Ultrasound Contrast Agents

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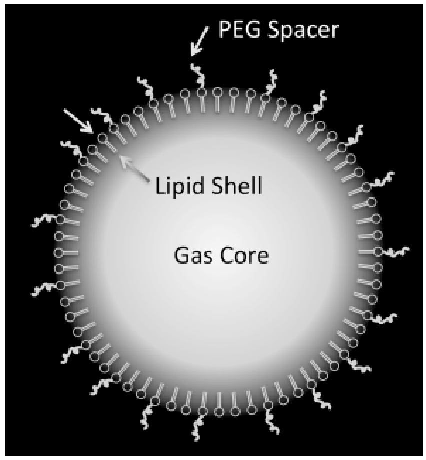
Charlotte, NC



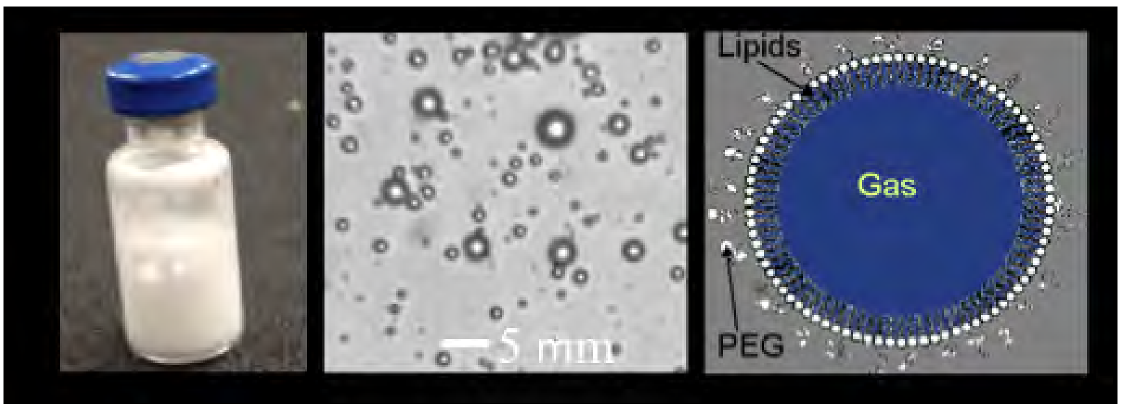
Discussion Points

- Part I
  - Microbubble Basics
  - Fundamentals in Contrast Imaging
  - Basic Imaging Applications
- Part II
  - Advanced Imaging Applications
  - Bioeffects and Therapeutic Applications
  - Safety

Microbubble Introduction

What are Microbubble Contrast Agents's

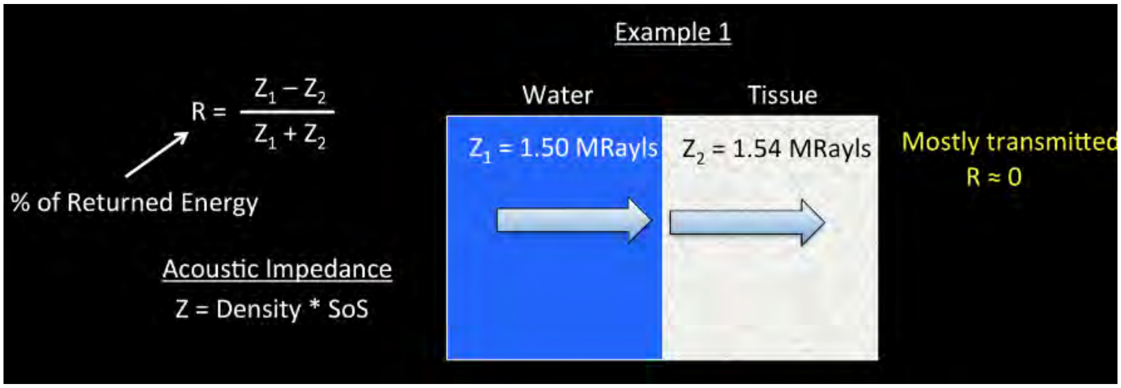
- Gas: Air, Perfluorocarbon, Sulfur Hexafluoride, etc
- Shell: Polymer, Lipid, Albumin, etc
- Size: Typically $< 8\ \mu$m (Size of RBC)
- Confined to the Vascular Space

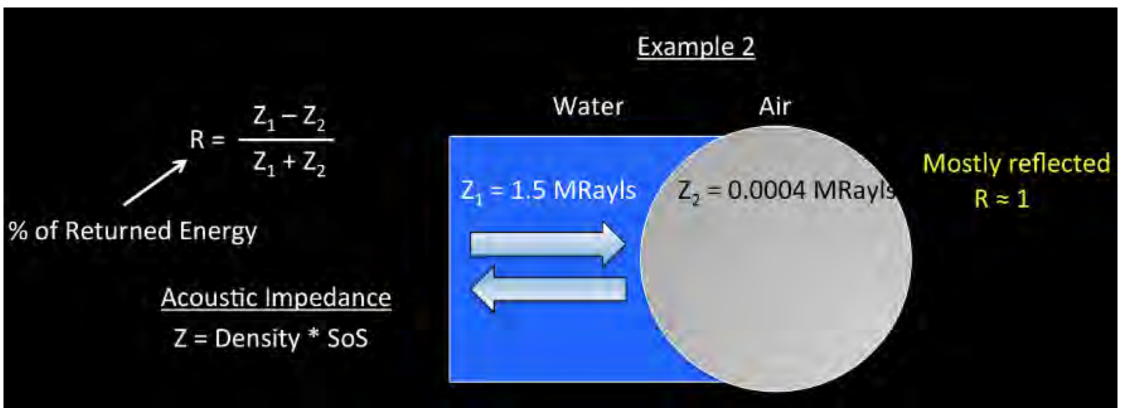


Notes

Microbubble Properties

Microbubbles are Highly Echogenic





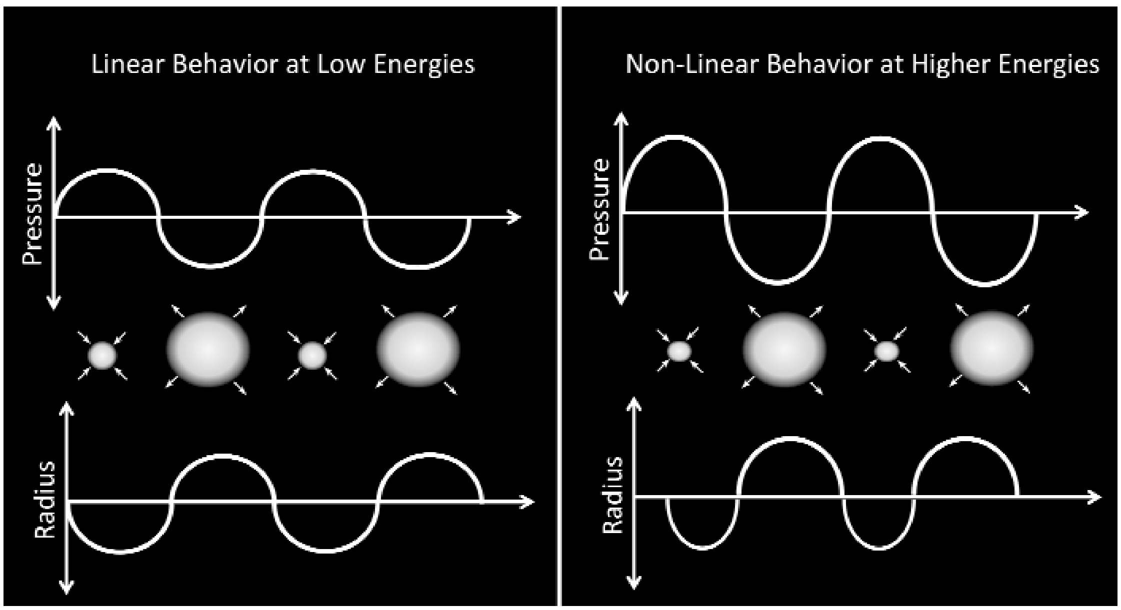
Reference: Szabo 2006

Notes

Microbubble Properties

Microbubbles Oscillate and are Governed by...

