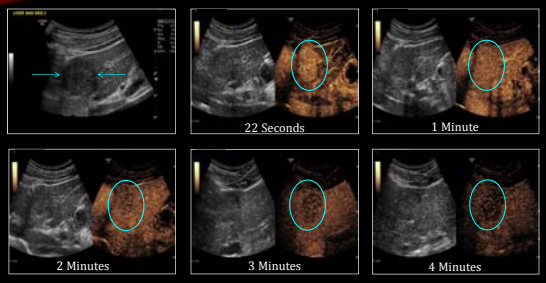
Nonlinear Contrast Spectrum



FDA Approved Contrast Agents

Name & manufacturer	Indications
Optison GE Healthcare, Princeton, NJ	LVO & EBD
Definity Lantheus Medical, N Billerica, MA	LVO & EBD
Lumason (SonoVue) Bracco, Milan, Italy	LVO & EBD focal liver lesions vesicoureteral reflux

Liver Lesion Characterization

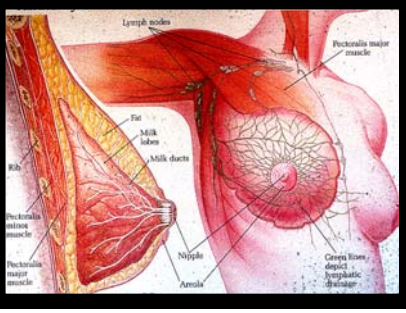


Diagnosis: HCC

Subdermal Applications of Ultrasound Contrast

Supported in part by NIH R01 CA100370, R01 CA172336 and R21 CA137733 as well as by GE Healthcare

SLNs of the Female Breast



Animal Tumor Model

- 63 Sinclair swine with naturally occurring melanoma
- Weights 3.0 to 17.0 kg
- Melanomas are similar to human superficial spreading melanoma
- 70% incidence of SLN metastases
- 105 primary melanomas (average tumor diameter: 17 mm)

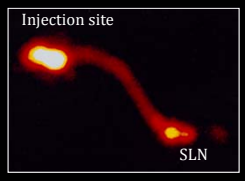
[Goldberg et al., JUM, 2011]

Lymphosonography

- Four subcutaneous injections (0.25 mL) of an ultrasound contrast agent
- Sonazoid (GE Healthcare, Oslo, Norway)
- Elegra ultrasound scanner with 7.5 MHz linear array (Siemens Healthineers, Mountain View, CA)
- Baseline: grayscale and color flow imaging
- Post contrast: Grayscale phase inversion harmonic imaging (PIHI)
- Mechanical index (MI) from 0.2 to 0.4

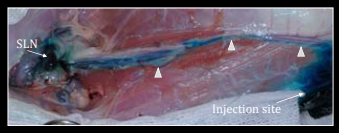
Lymphoscintigraphy

- 50 µCi filtered Tc-99m sulfur colloid was injected in 4 locations around melanomas
  - Area massaged for 5 minutes
  - Starcam 300 Gamma camera (GE Healthcare, Milwaukee, WI)



Gold Standard: Blue Dye Injection

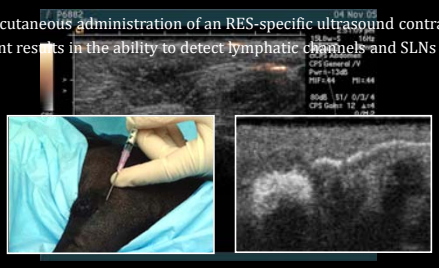
- Peritumoral injections of blue dye and surgical dissection after euthanasia
  - 0.5 mL Patent Blue V Sodium (Guerbet, Cedex, France) was injected at the same sites as Sonazoid and Tc-99m
  - Areas massaged to enhance up-take of dye



- Accuracy of sonography and scintigraphy for SLN detection was compared to the gold standard using McNemar's test

SLN Identification

Subcutaneous administration of an RES-specific ultrasound contrast agent results in the ability to detect lymphatic channels and SLNs



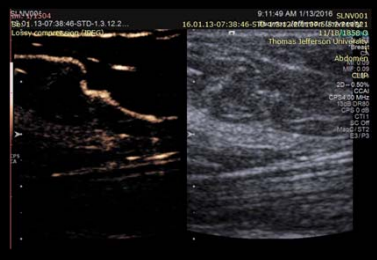
Overall Detection of SLNs

	SLNs	FP
Lymphosonography	318	11
Lymphoscintigraphy	240	20
Blue dye / surgery	358	

Accuracy:

