QUANTITATIVE SUBHARMONIC PRESSURE ESTIMATION *IN VIVO*

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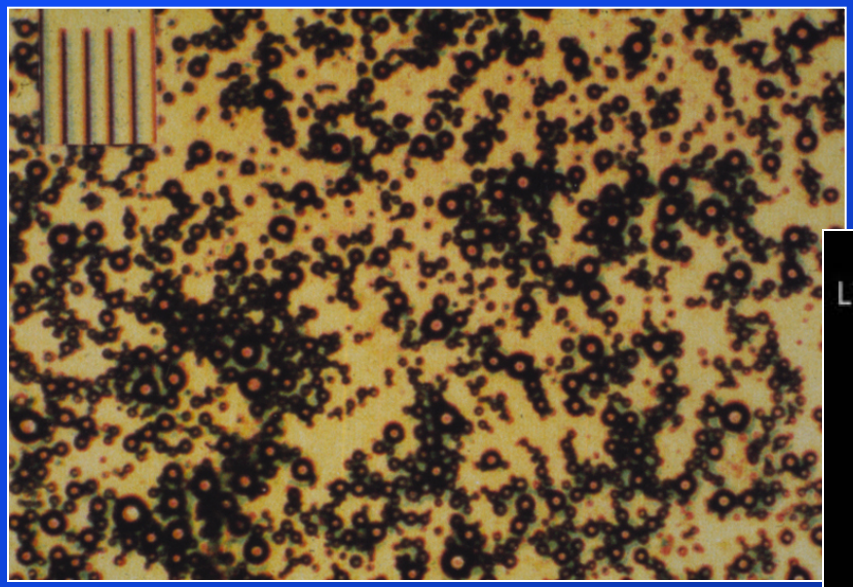
GE Healthcare
Analogic Ultrasound

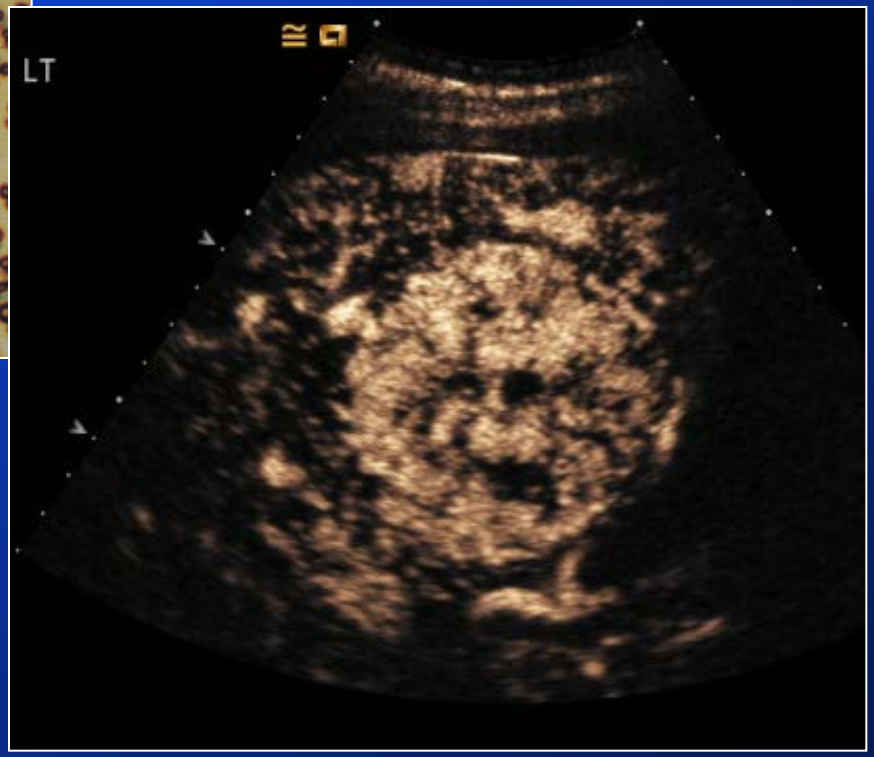
Ultrasound Contrast Agents

- Gas filled 1 to 10 μm bubbles
- Injected intravenously and transpulmonary
- Air or higher molecular weight gasses
- Bubbles are encapsulated:
  - Albumin or polymer hard shell
  - Lipid or surfactant coated

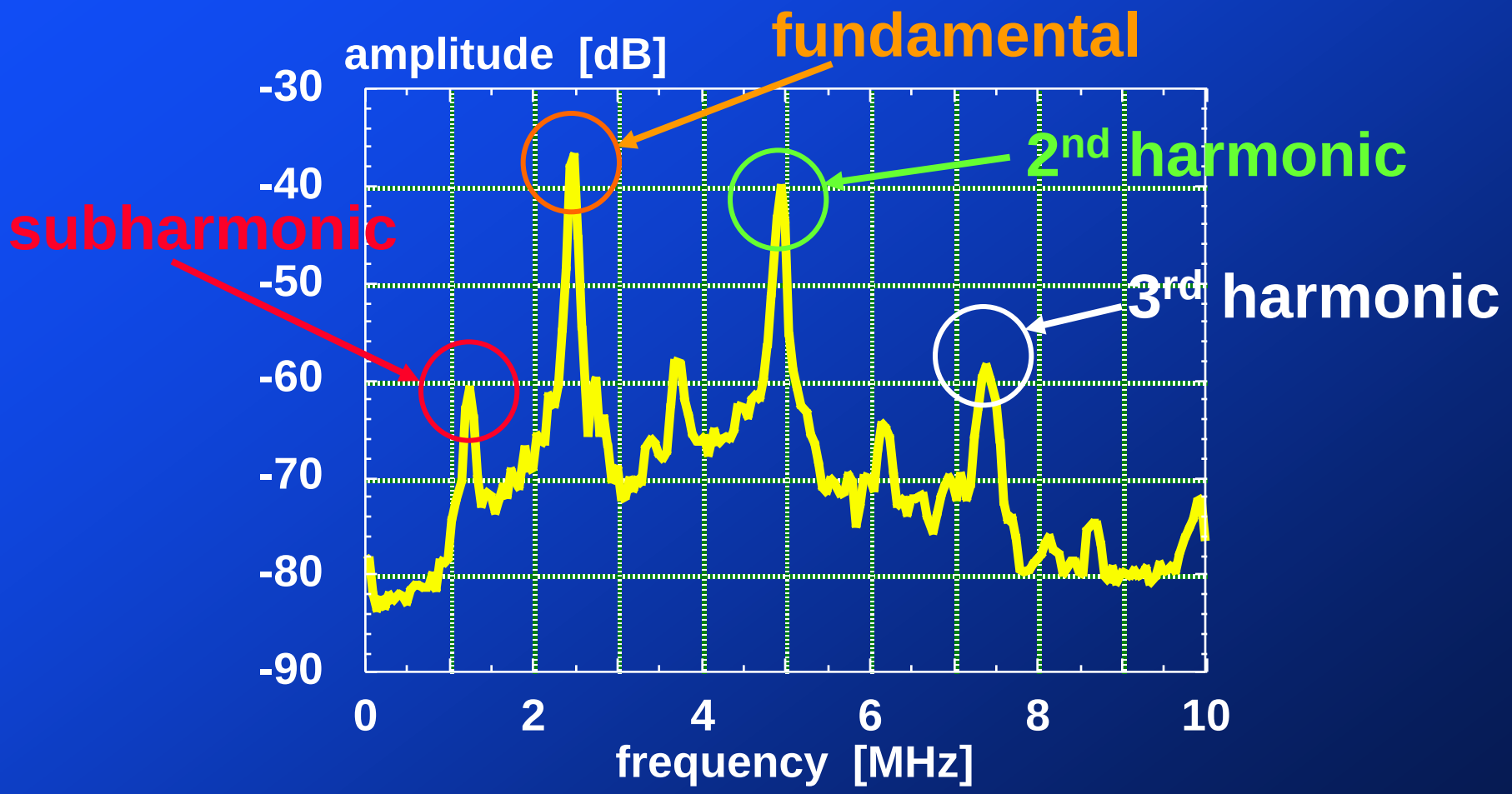
  for longevity
- Up to 30 dB increase in SNR
- Signals mainly from vessels 20 - 40 μm

Ultrasound Contrast Imaging



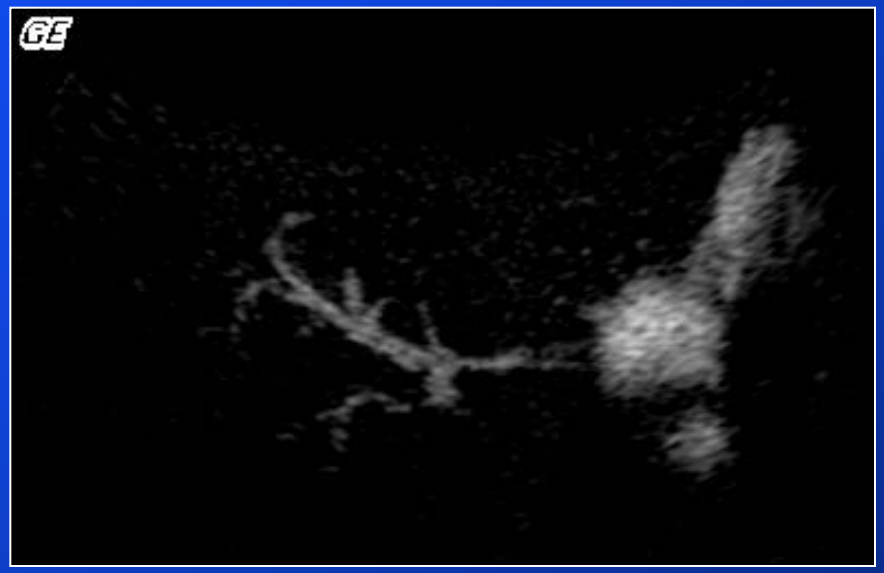


Nonlinear Contrast Spectrum

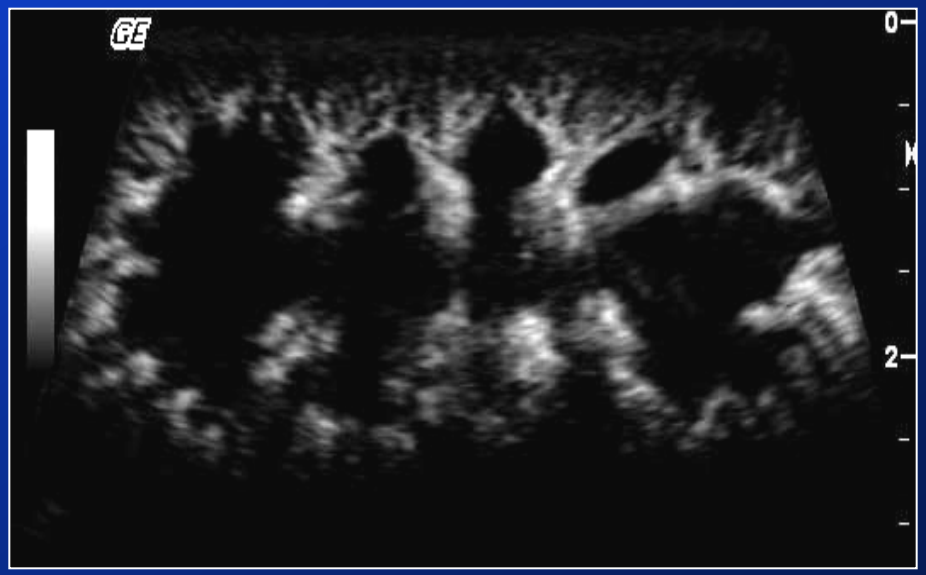


Contrast-Enhanced SHI

- Improve tissue suppression
- Increase microbubble visualization
- Improve depiction of tumor blood flow
- Obtain quantitative perfusion data



Hepatic blood flow



Renal blood flow

Implementation:
3D/4D Linear Array

4D10L broad bandwidth array

- **3.5 – 11 MHz bandwidth**
- **50 x 58 mm footprint**
- **37.4 mm x 29º volume**

Experimental software implemented on Logiq 9 provided:

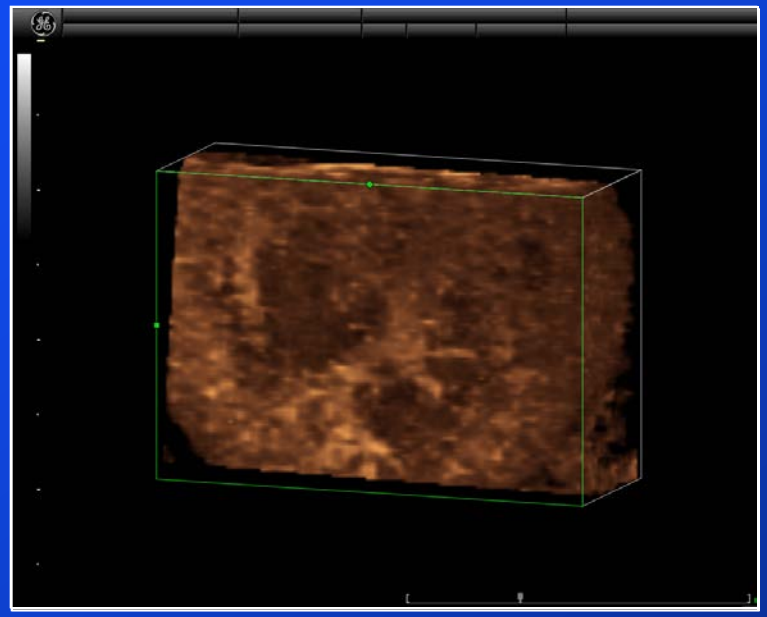
-Three-dimensional pulse inversion HI transmitting 2 cycle pulses at 5.0 MHz and receiving at 10 MHz by equalization filtering (peak MI = 0.36)

-Three-dimensional pulse inversion SHI transmitting 4 cycle pulses at 5.8 MHz and receiving at 2.9 MHz by equalization filtering (peak MI = 0.33)