- Frequency
- Acoustic Power
- Pulse Repetition Frequency
- Type of Gas Core
- Damping Coefficients
- Shell Properties

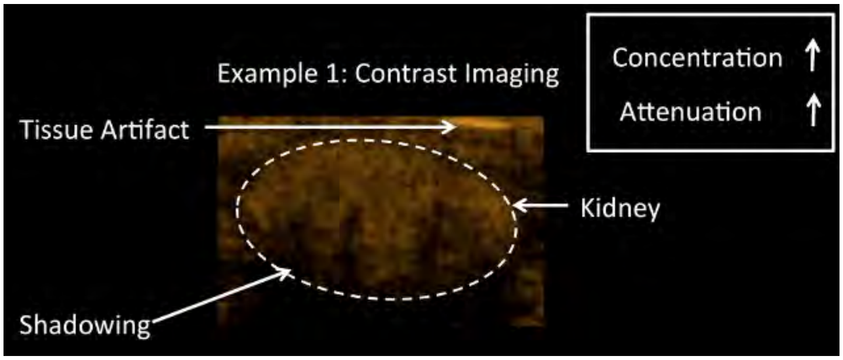


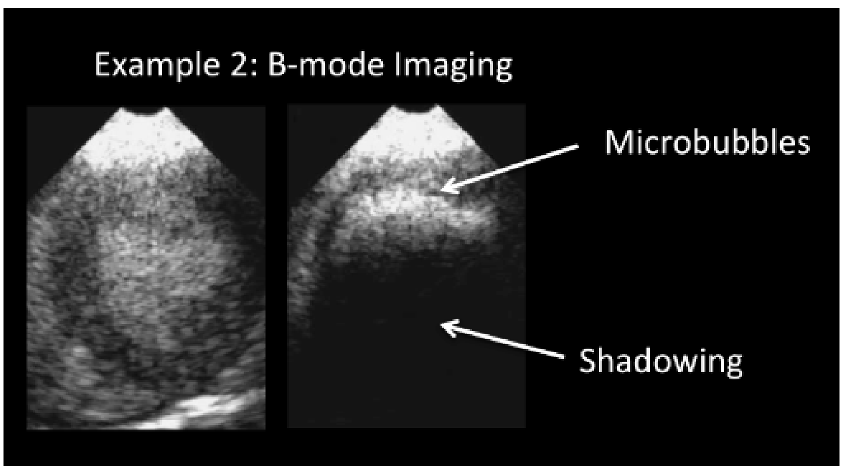
Reference: Quaia 2005

Notes

Microbubble Properties

Microbubbles Attenuate





Reference: Quaia 2005

Notes

Microbubble Properties

Describing the Motion of Microbubbles

Rayleigh - Plesset:

$$\rho R\ddot{R} + \frac{3}{2}\rho \dot{R}^2 = p_L - p_o \rho \dot{R}^2 = p_L - p_\infty$$

ρ = Density of Medium
R = Microbubble Radius
$\dot{R}$ = 1st Time Derivative of Radius
$\ddot{R}$ = 2nd Time Derivative of Radius
p_L = Liquid Pressure at Wall
p_∞ = Liquid Pressure Away From Wall

Reference: Quaia 2005

Notes

Microbubble Properties

Describing the Motion of Microbubbles

If you include the shell properties like viscosity and elasticity...

$$\rho R\ddot{R} + \frac{3}{2}\rho\dot{R}^{2} = p_{go}\left(\frac{R_o}{R}\right)^{3\Gamma} - \frac{2S_T}{R} - \frac{4\eta\dot{R}}{R} - p_o + P_{(t)}\sin(wt)$$

S = Surface Tension

η = Liquid Shear Viscosity

This is a complex equation and is very difficult to model and simulate!

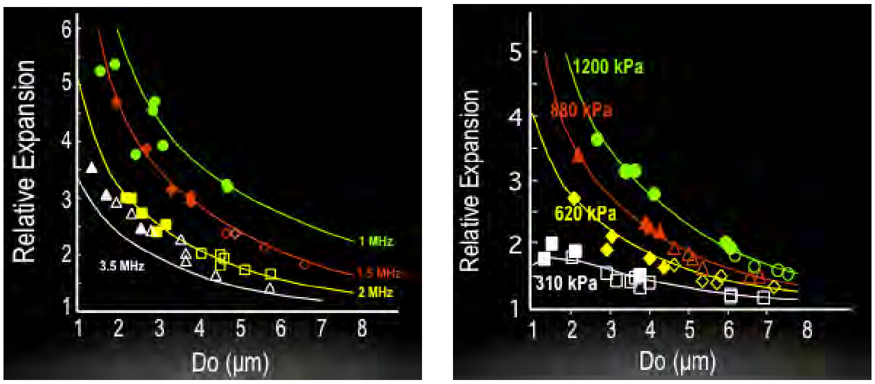
If you consider concentration and size distributionm the complexity is exacerbated.

Reference: Quaia 2005

Notes

Microbubble Properties

Microbubble Destruction Increases for High Acoustic Power, Long Pulse Lengths and Low Frequencies