- Lymphosonography 82 % (318/387)
- Lymphoscintigraphy 63 % (240/380)
- Difference was statistically significant ($p < 0.0001$)

Human Study

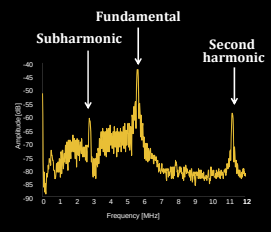


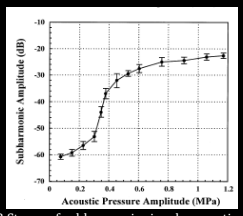
[Machado et al., JUM, 2018]

Subharmonic Pressure Estimation *In Vitro* and *In Vivo*

Supported in part by the U.S. Army Medical Research Material Command under W81XWH-08-1-0503, by AHA grant no 0655441U as well as by NIH R21 HL081892, RC1 DK087365 and R01 DK098526 as well as by GE Healthcare, Oslo, Norway

Subharmonic Imaging (SHI)

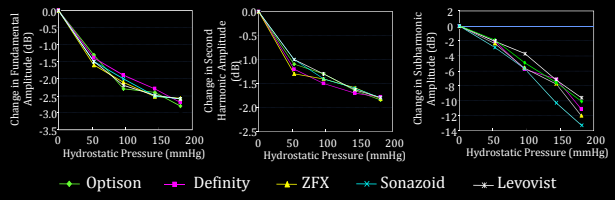




3 Stages of subharmonic signal generation:

- Occurrence
- Growth
- Saturation

Subharmonic Aided Pressure Estimation (SHAPE)

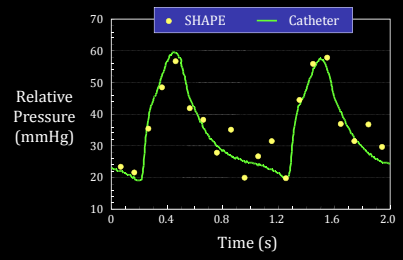


N = 3

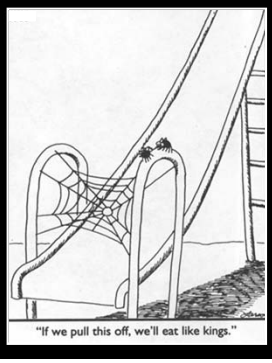
[Halldorsdottir et al., Ultrasonic Imaging, 2011]

In Vivo Setup

In Vivo Pressure Measurements; Proof of Concept



[Forsberg et al., IEEE UFFC, 2005]

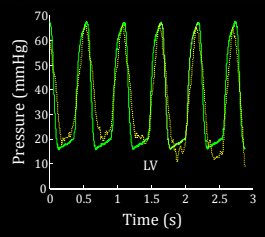


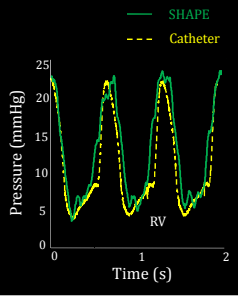
In Vivo Cardiac Setup

Closed-chest dog model

[Dave et al., JACC Cardiovasc Img, & Am J Physiol Heart Circ Physiol, 2012]

Cardiac Pressure Waveforms





LV Pressures with Individual Calibration Factor

LV Pressures	Canine 1			Canine 2		
	SHAPE (mmHg)	Catheter (mmHg)	Error (mmHg)	SHAPE (mmHg)	Catheter (mmHg)	Error (mmHg)
Mean Diastolic	20.1	17.6	2.5	14.2	13.4	0.8
Min. Diastolic	15.9	15.7	0.2	7.5	8.9	-1.4
End Diastolic	22.1	19.7	2.3	19.1	16.9	2.2
Mean	41.1	35.6	5.5	36.2	39.1	-2.8
Range	54.3	53.1	1.2	76.3	73.2	3.1