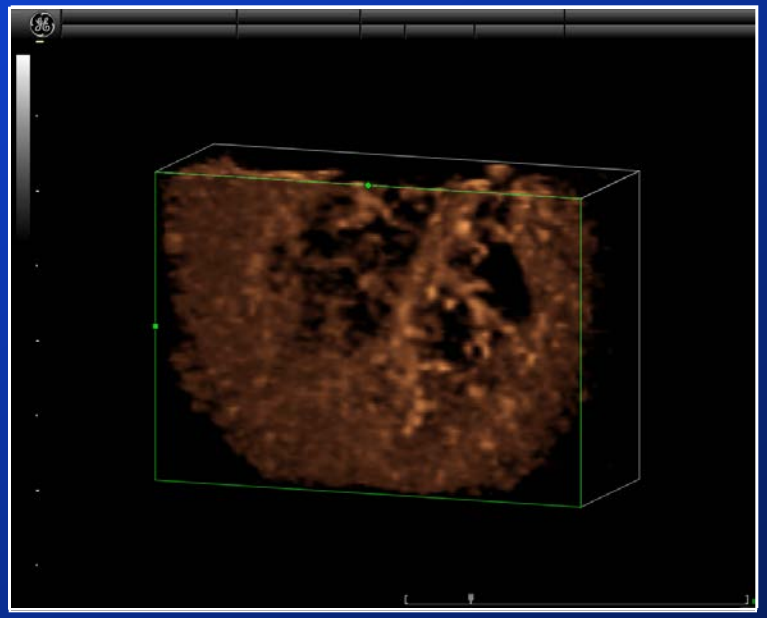
[Eisenbrey et al., Acad Radiol, 2012]

In Vivo Renal 3D HI and SHI

HI



SHI

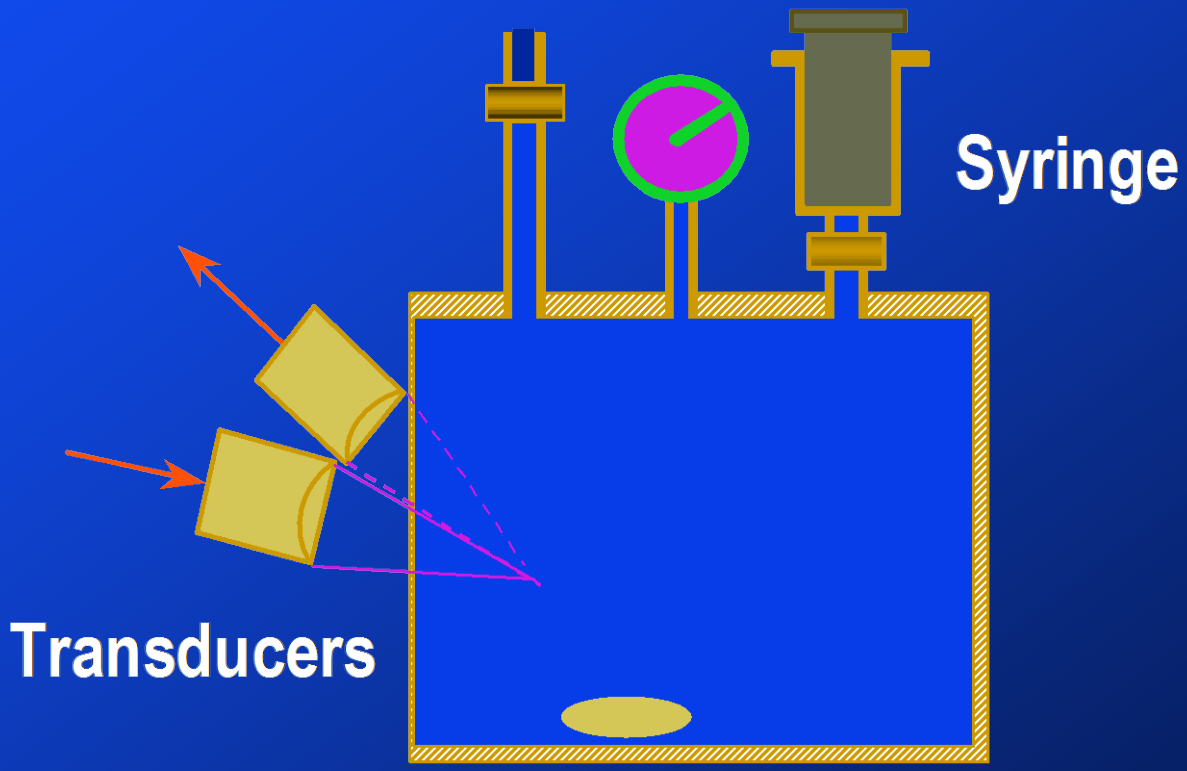


t = 1.45 sec

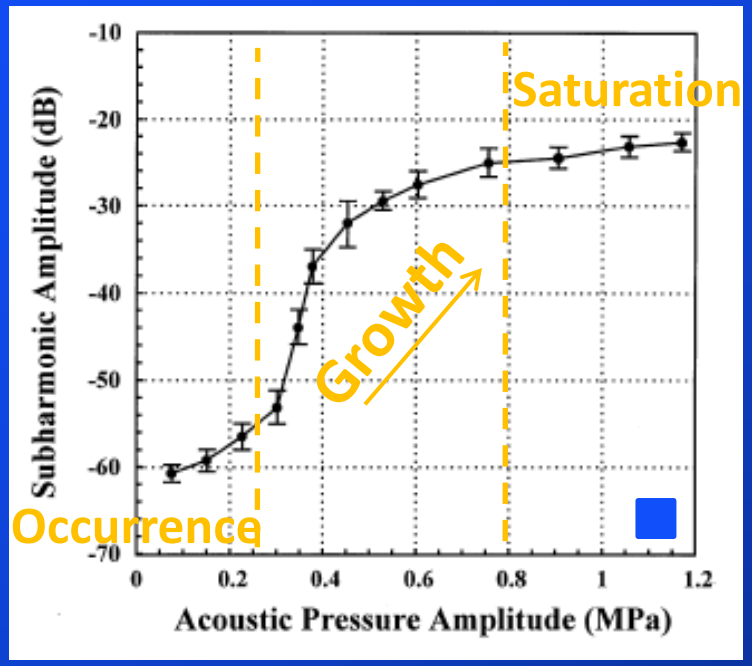
Pressure Estimation Using Contrast - an Overview

	Ambient pressure sensitivity related to…	Analysis
Fairbank, 1977	Shift in resonance frequency of bubbles	Suffered from nonuniform bubble sizes resulting in broad band receive signal
Hök, 1981	Single bubble echo	Localization of single bubbles *in vivo* not realistic, *in vitro* relative errors of 30 %
Miwa, 1984	Cavitation onset	Difficult to detect low pressure changes, induced bubbles may lead to embolism
Shankar, 1986	Sum and difference frequency components	Errors in the range of 10 to 15 mmHg
Bouakaz, 1999	Disappearance time of bubbles	Errors in the range of 50 mmHg
Shi, 1999	Subharmonic signal amplitude	*Let's study…*

Experimental Setup

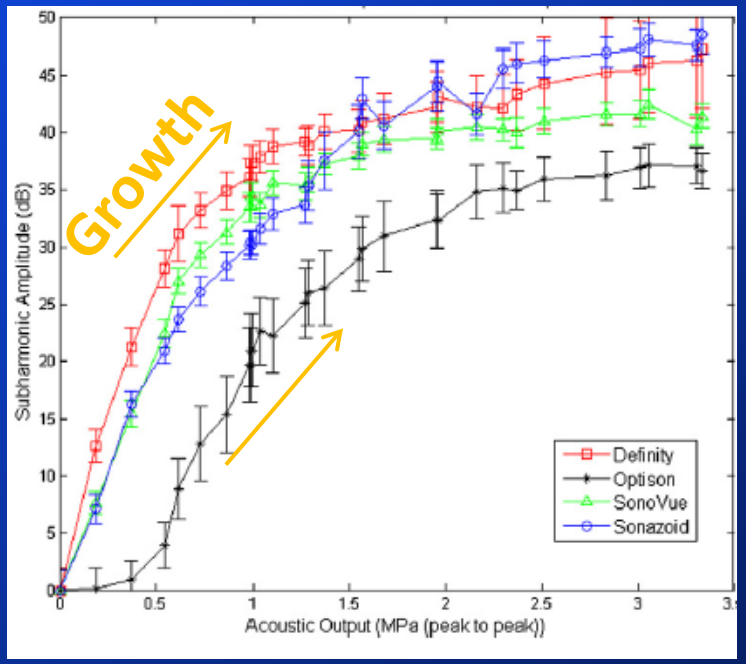


Subharmonic Response *In Vitro*



Using single element transducers

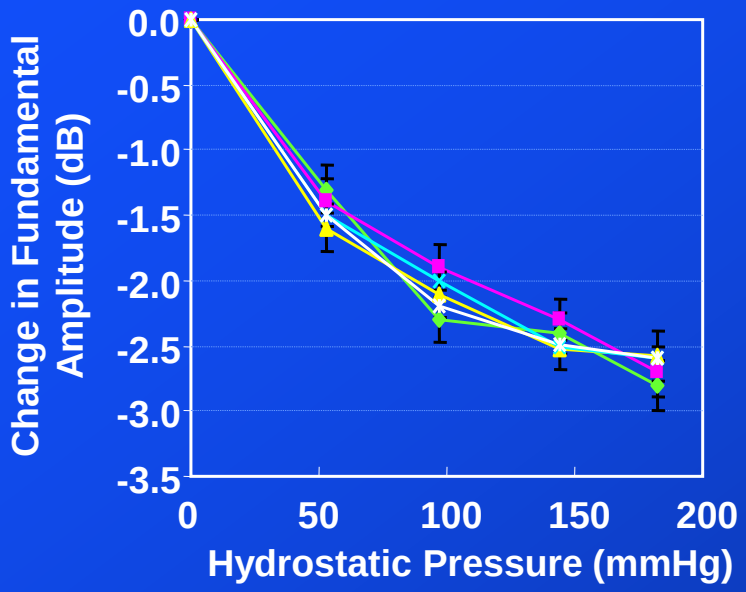
[Shi et al., Ultrasound Med Biol, 1999]

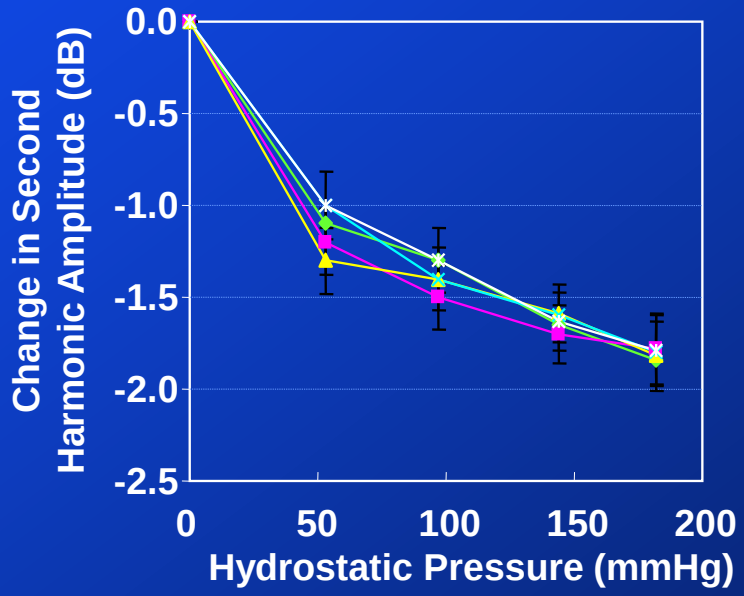


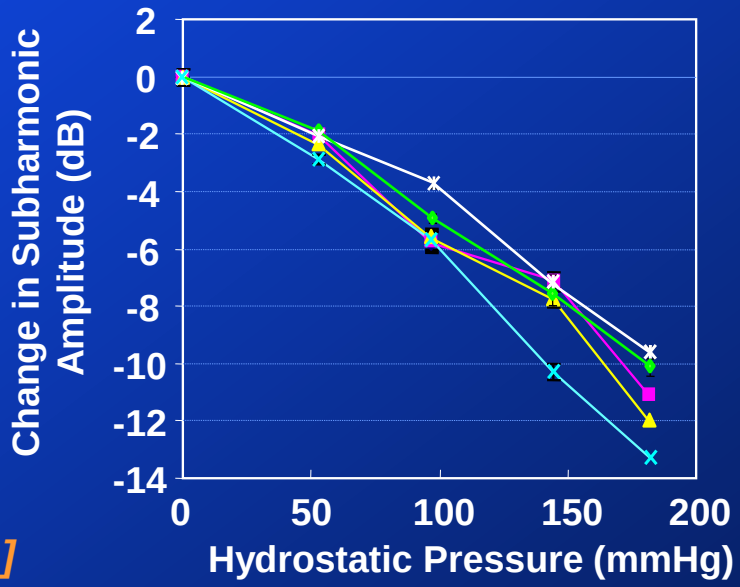
Using a commercially available ultrasound scanner

[Eisenbrey et al., Ultrasonics, 2011]

Bubble Signal Pressure Dependence







N = 3

Optison
Definity
ZFX
Sonazoid
Levovist

[Halldórsdóttir et al., Ultrason Imaging, 2011]

Sub-Harmonic Aided Pressure Estimation (SHAPE)

Based on the correlation ($r^2 \geq 0.97$) between the static pressure and the sub-harmonic signal amplitude, a novel technique called Sub-Harmonic Aided Pressure Estimation (*SHAPE;* U.S. patent 6,302,845) has been proposed for non-invasive pressure measurements