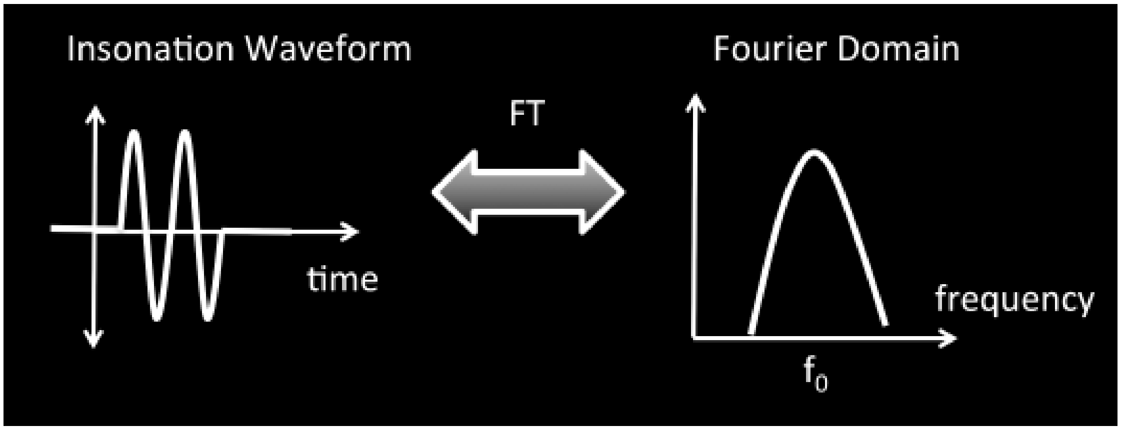


Reference: Quaia 2005

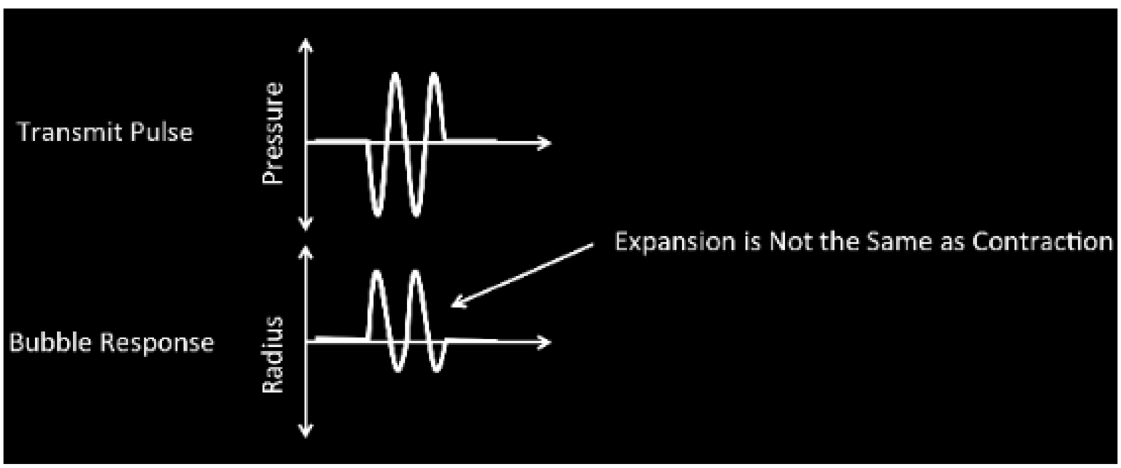
Notes

Imaging Microbubbles

Microbubble response is related to the insonation frequency



Microbubble response is non-linear

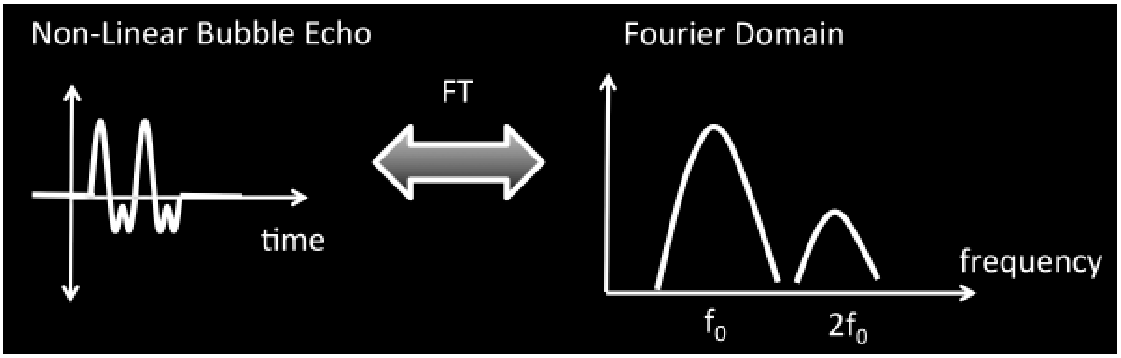


Reference: Quaia 2005

Notes

Imaging Microbubbles

Microbubbles generate harmonic and subharmonic energy



Imaging techniques take advantage of the microbubble properties

Goal: Separate the microbubble signal from the tissue

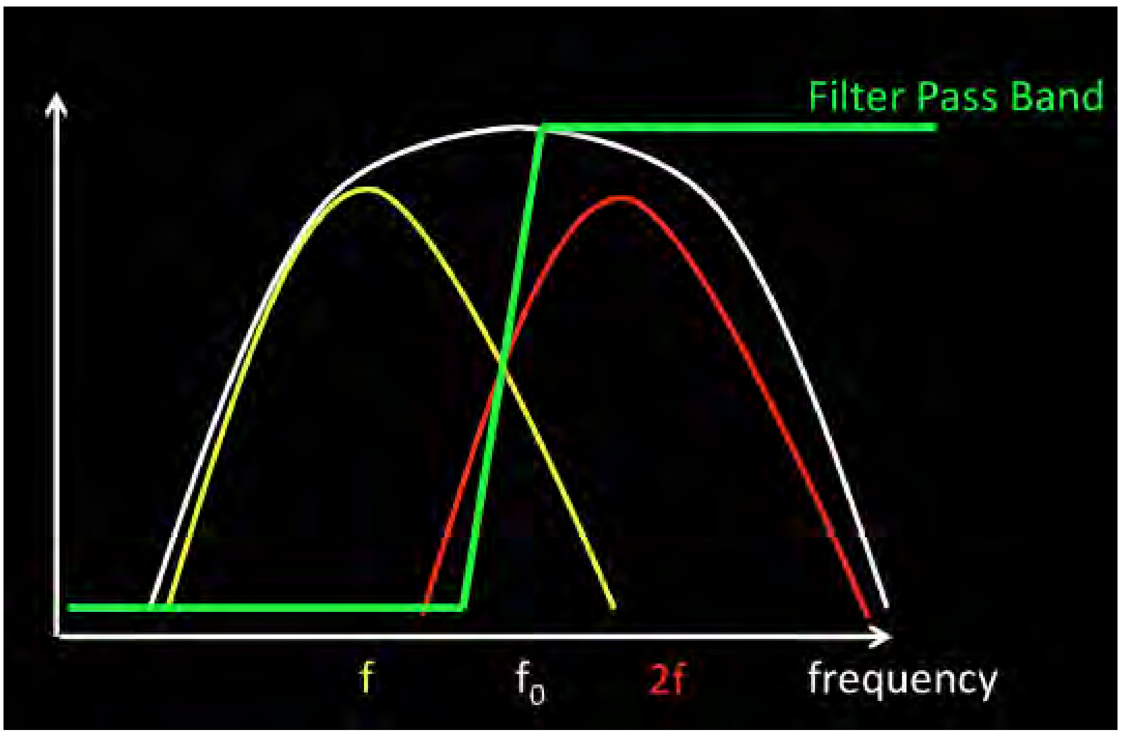
Reference: Quaia 2005

Notes

Harmonic Imaging

Harmonic Imaging

- Transducers have a finite bandwidth or frequency response
- Insonify microbubbles at frequency f
- Receive the returned signal at 2x f
- Use a high pass filter to eliminate unwanted low frequency signals
- NOTE: Strong tisuue signal can overpower weak harmonic signals