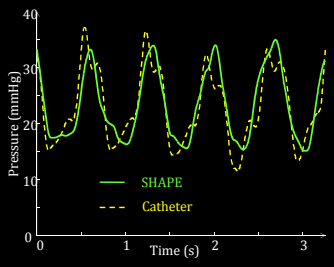
RV Pressures

Individual calibration factor

Canine		SHAPE (mmHg)	Catheter (mmHg)	Error (mmHg)
1	Peak Systolic	24.5	22.2	-2.3
	Minimum Systolic	5.4	4.5	-0.9
2	Peak Systolic	21.3	21.3	0.0
	Minimum Systolic	5.0	4.2	-0.8
3	Peak Systolic	23.6	20.2	-3.4
	Minimum Systolic	5.3	5.0	-0.3
4	Peak Systolic	21.2	18.1	-3.1
	Minimum Systolic	3.6	3.5	-0.1
5	Peak Systolic	32.8	30.2	-2.6
	Minimum Systolic	8.2	6.4	-1.8

RV Pressure Waveform in a Patient

Peak systolic RV pressure
Catheter: 36.6 ± 2.9 mmHg
SHAPE: 34.0 ± 1.6 mmHg



[Dave et al., Ultrasound Med Biol, 2017]

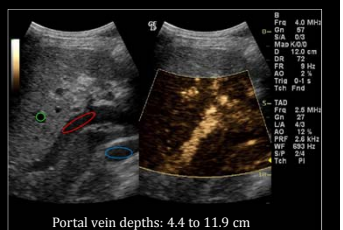
Pilot Study of SHAPE in Portal Hypertension

- 45 patients (27 M; 18 F) scheduled for a transjugular liver biopsy
  - HVPG measurements as reference
- IRB and FDA approved (IND: 100,083)
- Subjects provided written consent
- 12 subjects post-liver transplantation
- Subjects were 19 to 71 years old
- BMIs ranged from 17.2 to 57.2
- Sonazoid 0.72 µL microbubbles/kg/hour

[Eisenbrey et al., Radiology, 2013]

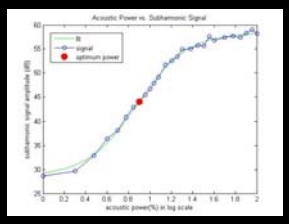
In Vivo Techniques and Analysis

- Modified Logiq 9 scanner with 4C probe
- Grayscale SHI (Tx/Rx: 2.5/1.25 MHz)
- Acoustic output power optimized for each patient; 6 – 60 % (1-3 MPa_{pk-pk})
- Pulse length: 4 cycles
- RF data acquired over 5 seconds (N = 3)
- Subharmonic signals analyzed off-line
- Linear regression analysis



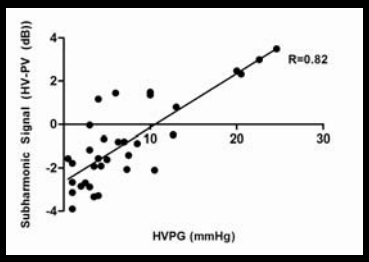
Portal vein depths: 4.4 to 11.9 cm

Acoustic Power Optimization

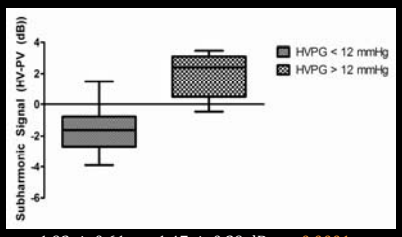


[Dave et al., Ultrasonics, 2013]

Subharmonic Signal versus HVPG



Predicting Portal Hypertension



1.93 ± 0.61 vs. -1.47 ± 0.29 dB; $p < 0.0001$

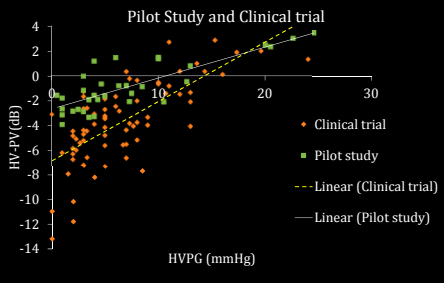
Clinical Study of SHAPE for Diagnosing Portal Hypertension