In Vivo Cardiac SHAPE

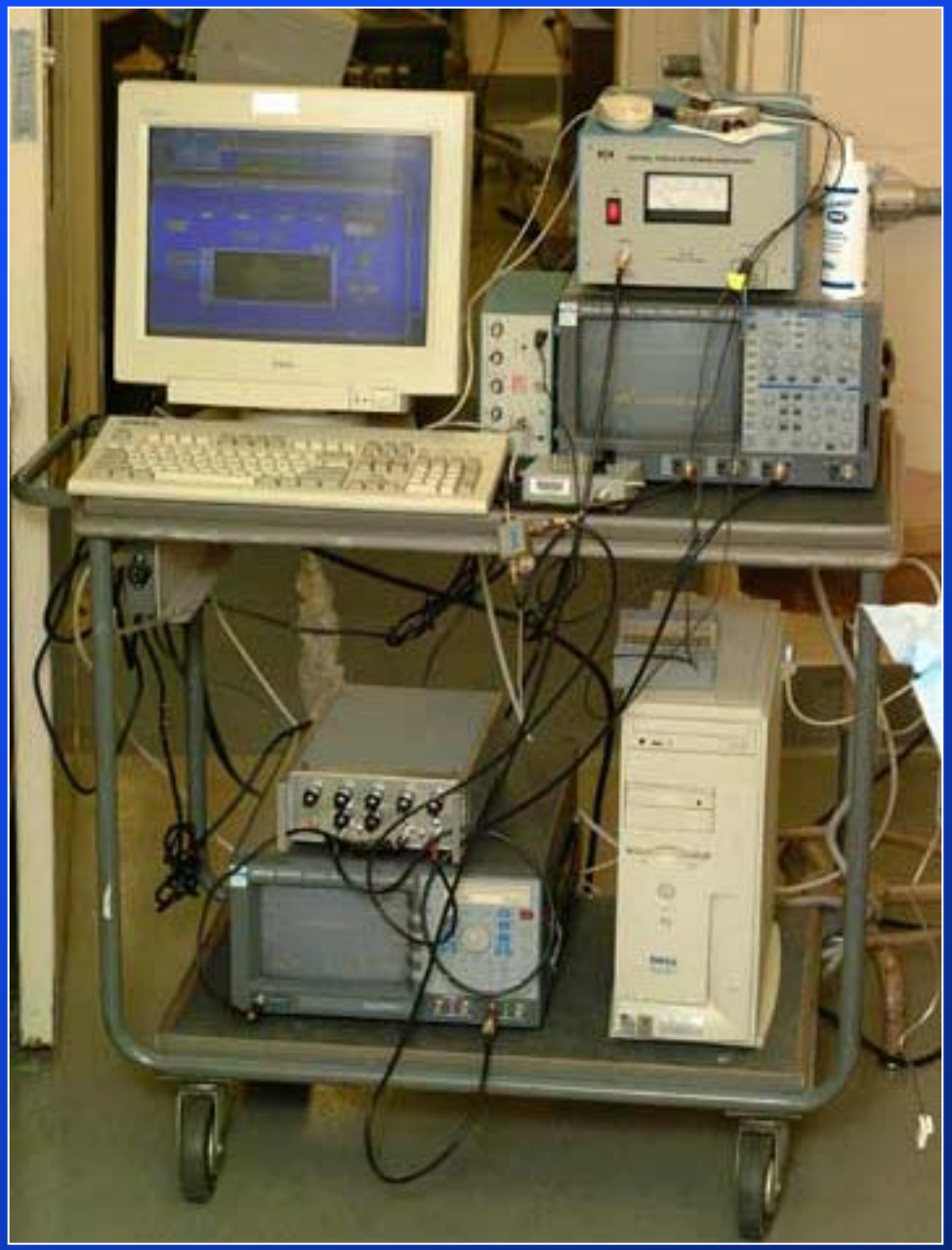
Supported in part by the U.S. Army Medical Research Material Command under W81XWH-08-1-0503, by AHA grant no 0655441U as well as by NIH R21 HL081892 and by Lantheus Medical, N Billerica, MA

Motivation for Cardiac Pressure Estimation

There are about 83.6 million Americans suffering from more than one type of cardiovascular disease with 77.9 million Americans having high blood pressure and 15.4 million Americans having coronary heart diseases

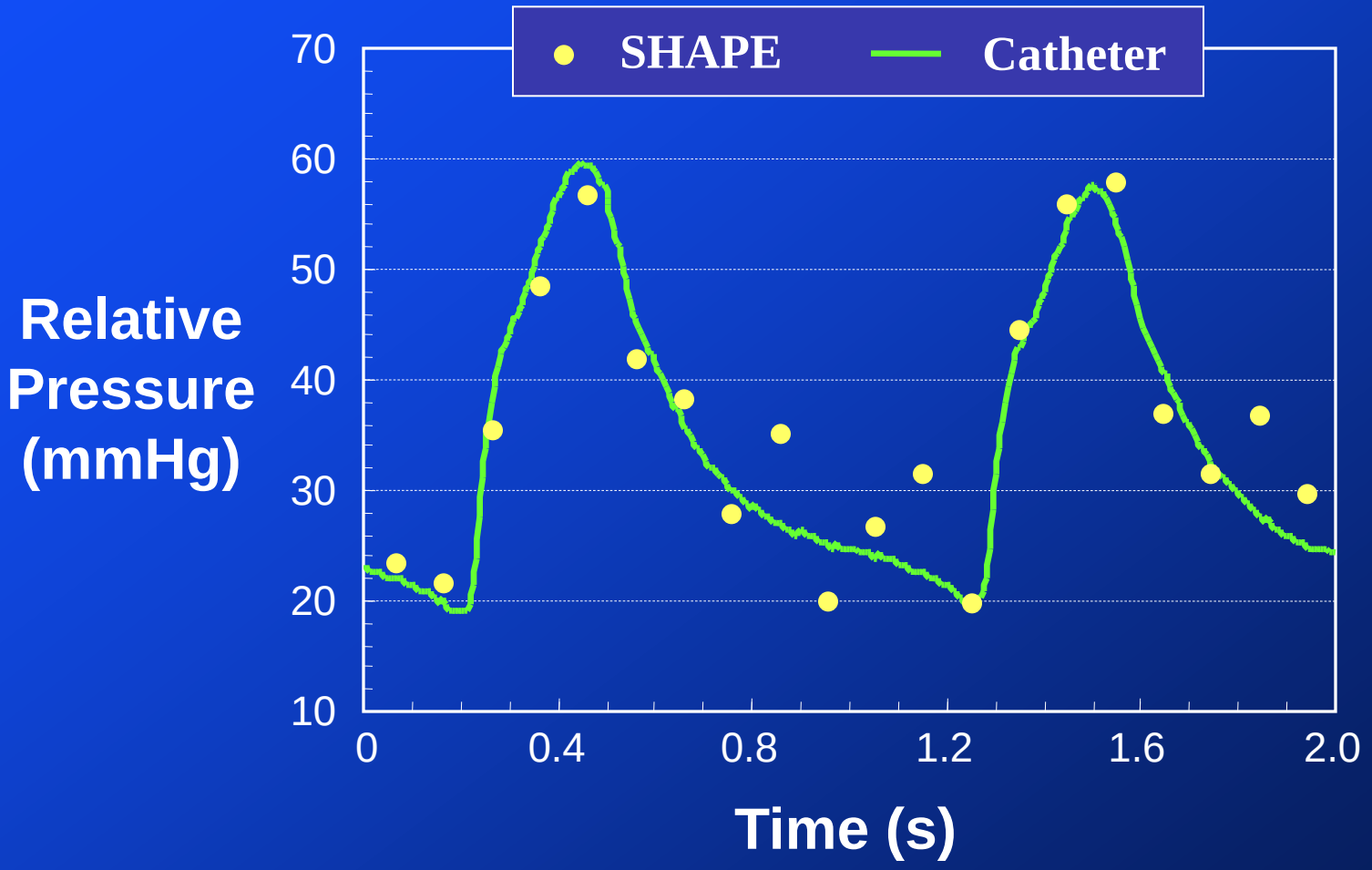
- Monitor effects of different treatment regimens
- Monitor systolic/diastolic heart failure patients
- Cardiac transplantation work-up
- Identify biopsy-negative transplant rejections
- Monitor efficacy of cardiac resynchronization therapy

About 500,000 new cases of heart failure are diagnosed each year in the United States and ten times that number of Americans is currently affected by heart failure

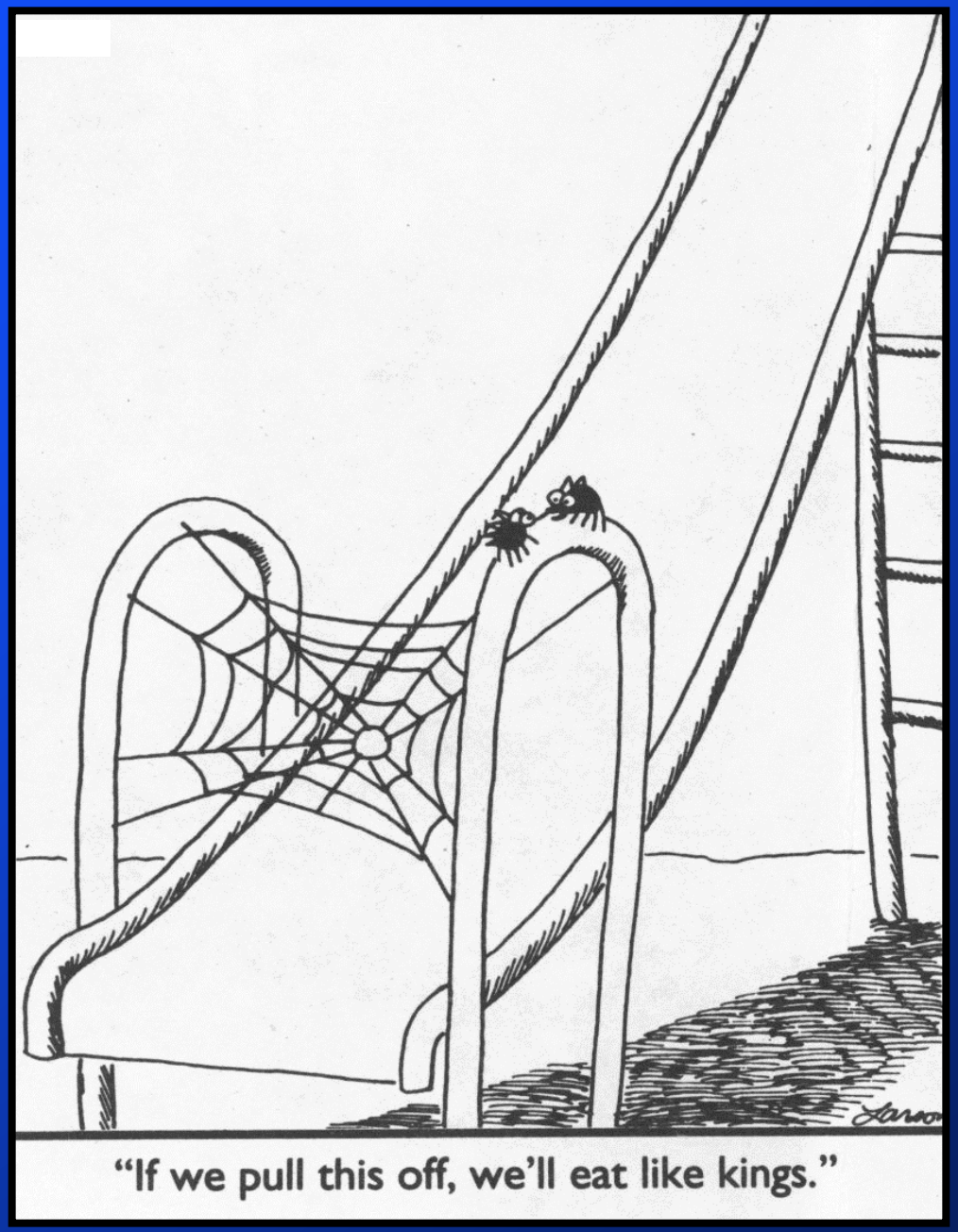


In Vivo Setup

In Vivo Pressure Measurements; Proof of Concept



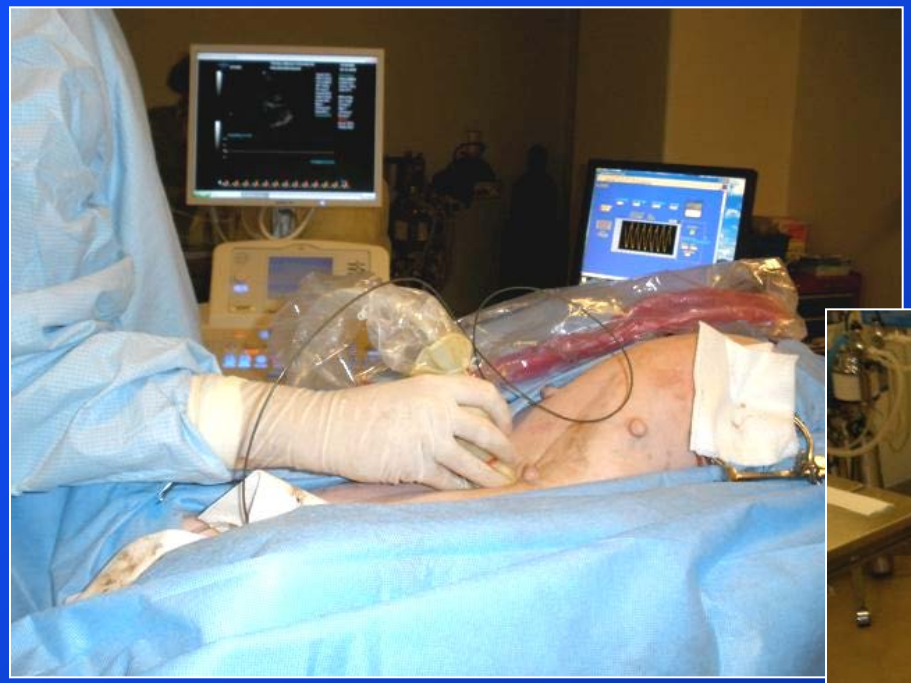
[Forsberg et al., IEEE UFFC, 2005]


"If we pull this off, we'll eat like kings."