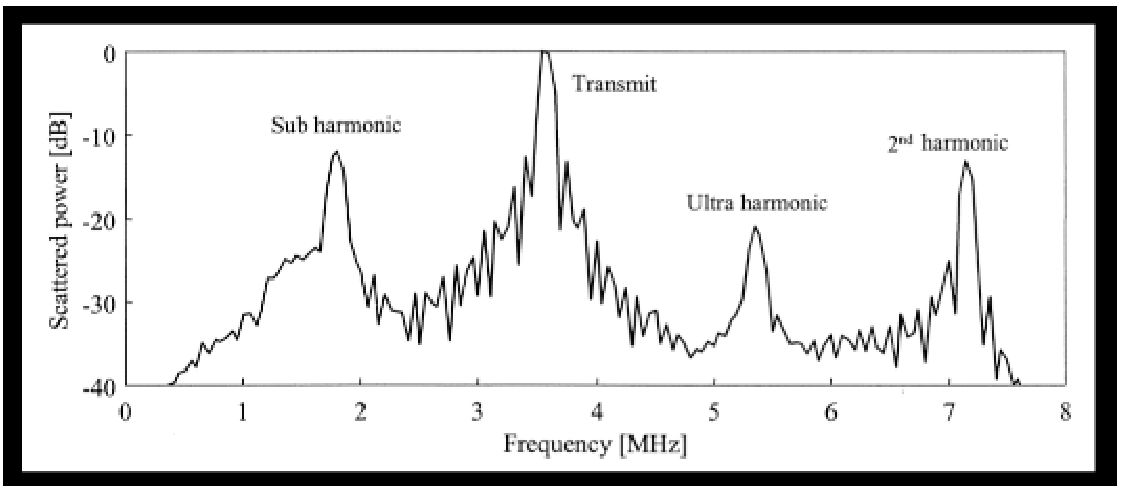
Reference: Quaia 2005

Notes

Subharmonic Imaging

Subharmonic Imaging

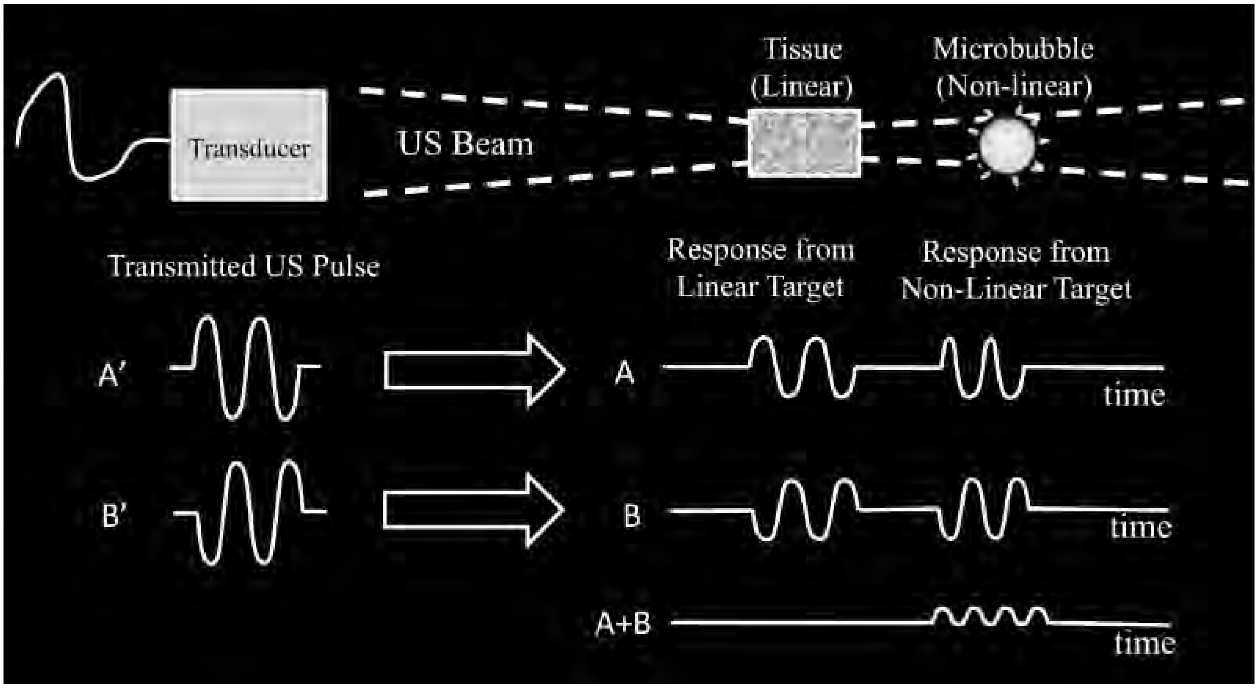
- Microbubbles have subharmonic energy
- Subharmonics occur at $\sim \frac{1}{2}$ of the transmitted frequency
- Tissue generated harmonic energies at high acoustic pressures
- Subharmonics allow for easy separation of signal from tissue
- Lower frequencies imply less attenutaion



Reference: Frinking 2000

Notes

Pulse Inversion Imaging



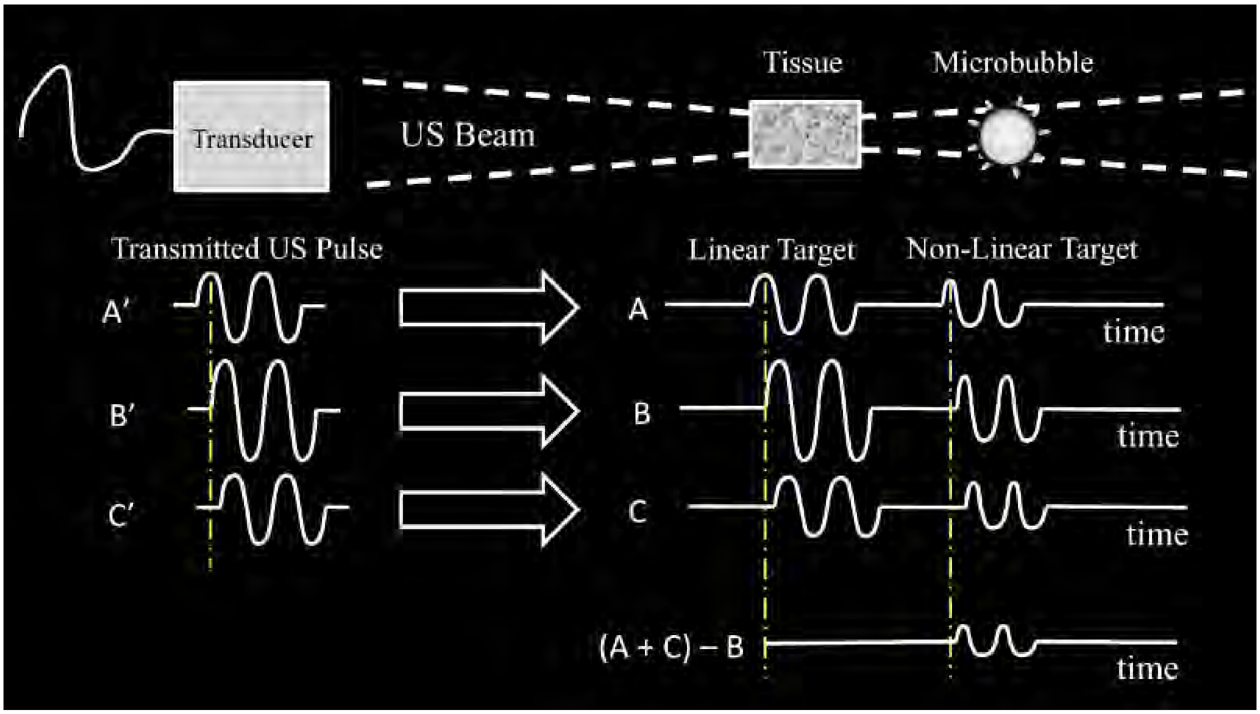
At high enough pressures, tissue behaves non-linearly

Reference: Quaia 2005

Notes

Amplitude Modulation Imaging

Amplitude Modulation

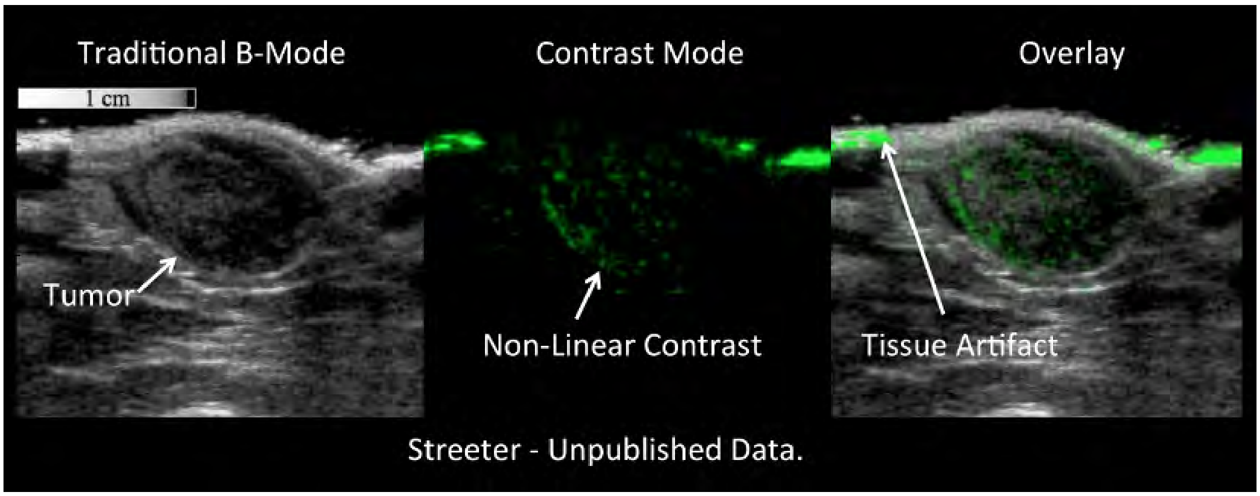


Notes

Combining Imaging Techniques

Example:

- Siemens Sequoia - 15L8 Linear Array Transducer
- Cadence Pulse Sequencing Mode (Contrast Imaging)
- Amplitude Modulation and Pulse Inversion



Reference: Quaia 2005, Streeter Unpublished

Notes

Contrast-Enhanced Ultrasound

Contrast-Enhanced Ultrasound

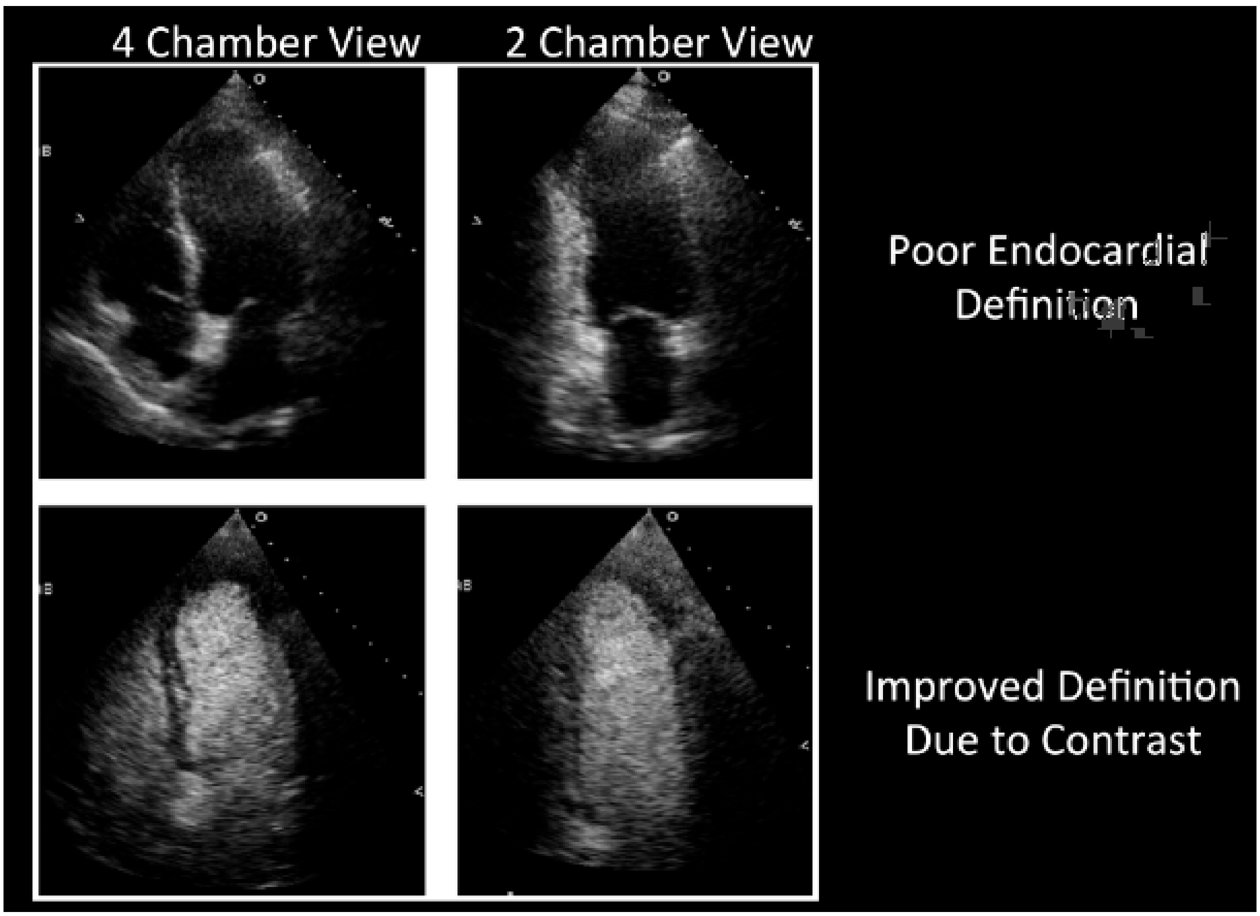
- Blood is a weak scatterer
- Microbubbles help delineate the tissue from blood
  - Provides a clearer picture for clinicians
- Ability to quantify tissue perfusion
  - Transit time measurements
  - Evaluation of blood volume
  - Replenishment Kinetics

Reference: Quaia 2011

Notes

Contrast Echocardiography

- Assessment of Left Ventricular Cavity
  - Requires endocardial border visualization
  - Adequate visualization not possible in 15% of patients
- Left ventricular opacification
  - Microbubbles improve visualization
  - Produces homogenous opacification
  - Improves reader accuracy and confidence



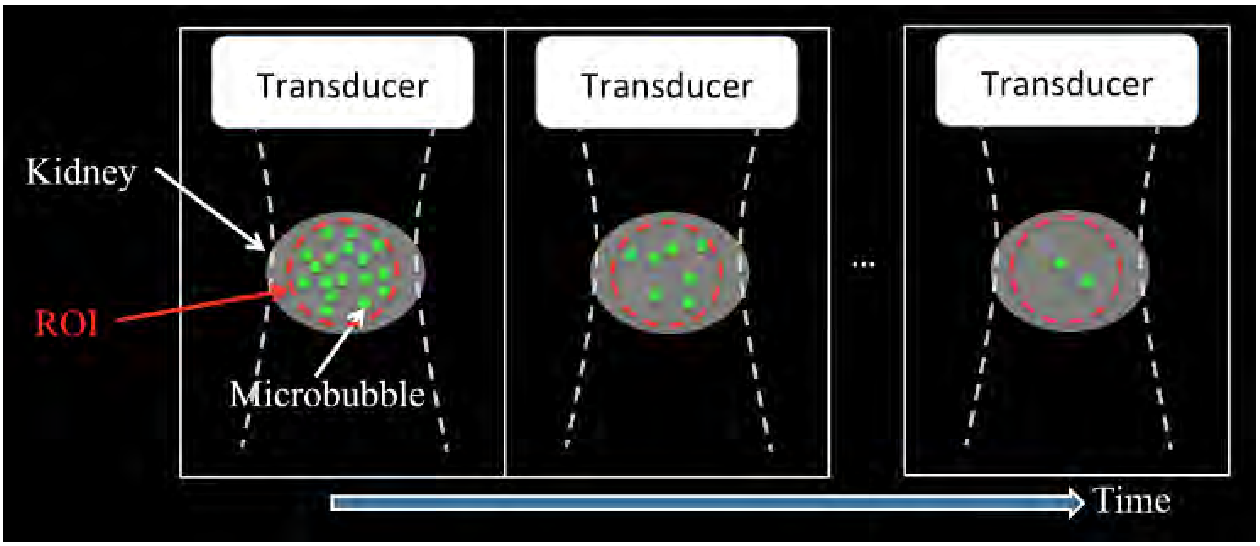
Reference: Kaufmann 2005

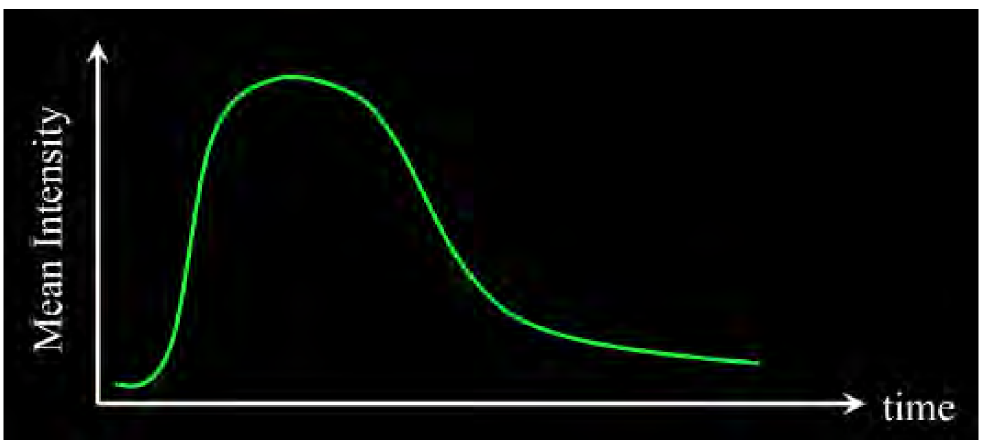
Notes

Time Intensity Curves

Time Intensity Curve

- Contrast-enhanced monitoring over time
- Select a region of interest
- Evaluate the intensity of the microbubbles