- 178 patients scheduled for a transjugular liver biopsy at TJU or HUP
  - HVPG measurements as reference
- IRB and FDA approved (IND: 124,465)
- Subjects provided written consent
- Modified Logiq 9 scanner with 4C probe (Tx/Rx: 2.5/1.25 MHz)
- Output power optimized individually
- Gaussian windowed binomial filtered square wave
- Sonazoid 1.44 µL microbubbles/kg/hour

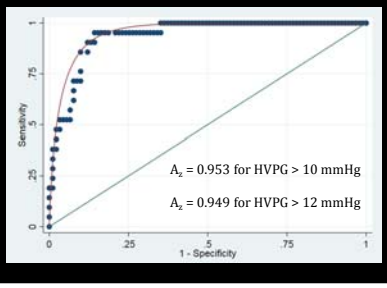
2 mmHg

10 mmHg

Subharmonic Signal versus HVPG



Diagnosing Portal Hypertension with SHAPE



N = 125

Contrast-Enhanced Ultrasound for Augmenting Therapy

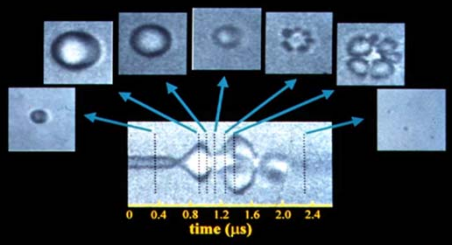
Supported in part by NIH R01 CA194307, R01 CA199646, R21 CA190926, and an SKCC Breast Cancer Pilot Award, by GE Healthcare, Princeton, NJ, USA, Siemens Healthineers, Mountain View, CA as well as Lantheus Medical Imaging, N Billerica, MA, USA

Tumor Hypoxia

- The tumor microenvironment is chronically hypoxic limiting the efficacy of radiation therapy
- A relatively small increase in oxygen partial pressure (pO_2) in hypoxic cells can result in significant sensitization to radiation therapy
- Approaches using systemic delivery of O_2 immediately prior or during radiotherapy have not translated to clinical usage, primarily due to the body's natural tendency to regulate O_2
- Current research is now focused on localized delivery of O_2 for improving radio-sensitivity

Ultrasound-sensitive oxygen-filled microbubbles may be a local, noninvasive, and effective method for overcoming hypoxia-associated radio-resistance

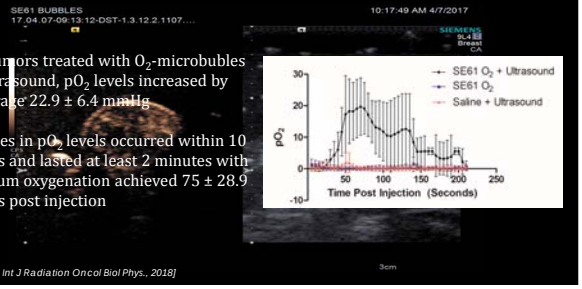
Microbubble Fragmentation



(1 cycle, 2.4 MHz at 1.1 MPa)

Chomas, Dayton, Ferrara. U.C. Davis,

O_2 Delivery from Microbubbles *In Vivo*



- In all tumors treated with O_2-microbubles and ultrasound, pO_2 levels increased by on average 22.9 ± 6.4 mmHg
- Increases in pO_2 levels occurred within 10 seconds and lasted at least 2 minutes with maximum oxygenation achieved 75 ± 28.9 seconds post injection

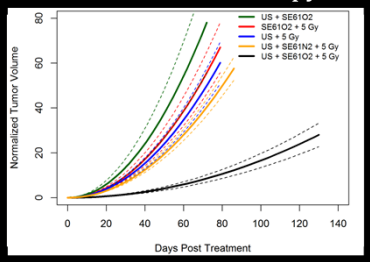
[Eisenbrey et al., Int J Radiation Oncol Biol Phys., 2018]

O_2 Microbubble Tumor Radiotherapy Sensitization

50 mice with MDA-MB-231 breast tumor xenografts received O_2- or N_2-microbubbles and 75 seconds of ultrasound with or without 5 Gy external beam radiation

Group	Radiation Therapy	Microbubble	Ultrasound
1	5 Gy	Oxygen	Yes
2	5 Gy	Oxygen	No
3	0 Gy	Oxygen	Yes
4	5 Gy	Nitrogen	Yes
5	5 Gy	None	Yes