Real-Time SHAPE

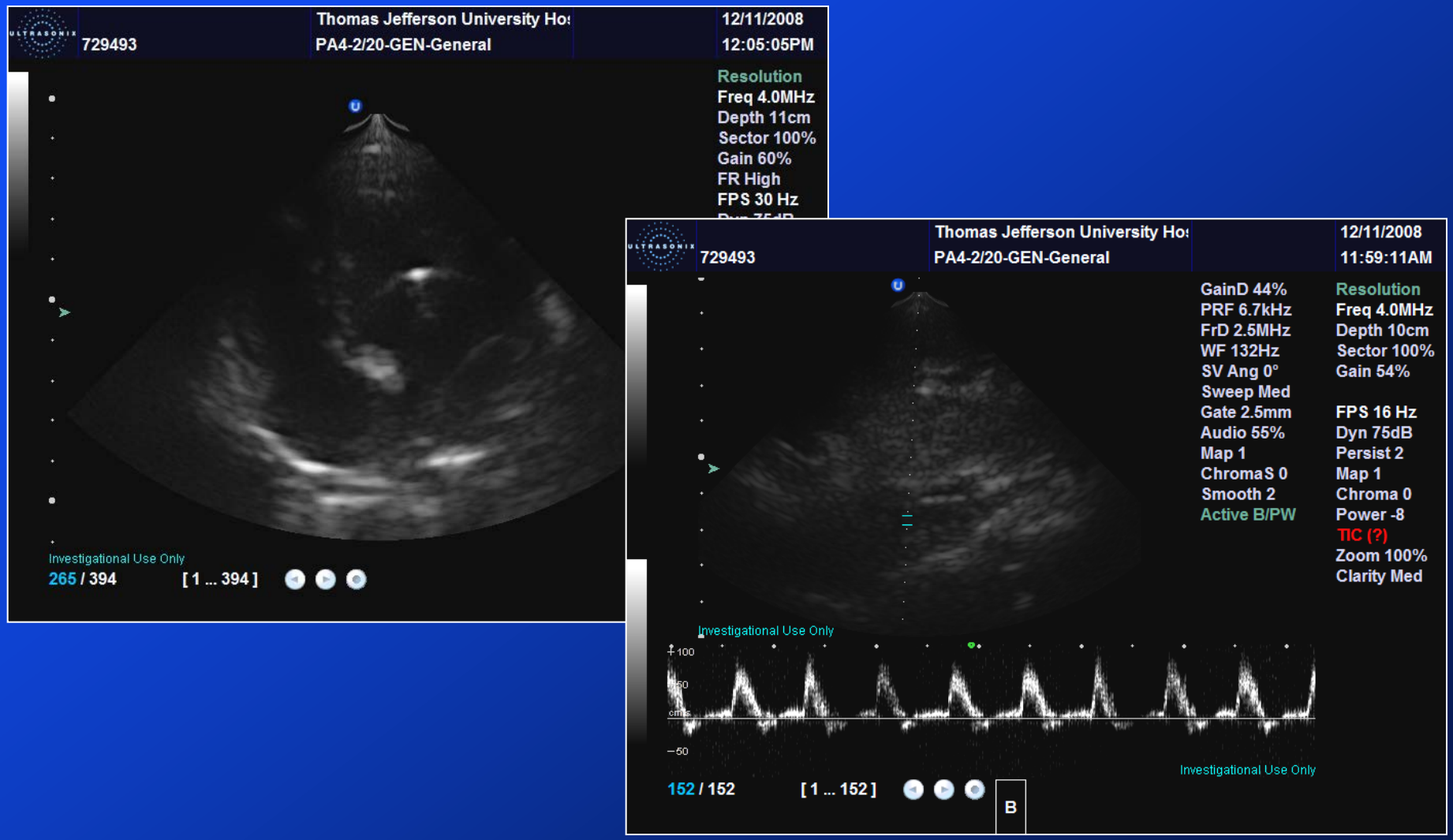
- Modified Sonix RP scanner (Analogic Ultrasound, Richmond, BC, Canada)
- Phased array PA4-2 (1.5-4.5 MHz)
- Grayscale SHI (Tx/Rx: 2.5/1.25 MHz)
- Acoustic output power: 0, -4 and -8 dB
- RF data acquired in (pulse inversion) pulsed Doppler mode over 5 seconds
- Subharmonic signals extracted off-line

In Vivo Cardiac Setup

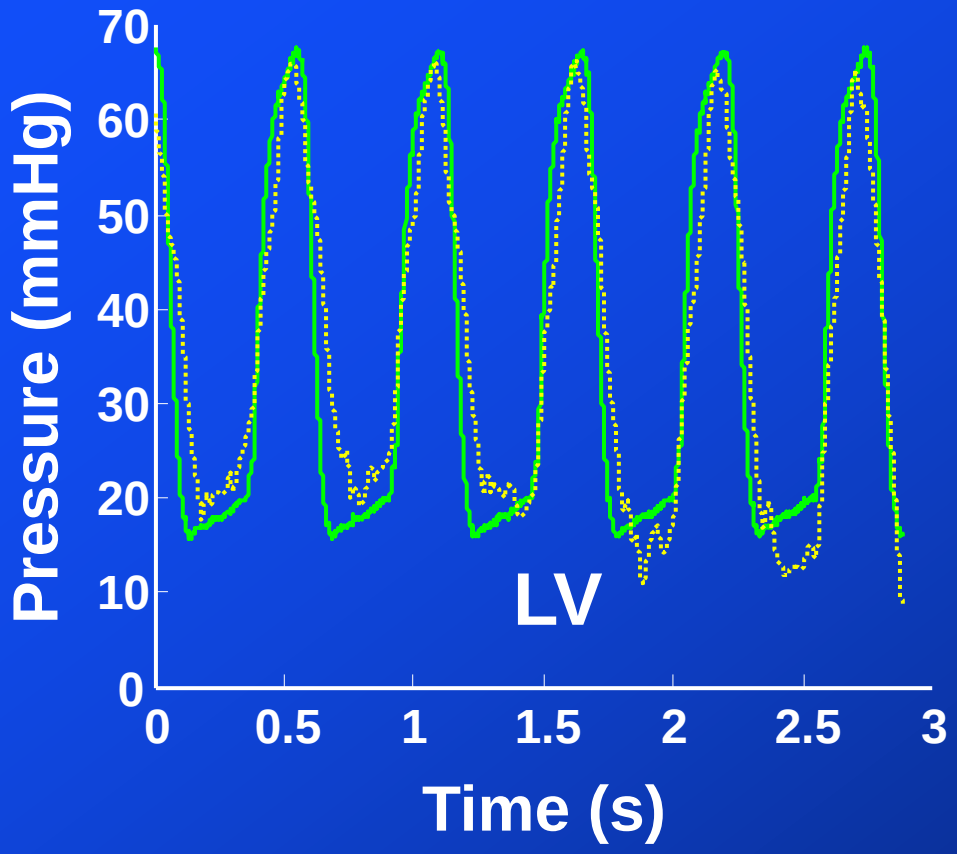


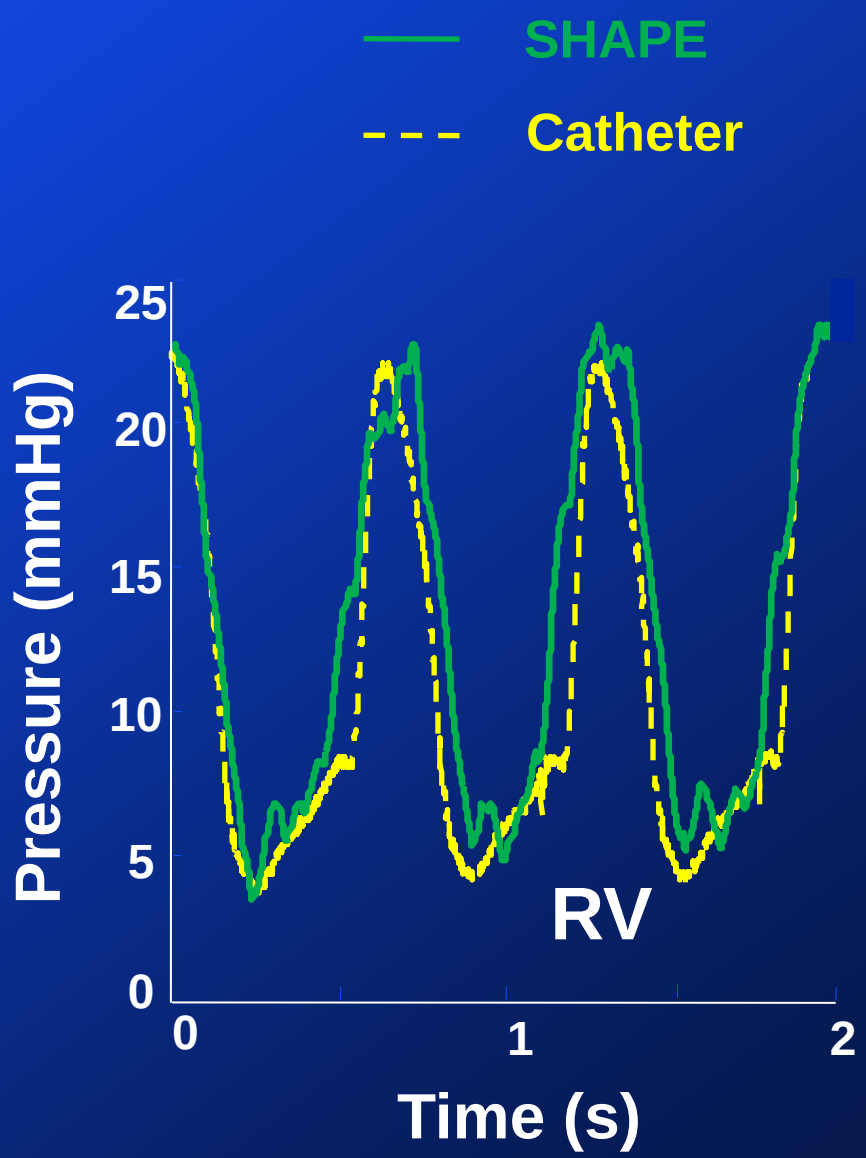
[Dave et al., JACC Cardiovasc Img, 2012]

Imaging Results



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

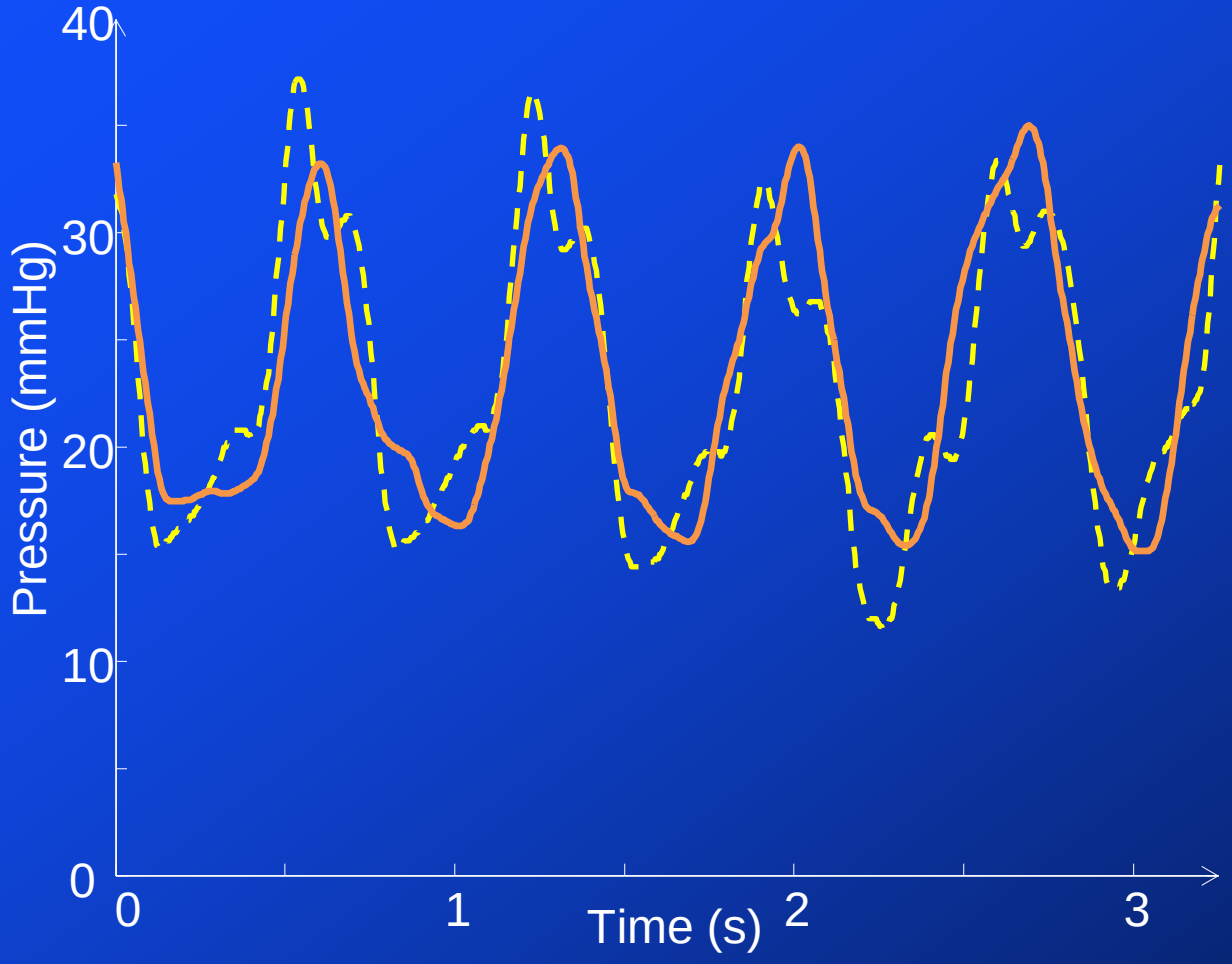
RV Pressures with Individual Calibration Factor

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

Cardiac SHAPE – a Pilot Study

- 15 patients with stable cardiac disease
- Scheduled for right and left heart catheterization
  - intra-cardiac pressures as reference
- SHI obtained in RV, LV and aorta
- Sonix RP with PA4-2 probe
- Definity infusion (3 mL in 50 mL saline)
- RF data processed off-line

RV Pressure Waveform in a Patient



Peak systolic right ventricle pressure:
Pressure catheter: 36.6 ± 2.9 mmHg
SHAPE: 34.0 ± 1.6 mmHg

SHAPE for the Diagnosis of Portal Hypertension

Supported in part by the U.S. Army Medical Research Material Command under W81XWH-08-1-0503, by NIH R21 HL081892, RC1 DK087365 and R01 DK098526 as well as by GE Healthcare, Oslo, Norway

Motivation for Estimating Portal Hypertension

NASH affects 2-5% of Americans resulting in about 5.5 million people with cirrhosis

Cirrhosis without portal hypertension has a small effect on mortality. However, it is the manifestations of portal hypertension, which predict survival

Approximately 25,000 Americans die each year from chronic liver disease and cirrhosis and more than 300,000 people are hospitalized