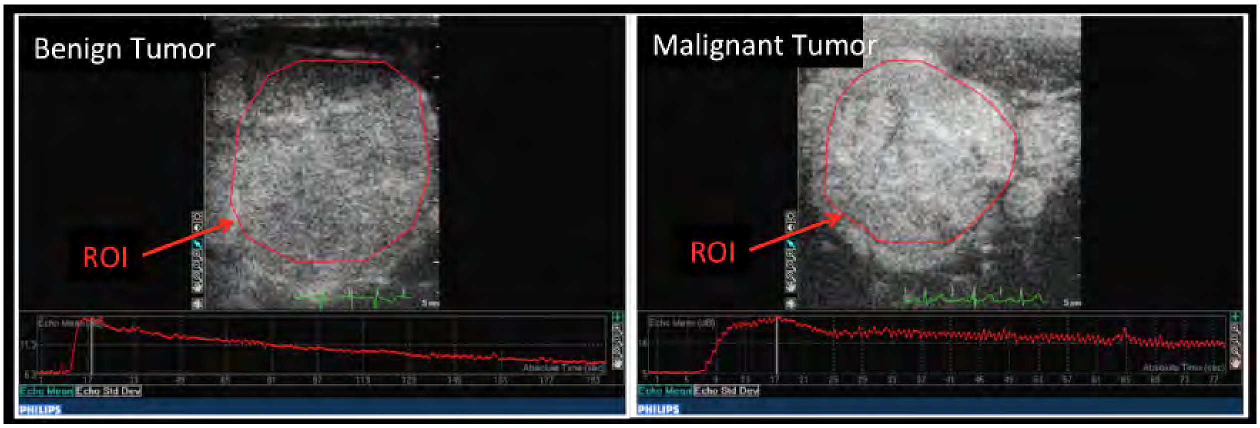


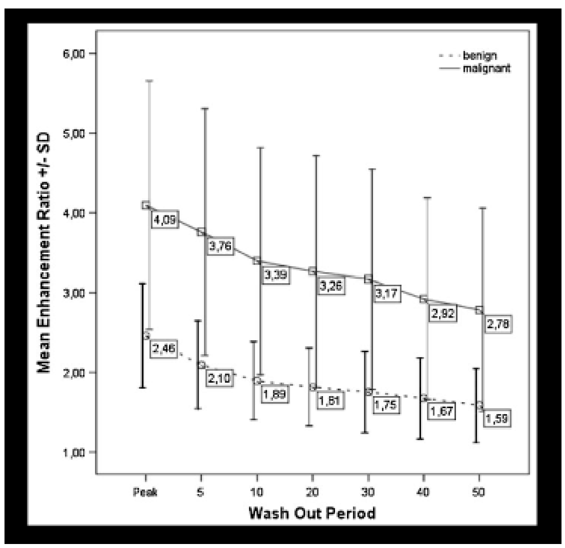
Reference: Quaia 2011

Notes

Time Intensity Curve Example

Example: Differentiation between benign and malignant thyroid tumors





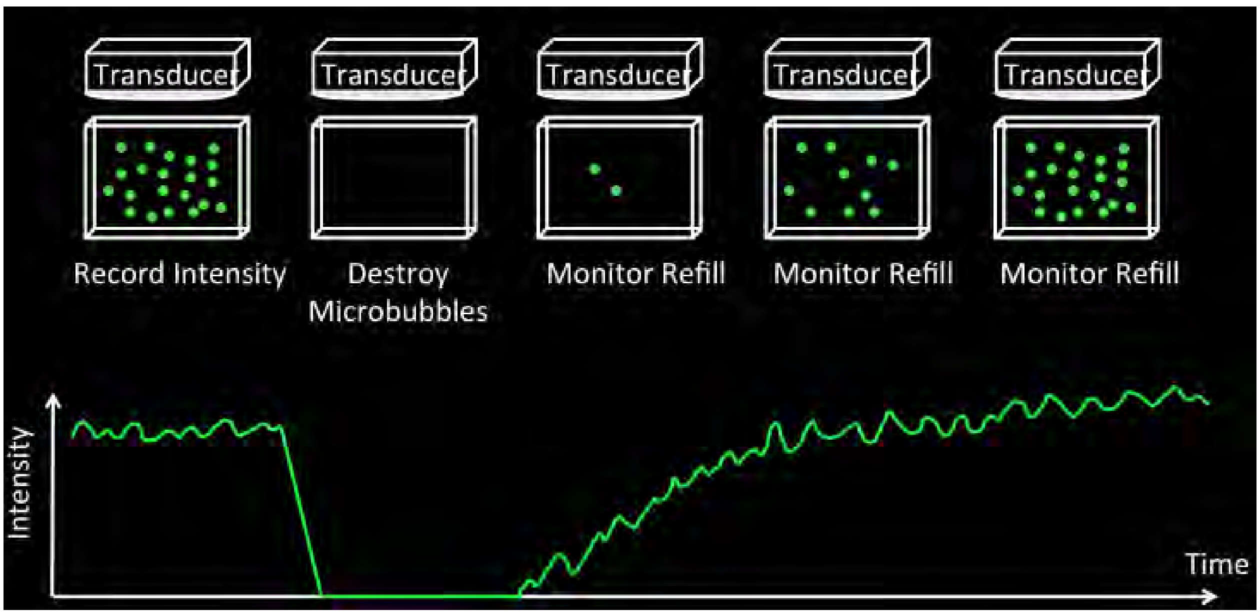
Reference: Nemec 2012

Notes

Destruction-Reperfusion

Destruction-Reperfusion

- Perfusion quantification helps understand diseased tissue
- Microbubbles are continuously infused
  - Steady-state clearance equals the inflow of microbubbles
- Microbubble destruction in a single plane
- Monitor the microbubble refill rate



Reference: Quaia 2011

Notes

Destruction-Reperfusion

Destruction-Reperfusion

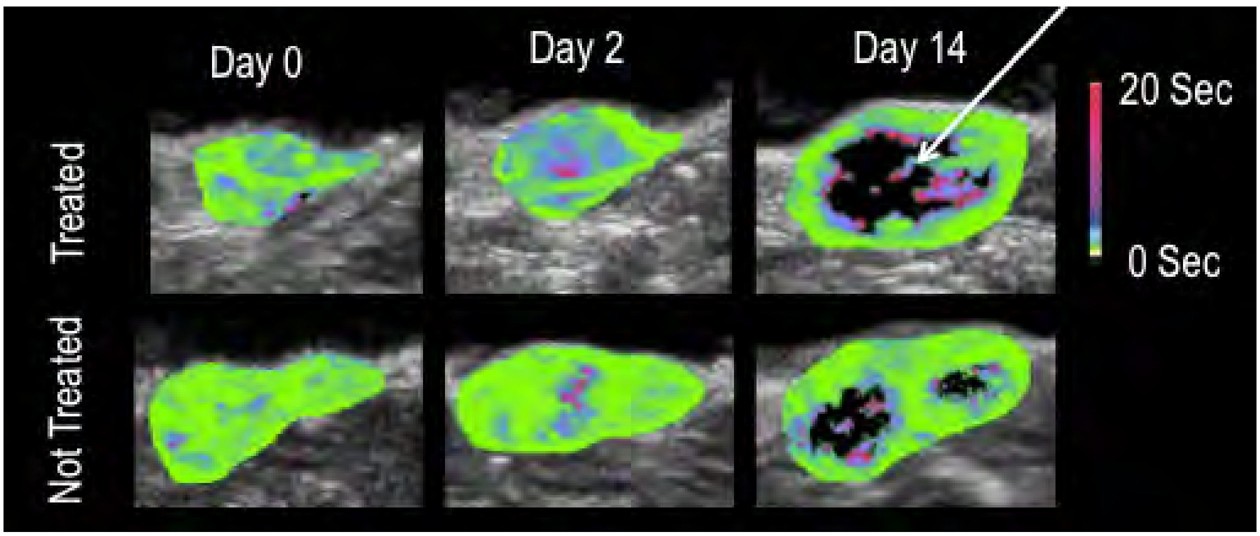
- Perfusion quantification helps understand diseased tissue
- What information do we get?
  - Time to peak intesity
  - Blood flow velocity (slope)
  - Fractional blood volume (Max Amplitude)
  - Blood volume (Area under the curve)
  - Mean transit time