O_2 Microbubble Tumor Radiotherapy Sensitization



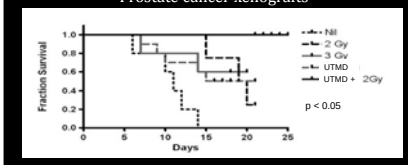
N = 50

[Eisenbrey et al., Int J Radiation Oncol Biol Phys., 2018]

Inertial Cavitation of Microbubbles Sensitizes Tumors to Radiation

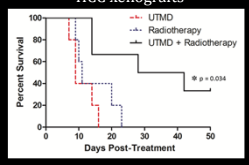
Ultrasound Targeted Microbubble Destruction (UTMD)

Prostate cancer xenografts



[Czarnota et al., Proc Natl Acad Sci USA, 2012]

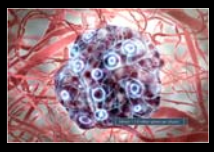
HCC xenografts



[Daecher et al., Cancer Lett, 2017]

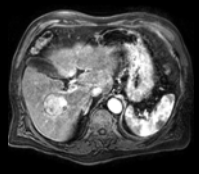
Phase 1/2 Clinical Trial of UTMD Augmented HCC Radioembolization

- Target is 52 patients with HCC scheduled for radioembolization with yttrium-90 (Y90) beads
- IRB and FDA approved (IND no: 126,768)
- Subjects randomized to a control group (Y90 alone) or to a UTMD + Y90 group
- Optison infusion (5 mL in 50 mL saline) over 10 min
- Siemens S3000 with 6C1 probe & flash-replenishment
- UTMD 2-4 hours, 1 week and 2 weeks post treatment
  - 3 safety outcomes (liver function test, physiologic & AE monitoring)
  - 3 efficacy outcomes (mRECIST, time to next treatment & survival)



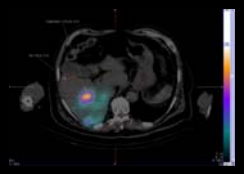
[https://www.utmedicalcenter.org/cancer-institute/cancers-by-site/liver-and-bile-duct-cancer/]

Example Case



Baseline MRI showing HCV male with 5.3 cm HCC in segment 6

Angiography showing segment 6 hepatic vein access and tumor localization prior to Y90 delivery

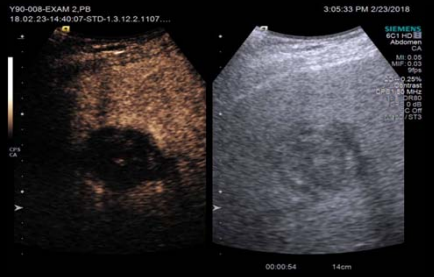


Nuclear medicine SPECT showing effective localized delivery to HCC via catheter

Example Case

UTMD session 3 hours post radioembolization

Example Case

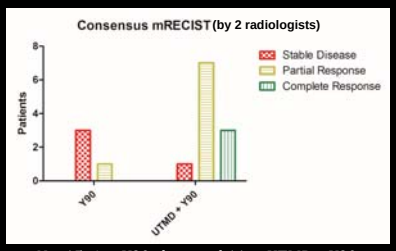


UTMD session 7 days post radioembolization

Results to Date

- 19 patients enrolled to date (12 in UTMD + Y90 group and 7 in Y90 alone)
- 2 AE in control group (fatigue, MI), 1 AE in UTMD group (fatigue)
- 3 deaths in Y90 alone group, 1 death in UTMD + Y90 (unrelated)
- No differences in physiological parameters pre to post UTMD ($p \geq 0.10$)
  - Heart rate, temperature, systolic and diastolic pressures
- No difference in blood work after 1 month ($p \geq 0.17$)
  - Billirubin, AST, ALT, creatinine, WBC, albumin
- Follow up imaging available on 15 patients to date

Preliminary Efficacy Results to Date



N = 15; 4 in Y90 alone and 11 in UTMD + Y90

Conclusions

An introduction to IV as well as subdermal contrast enhanced ultrasound imaging was given

SHI and SHAPE are new techniques for contrast specific imaging and non-invasive pressure estimation based on subharmonic signals from contrast microbubbles

Augmenting Y90 radiation treatment of HCC using contrast microbubbles was described

THANK YOU !

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