Clinical Trial of SHAPE in Portal Hypertension

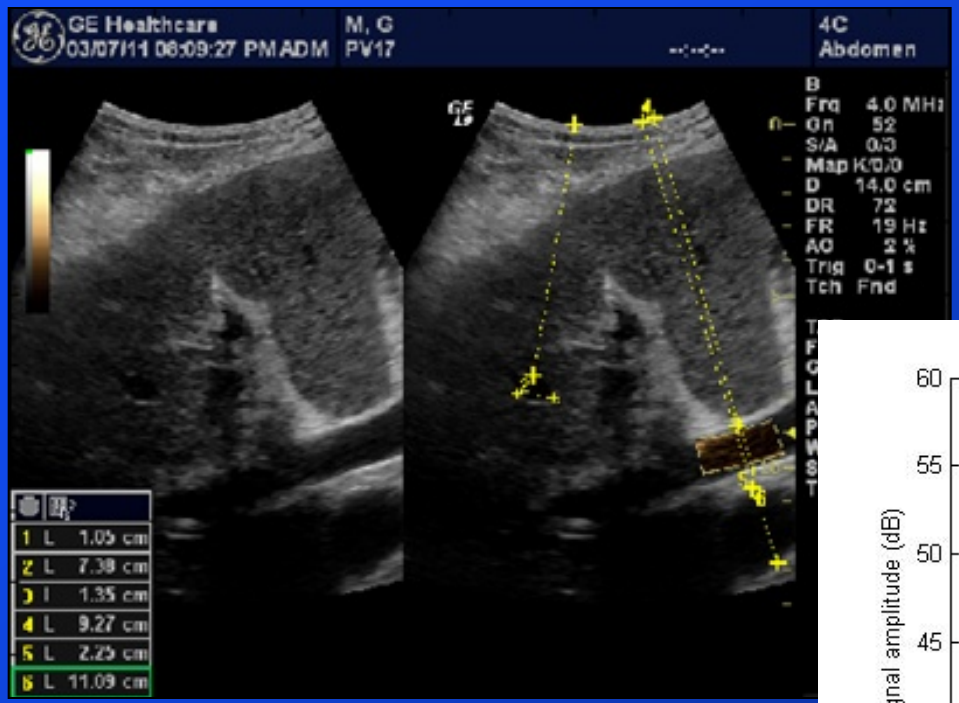
- 45 patients (27 M; 18 F) scheduled for a transjugular liver biopsy
  - HVPG measurements as reference
- Subjects provided written consent
- 12 subjects post-liver transplantation
- Subjects were 19 to 71 years old
- BMIs ranged from 17.2 to 57.2
- Sonazoid 0.72 µL microbubbles/kg/hour (IND: 100,083)

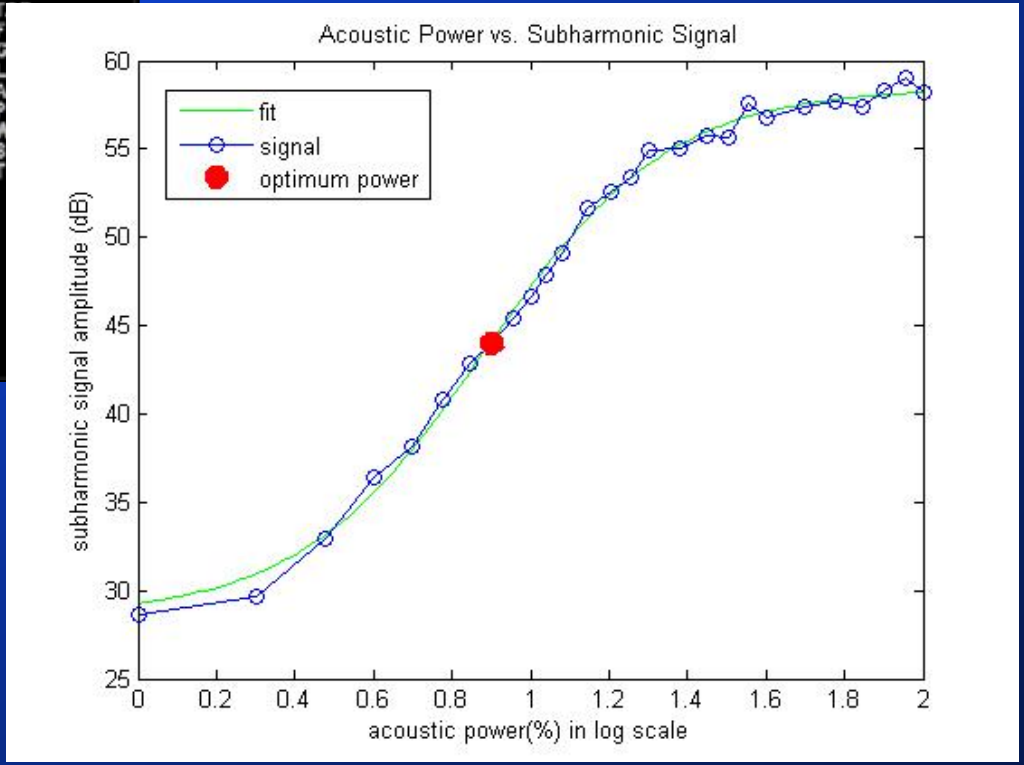
[Eisenbrey et al., Radiology, 2013]

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

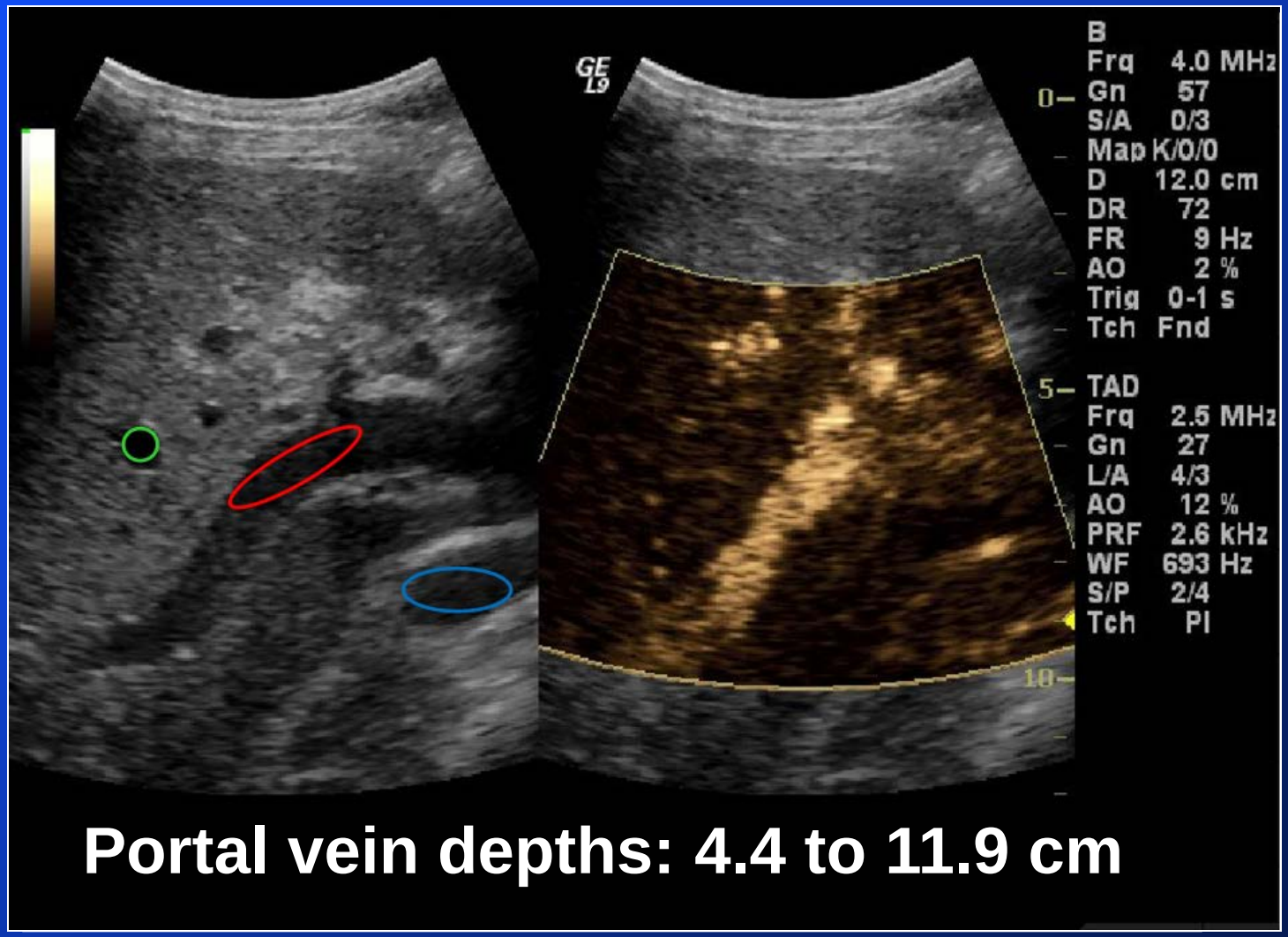
Acoustic Power Optimization



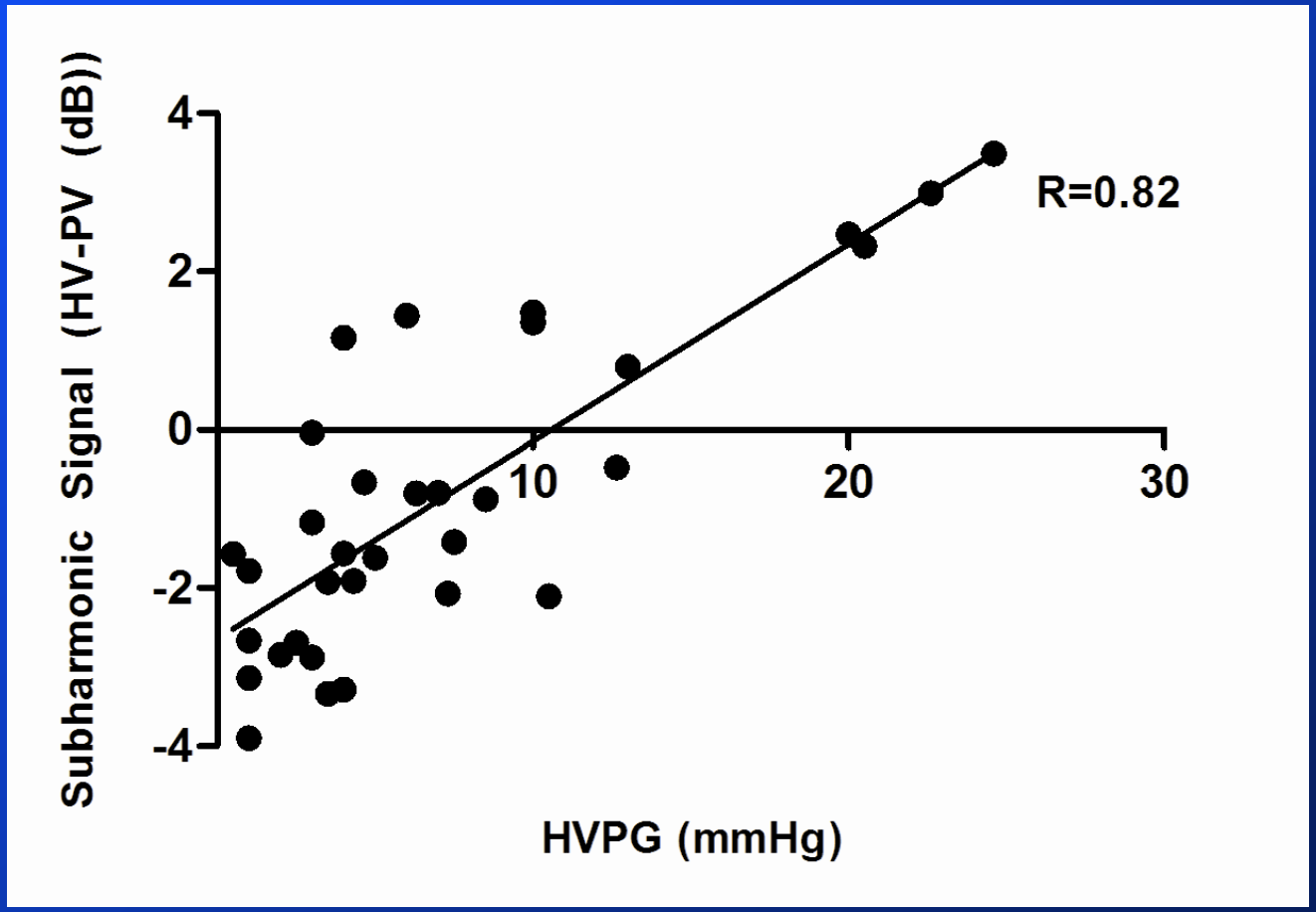


[Dave et al., Ultrasonics, 2013]