Reference: Quaia 2011

Notes

Destruction-Reperfusion Example

- Perfusion quantification helps understand diseased tissue
- Example:
  - Destruction-reperfusion at the pixel level
  - Monitoring time to 20%
  - Volumetric evaluation via elevational stepping
  - Tumor Perfusion Monitoring During Therapy

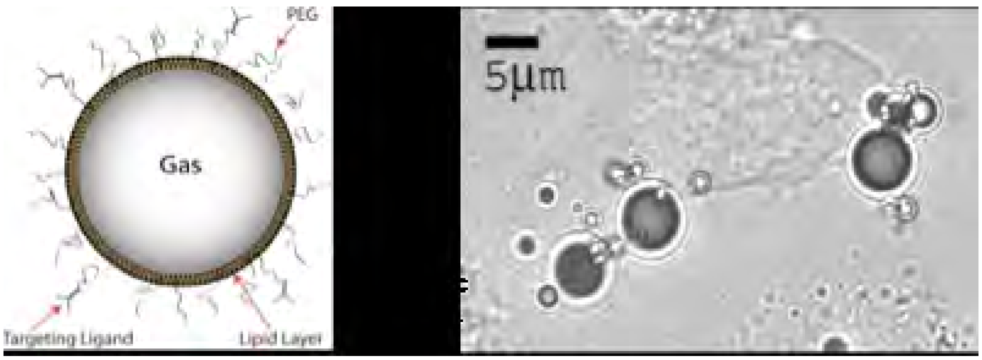


Reference: Streeter 2012

Notes

Molecular Imaging

- Functional technique to evaluate molecular activity
- Knowledge of molecular signature of pathology
  - Integrins, selectins etc... expresed on the endothelium
  - Angiogenesis markers: VEGFR2, $\alpha_v \beta_3$, etc...
- Targeted microbubble contrast agents
  - Lipid monolayer fitted with adhesion ligand

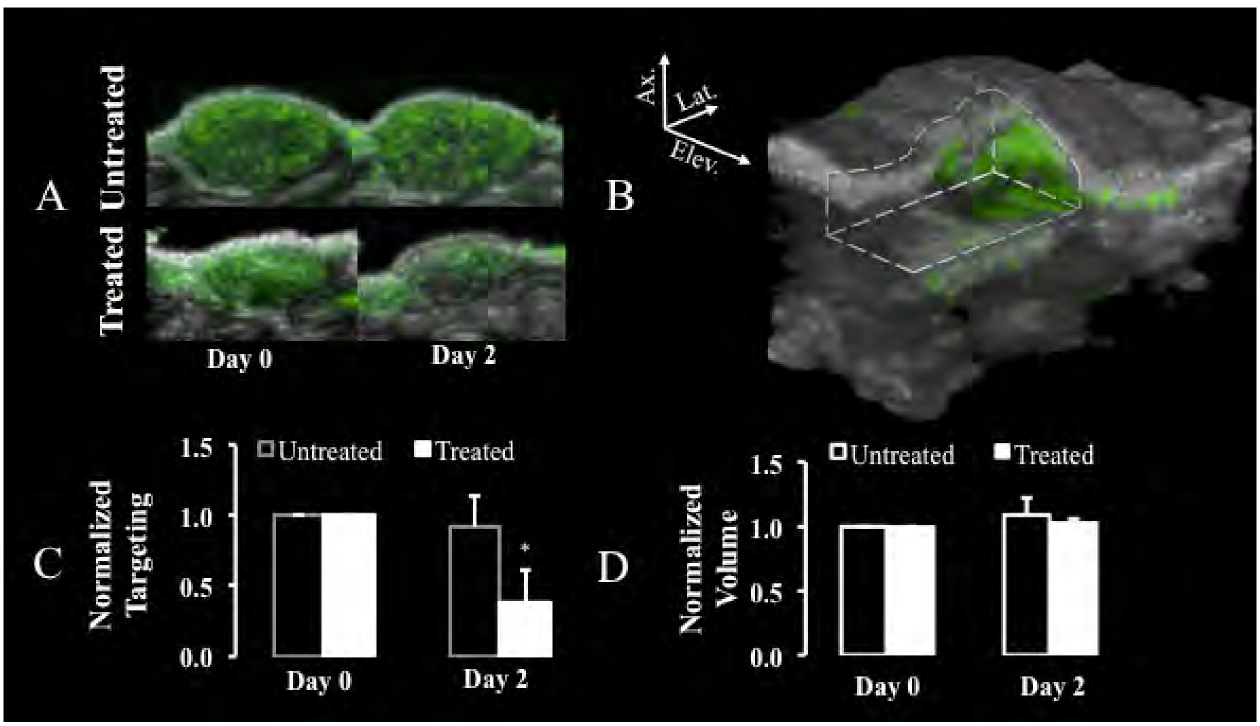


Reference: Dayton 2002, Dayton 2004

Notes

MI and Response to Therapy

- Traditional methods for quantifying tumor progression - volume measurements
- Volume measurements provide slow feedback
- Molecular imaging is a good alternative with faster response
- Example:
  - Cancer Type: Pancreatic adenocarcinoma
  - Therapy: Aurora Kinase Inhibitor
  - Target: $\alpha_v\beta_3$
  - Animal Model: Mouse