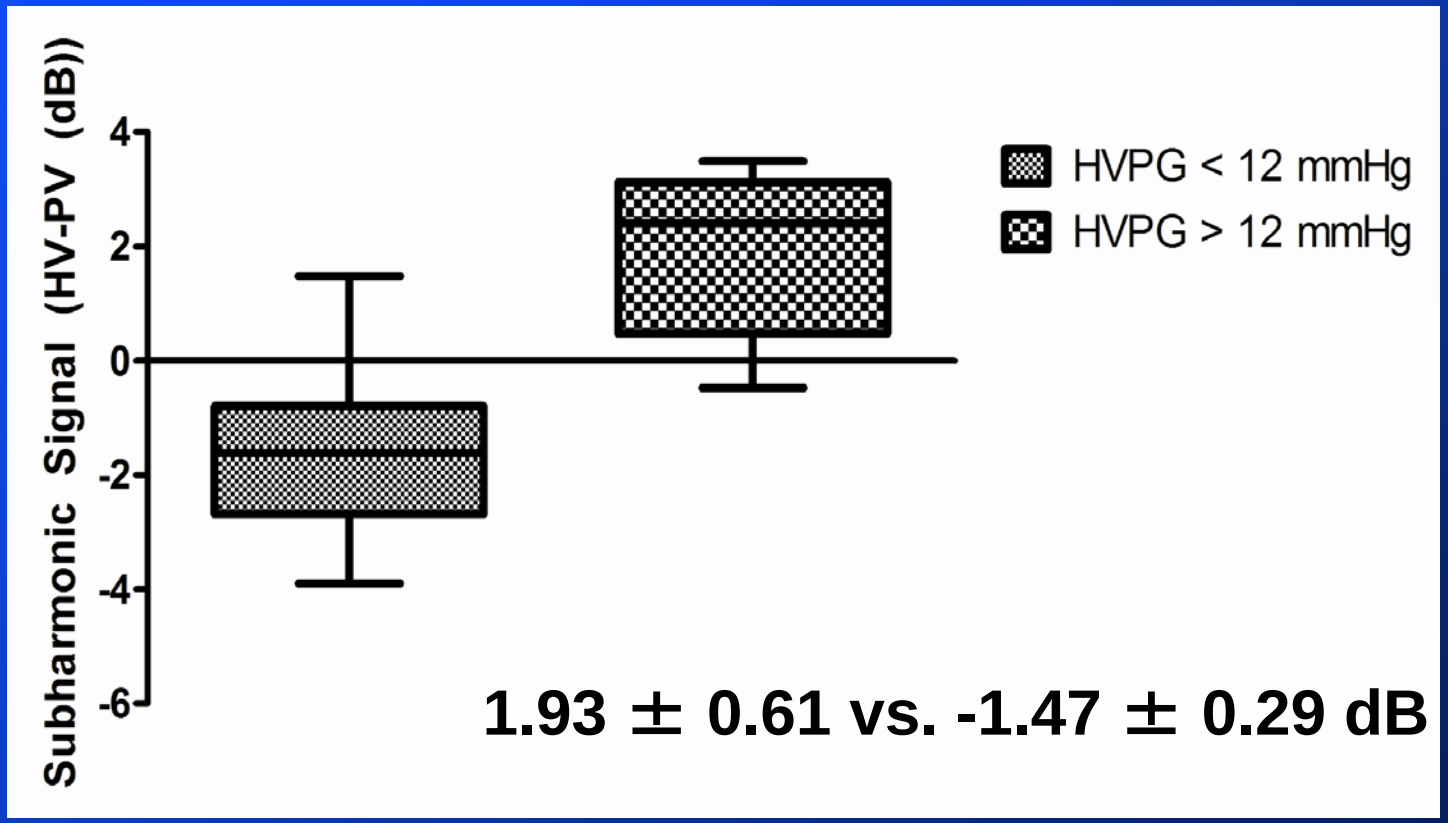
In Vivo Imaging Results



Subharmonic Signal versus HVPG

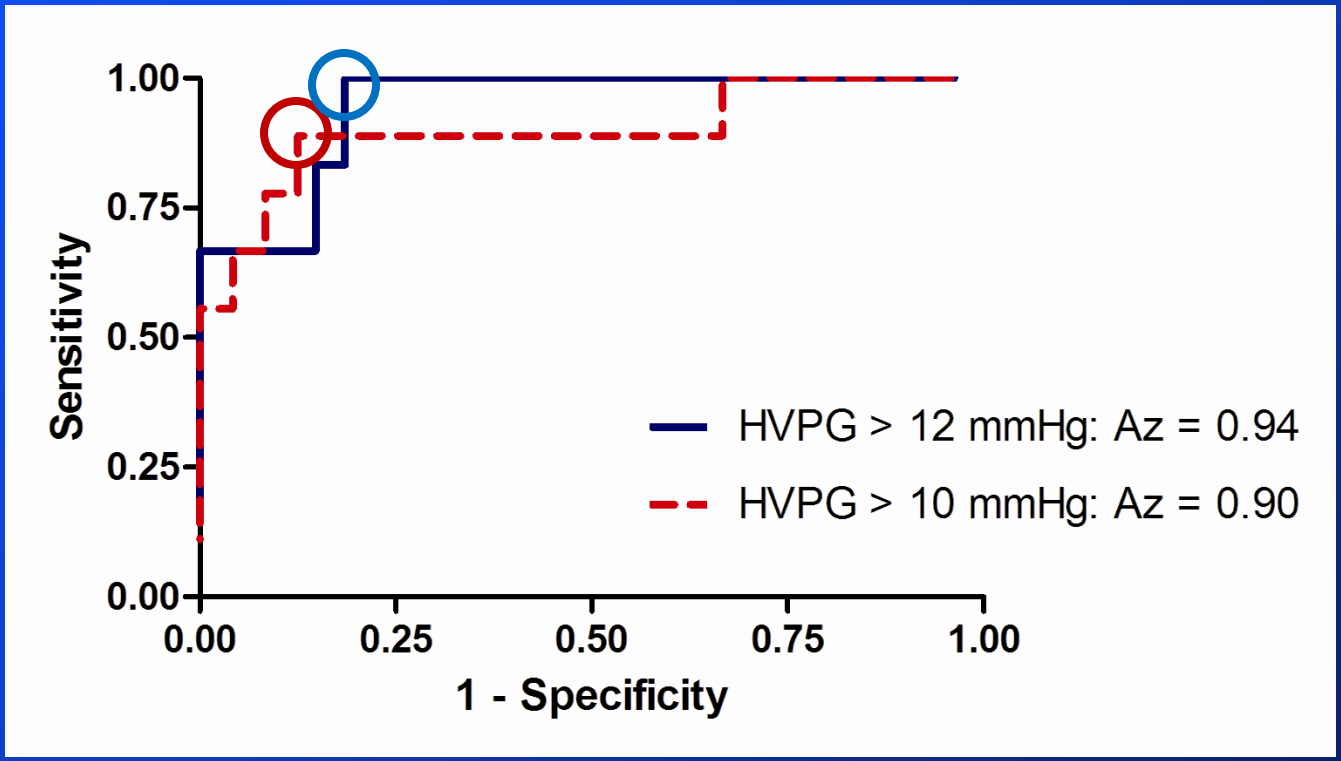


Predicting Portal Hypertension



p < 0.0001

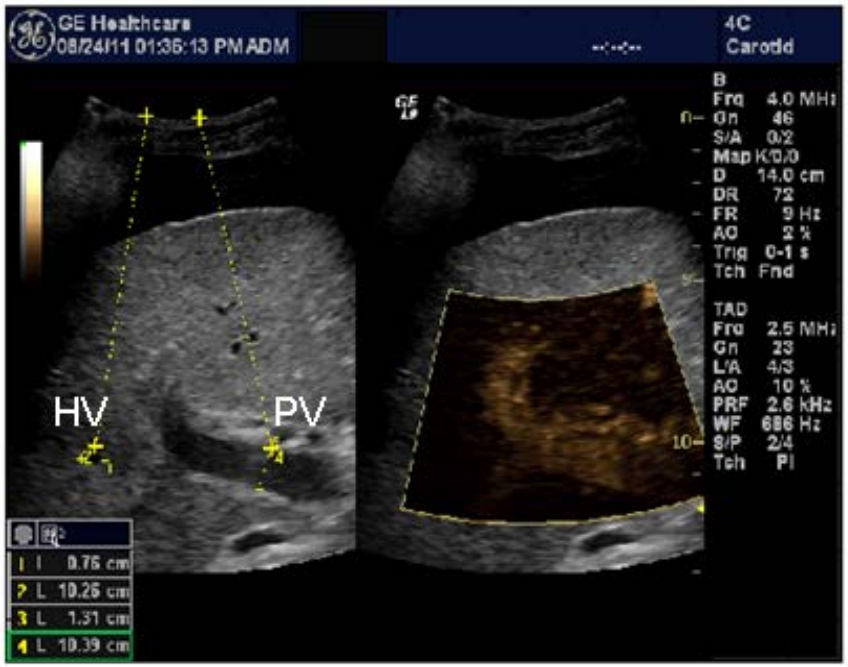
SHAPE as a Screening Tool

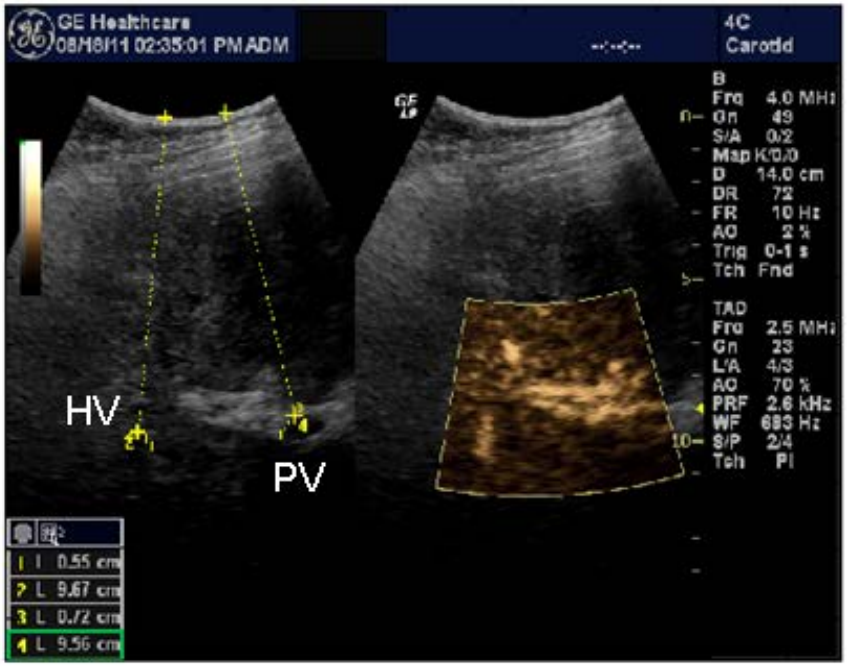


10 mmHg cutoff: HV-PV = -0.57 dB: Sensitivity = 89%, Specificity = 88%

12 mmHg cutoff: HV-PV = -0.57 dB: Sensitivity = 100%, Specificity = 81%

SHAPE as a Screening Tool for Portal Hypertension





SHAPE acquisitions in two patients (obtained at their respective optimal acoustic outputs). Left: A patient insonated at an acoustic output of 10% with HVPG = 5 mmHg

Right: A patient insonated at an acoustic output of 70% with HVPG = 23 mmHg

SHAPE for Monitoring Interstitial Fluid Pressure in Breast Cancer Patients During Neoadjuvant Chemotherapy

Supported in part by U.S. Army Medical Research Material Command under W81XWH-08-1-0503, W81XWH-11-1-0630 and W81XWH-12-1-0066 as well as by NIH grants R21 HL081892, R01 CA140338 and R01 CA137733

Locally Advanced Breast Cancer

LABC has not metastasized to distant tissue

IIIA:

Tumor size > 5 cm

AND

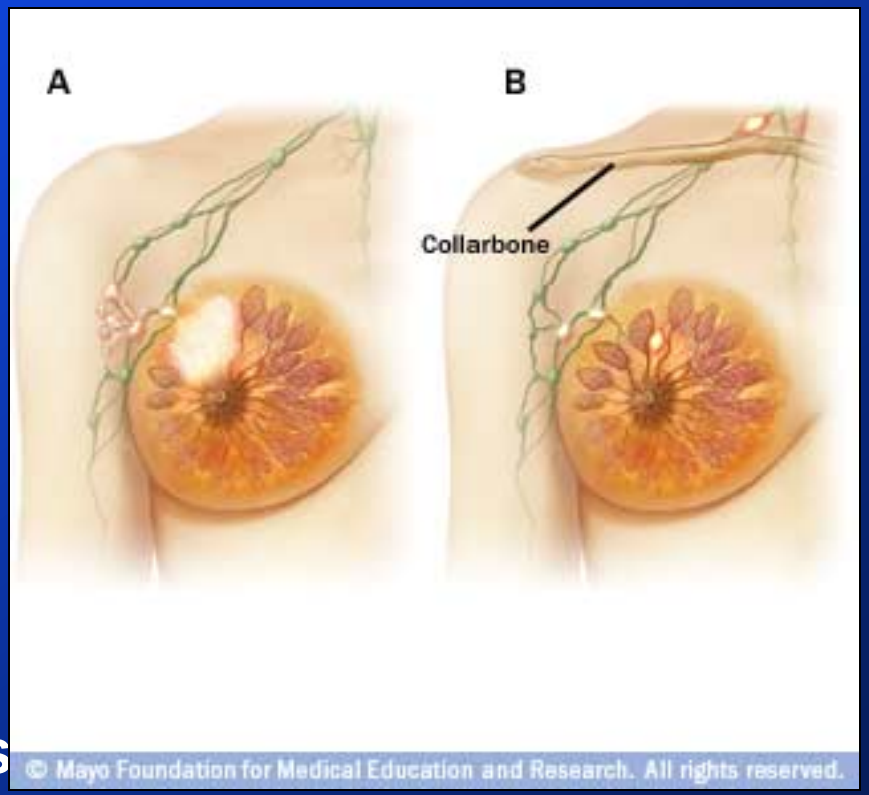
Cancer in axillary lymph nodes

IIIB:

Tumor of any size

AND

Cancer in lymph nodes above the collarbone



http://www.riversideonline.com/health_reference/Womens-Health/BR00011.cfm

Neoadjuvant Chemotherapy is the Standard of Care for LABC

- Reduces the size of breast cancers
  - more conservative surgical options
- Same overall survival as for adjuvant chemotherapy (70% in ACT vs. 69% in NCT)
- Same disease free survival as for adjuvant chemotherapy (55% ACT and 53% NCT)
- Provides an early assesment of tumor response to chemotherapy

[Wolmark et al., J Natl Cancer Inst Monogr, 2001]

Interstitial Fluid Pressure (IFP) is Higher in Tumors than in Normal Tissue

- **Typical IFP values:**
  - **Mean IFP in normal tissues: -1 to 3 mmHg**
  - **Mean IFP cancers: 10 to 30 mmHg**
- **Current method**
  - **Wick-in-needle technique**
  - **Invasive**
- **IFP may allow monitoring of response to neoadjuvant chemotherapy in breast cancer**

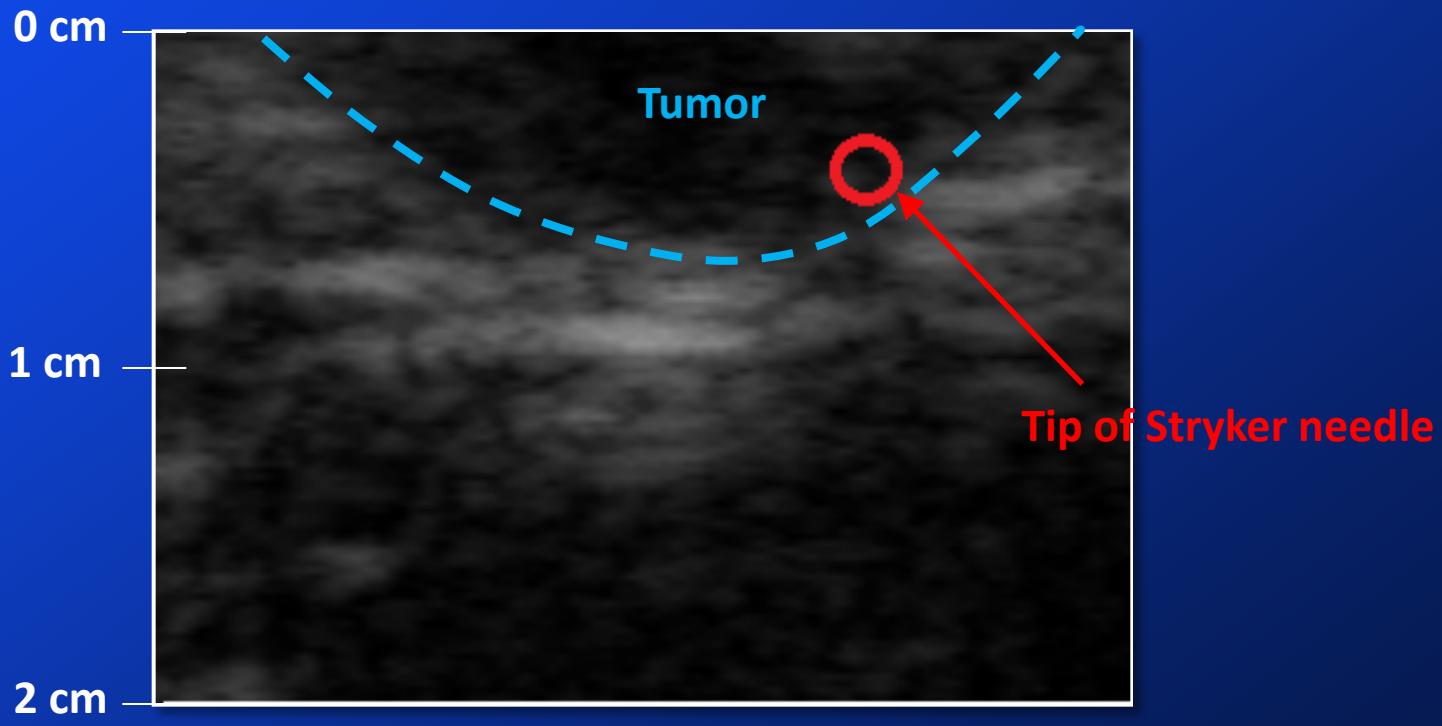
[Heldin et al., Nat Rev Cancer, 2004]

In Vivo Methods

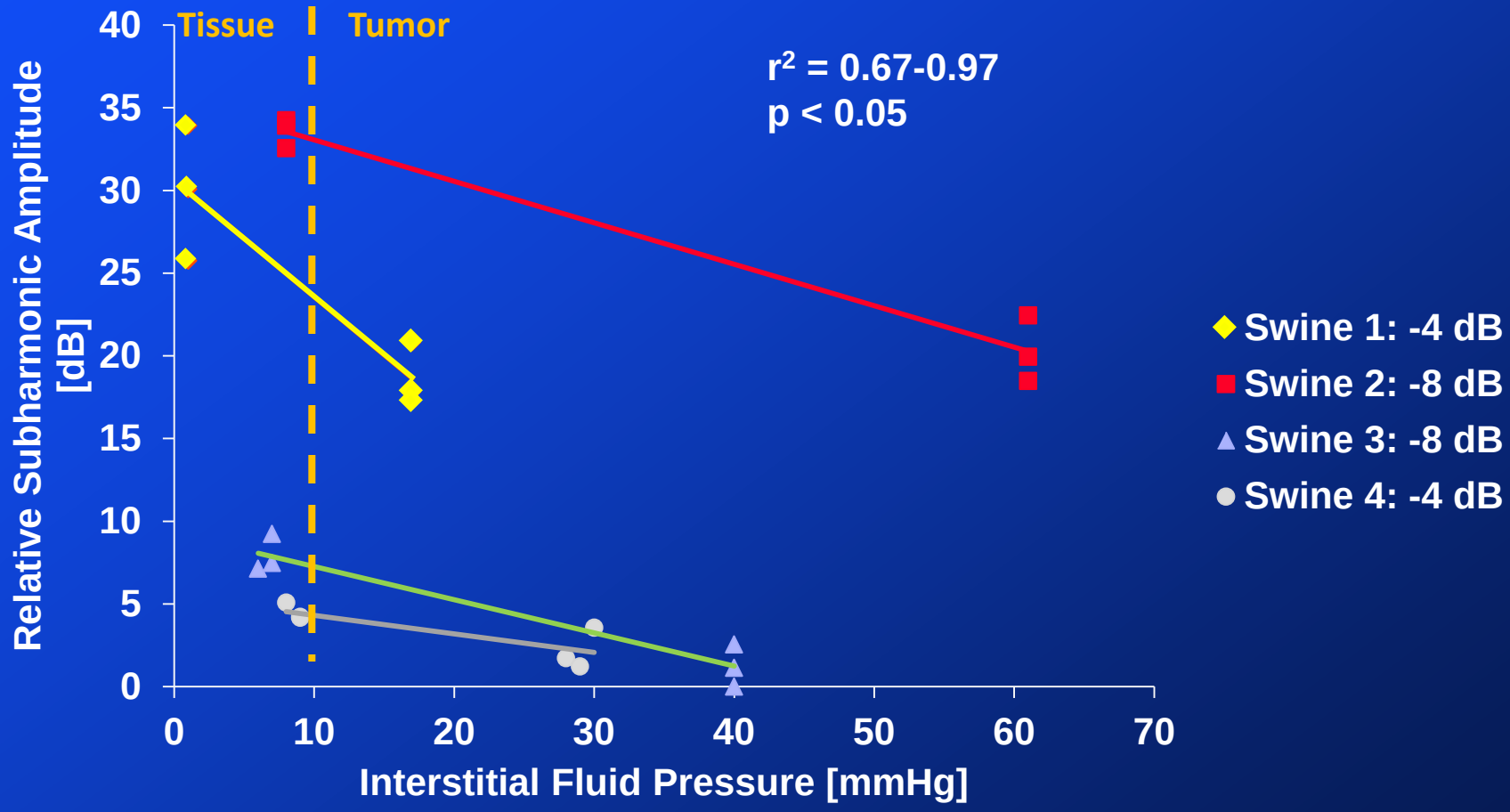
- **Five Sinclair swine**
  - Naturally occurring melanomas
  - One eliminated due to technical difficulties
  - Weight: 9.5 ± 4.1 kg
- **Definity contrast agent**
  - 3.0 ml of agent mixed in 50 ml of saline
  - Rate of infusion: 6.25 ml/min
- **Stryker pressure monitor IFP measurements**
  - Tumor
  - Normal tissue

In Vivo Data Acquisition

- Location of pressure monitor needle verified by radiologist
- ROI located close to needle tip



10 MHz *In Vivo* Results



[Halldorsdottir et al., Ultrasonics, 2014]

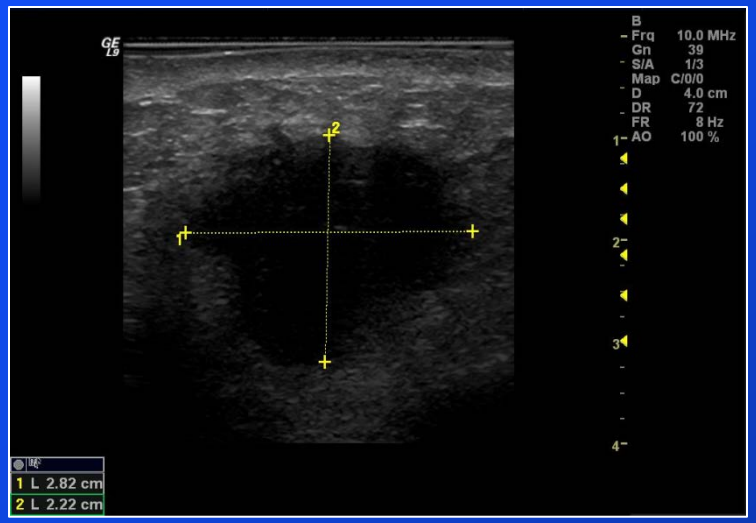
Human Clinical Trial of IFP Measurements

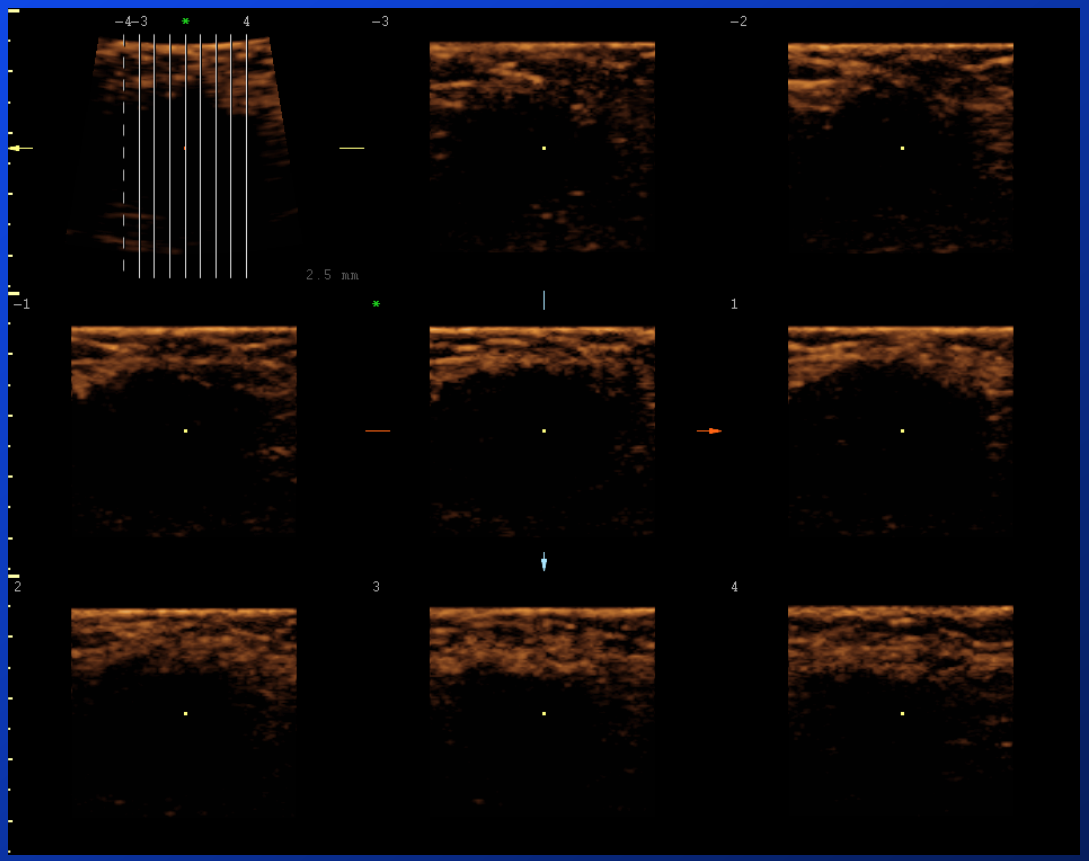
- 20-50 patients with breast cancer
- Scheduled for neoadjuvant chemotherapy
  - clinical outcomes and MRI as references
- 3D SHI before, during (twice) and after chemotherapy
- Modified Logiq 9 with 4DL10 probe
- Definity infusion (3 mL in 50 mL saline) (IND: 112,241)

Clinical Trial Recruitment

- 12 patients enrolled to date
- 4 subjects have completed all 4 scans
- 4 subjects have completed 3 scans
- 1 subject have completed 2 scans
- 3 subjects were lost to follow up (after baseline scans)

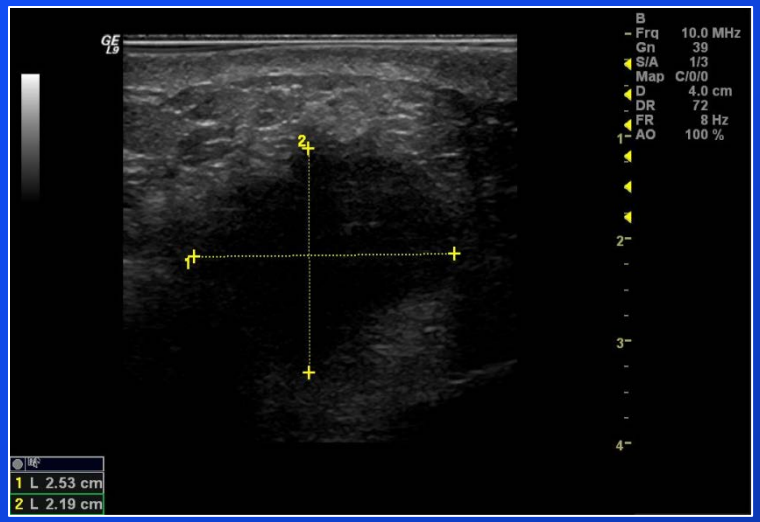
Example Case

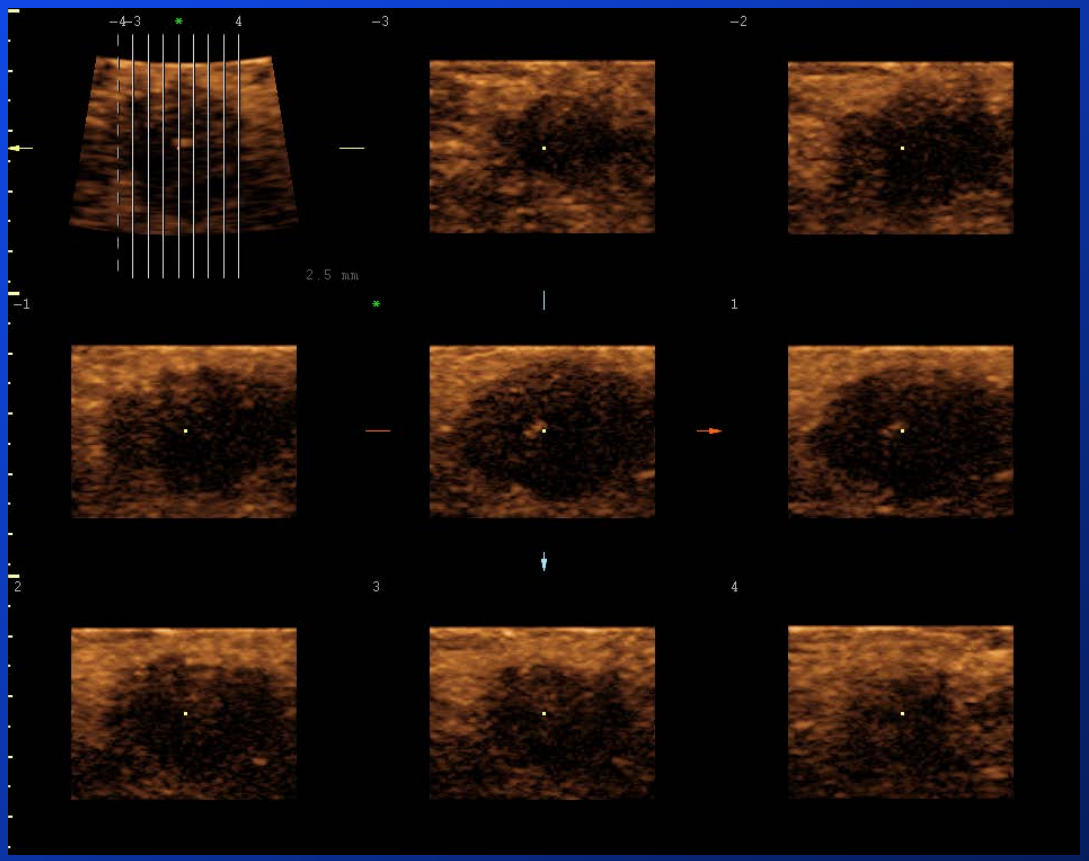




52 year old woman with 2.8 x 2.2 cm triple negative breast cancer
Morning prior to starting neoadjuvant chemotherapy

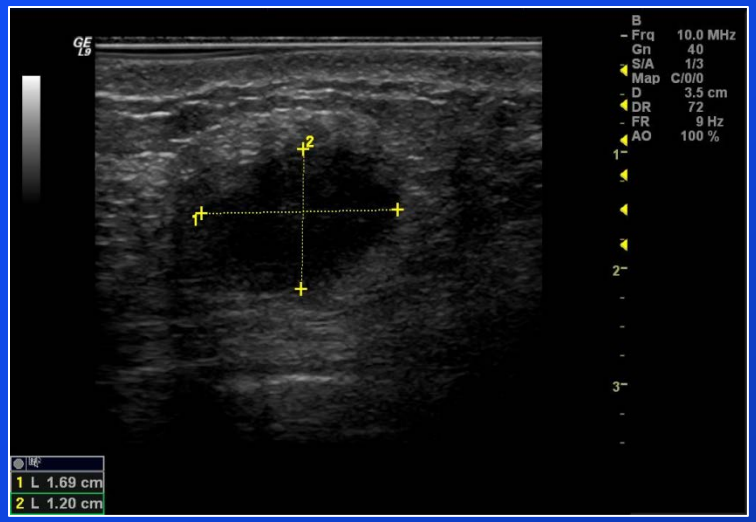
Example Case

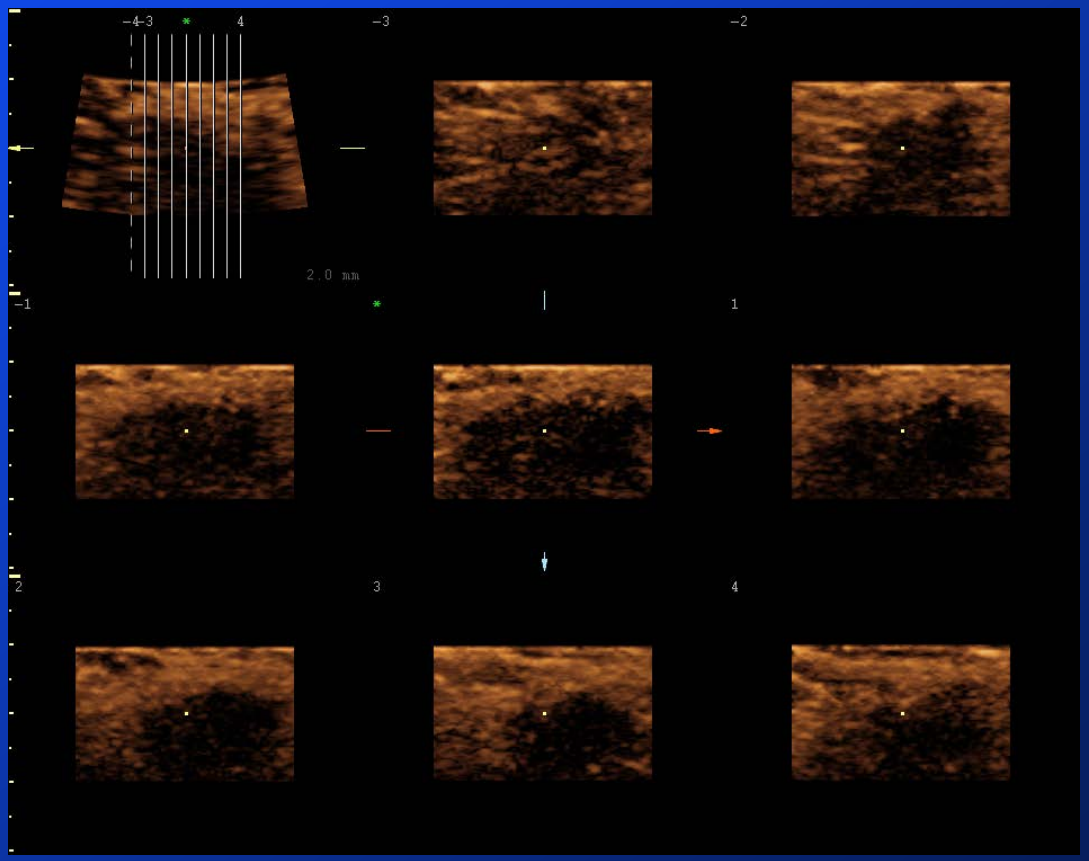




52 year old woman with 2.5 x 2.2 cm triple negative breast cancer
10% through course of neoadjuvant chemotherapy

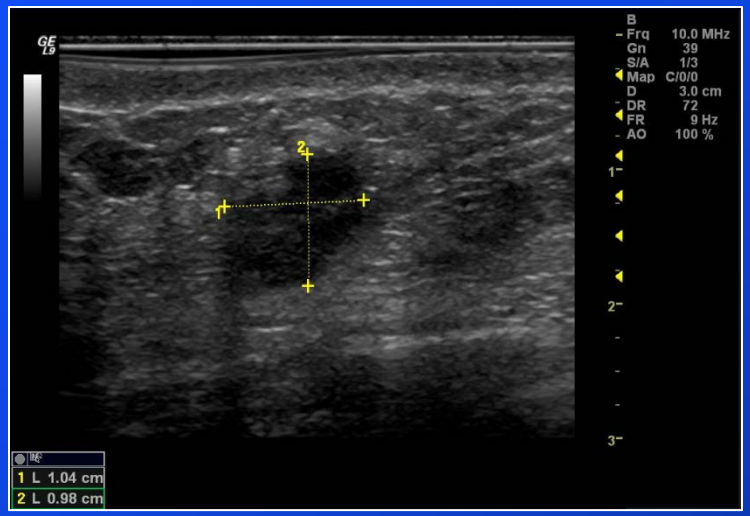
Example Case

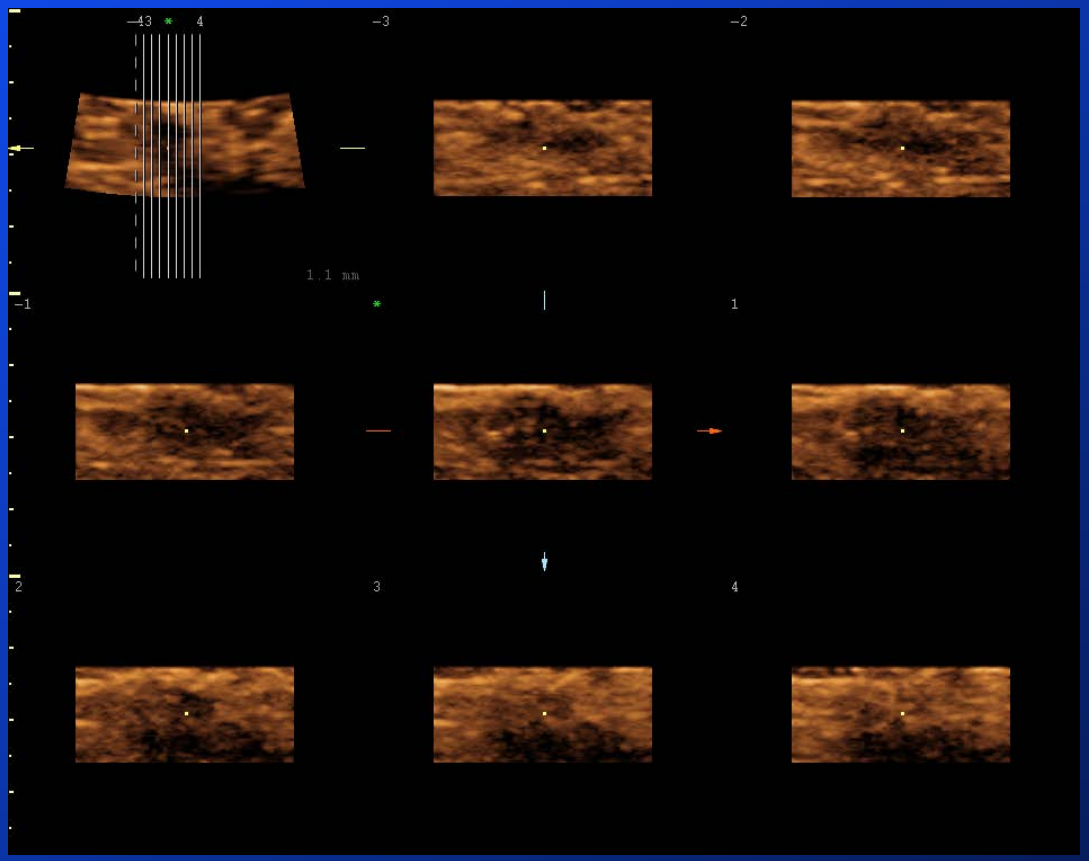




52 year old woman with 1.7 x 1.2 cm triple negative breast cancer 60% through course of neoadjuvant chemotherapy

Example Case





52 year old woman with 1.0 x 1.0 cm triple negative breast cancer 100% through course of neoadjuvant chemotherapy

Results to Date

Two patients saw complete resolution of the primary mass (2.5-2.0 cm at start of therapy), and 2 saw approximately 50-70% reduction in tumor volume (4.2-2.8 cm at start of therapy)

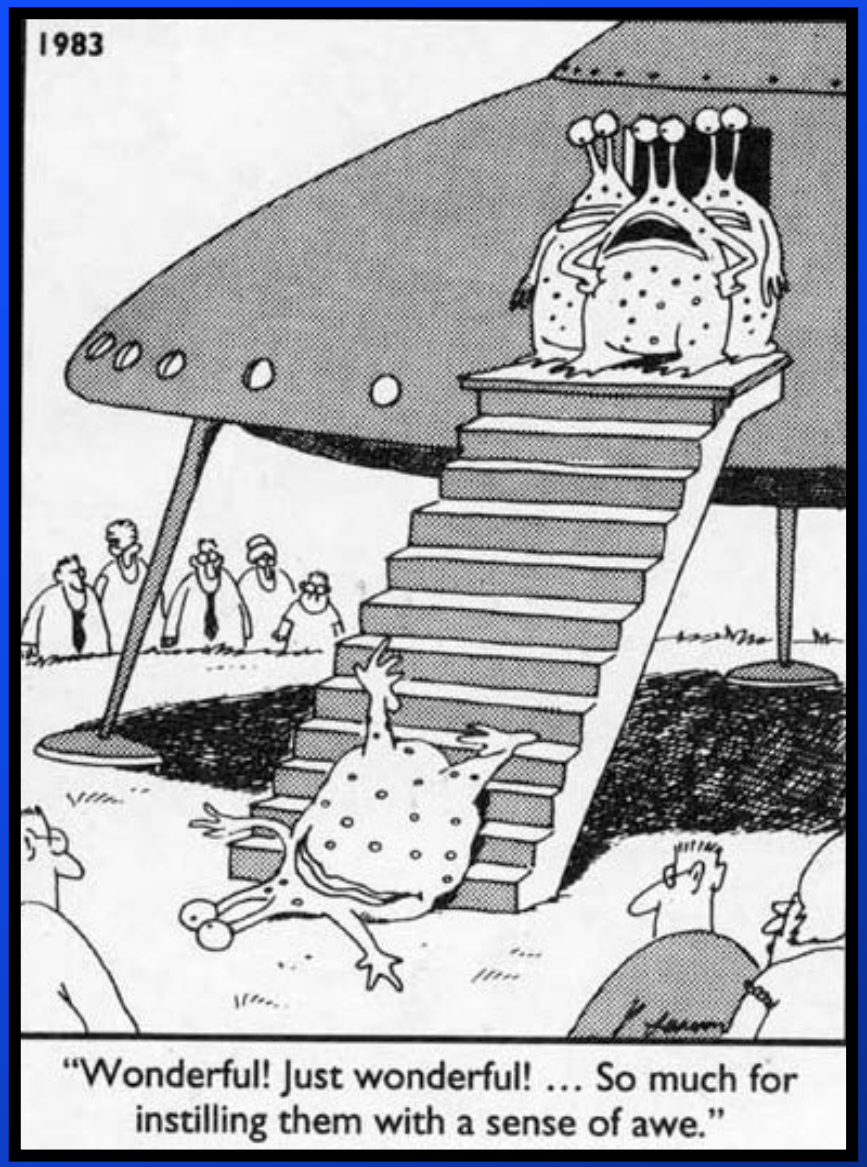
Complete responders demonstrated greater overall vascularity at baseline relative to partial responders, and showed a temporary increase in tumor vascularity at the 10% time point indicating a decrease in IFP

Conclusions

SHAPE is a new technique for non-invasive pressure estimation based on the subharmonic signals from contrast microbubbles

***In vivo* estimates of portal hypertension in humans obtained with SHAPE agree well with HVPG measurements (r = 0.82)**

Pilot studies in breast cancer and cardiology are underway



THANK YOU !

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