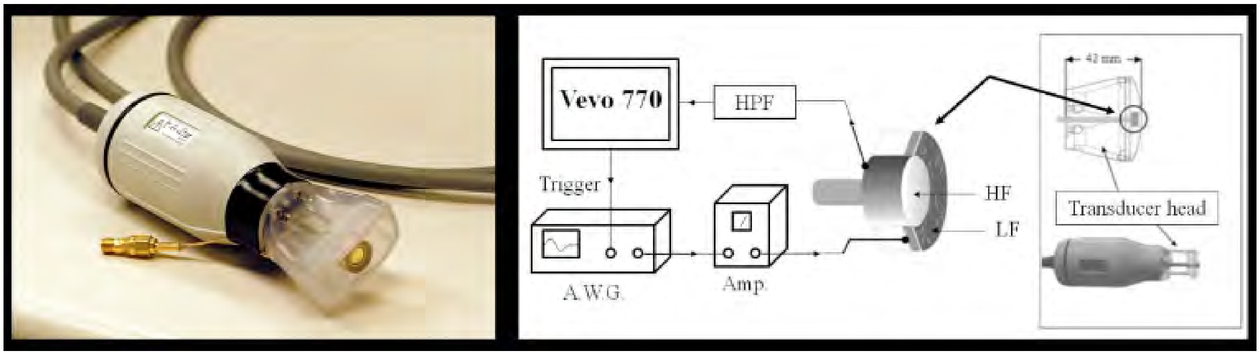
Reference: Streeter 2012

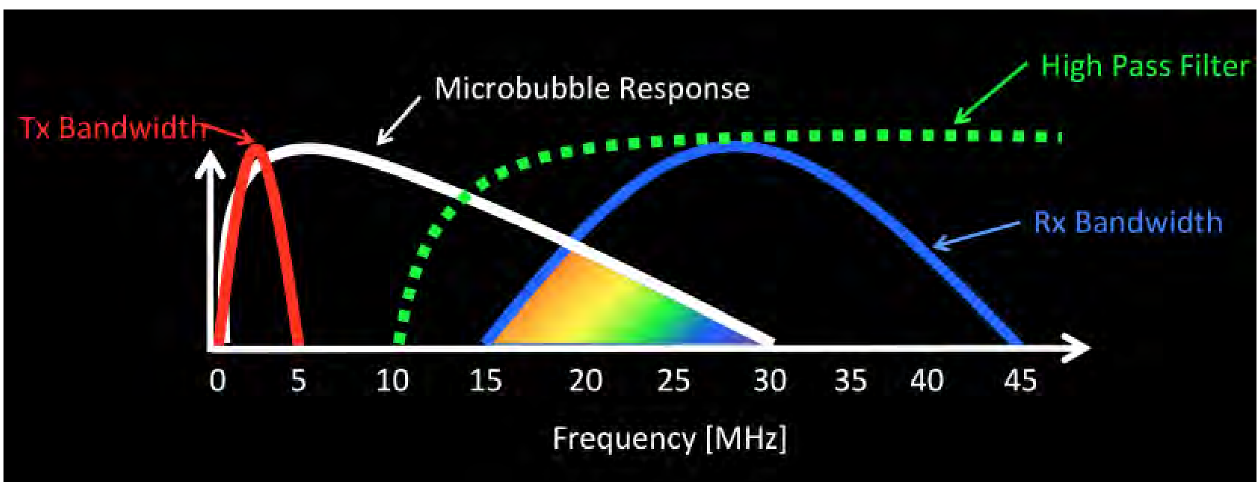
Notes

Acoustic Angiography

Acoustic Angiography:

- Traditional Ultrasound Transducer
  - Transmit and receive (x1 frequency bandwidth)
- Dual frequency imaging
  - Transmit using low frequency bandwidth
  - Receive using high frequency bandwidth





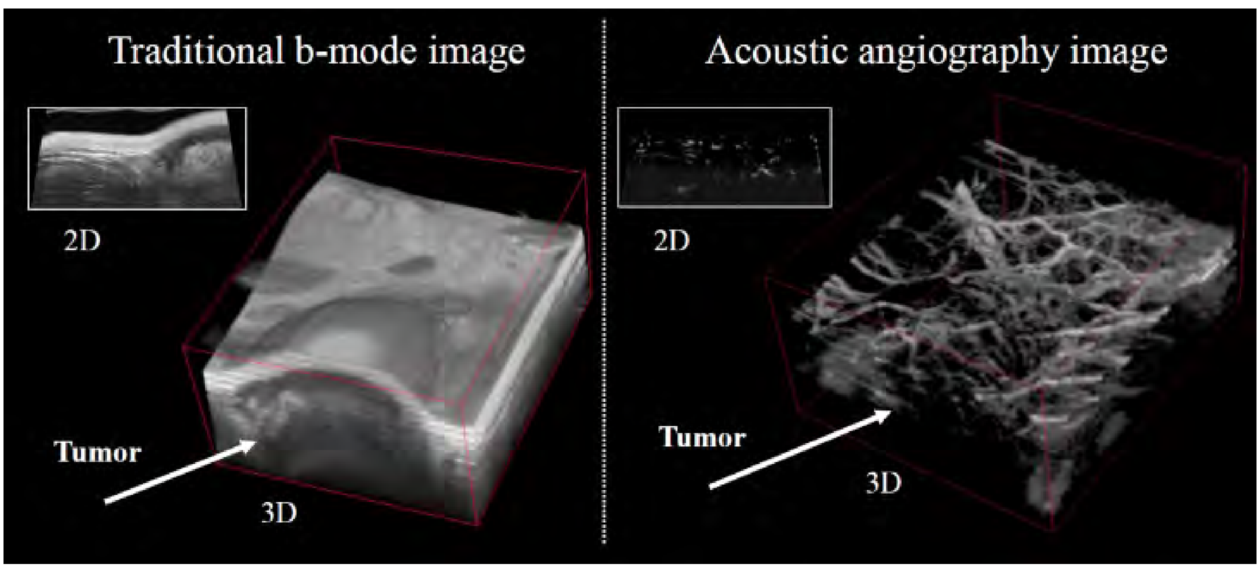
Reference: Kruse 2005, Gessner 2010

Notes

Acoustic Angiography

Acoustic Angiography:

- Advantages:
  - High frequency provides better resolution
  - Attenuation in one direction
  - Eliminates low frequency tissue signal
  - Less sensitive to breathing artifacts
- Disadvantages:
  - Transducers not yet commercial
  - High attenuation (shallow depth imaging)
  - Eliminates low frequency tissue signal
  - Not a low-MI imaging technique



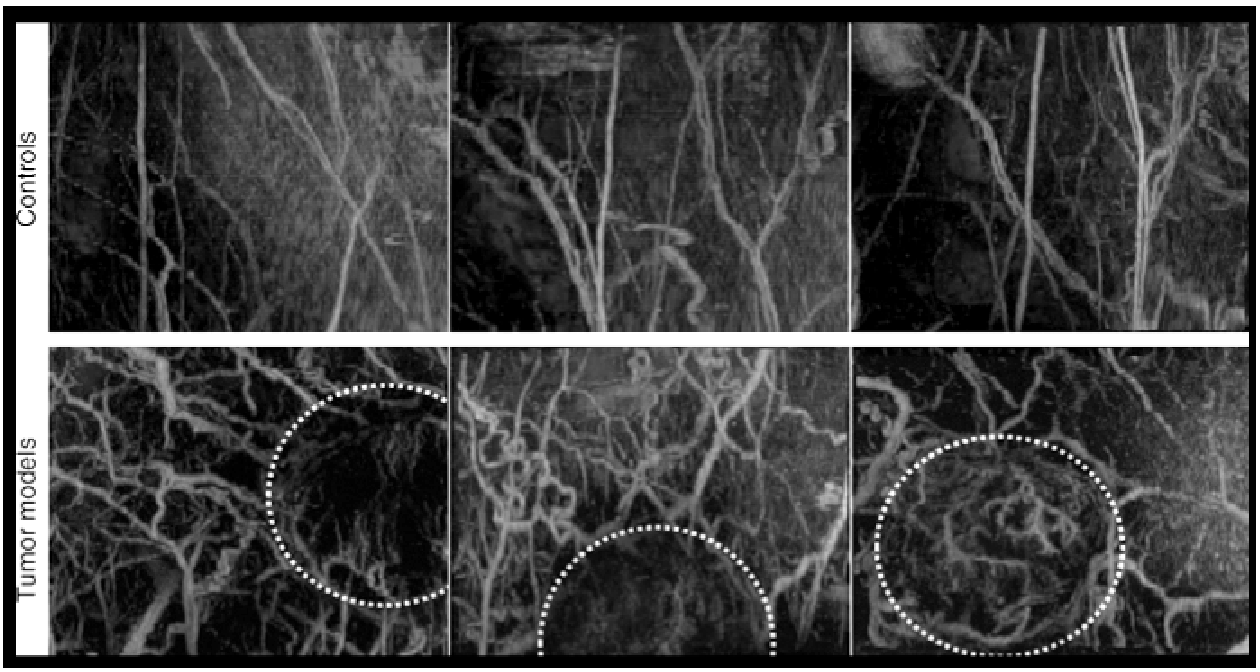
Reference: Gessner 2012

Notes

Acoustic Angiography

How can angiography be used in oncology research?

- Blood vessel structure, density, and pattern can be assessed non-invasively
- Microvascular tortuosity abnormalities are an indicator of tumor development
- Prior studies have shown that vessel morphological characteristics are related to tumor malignancy and response to treatment



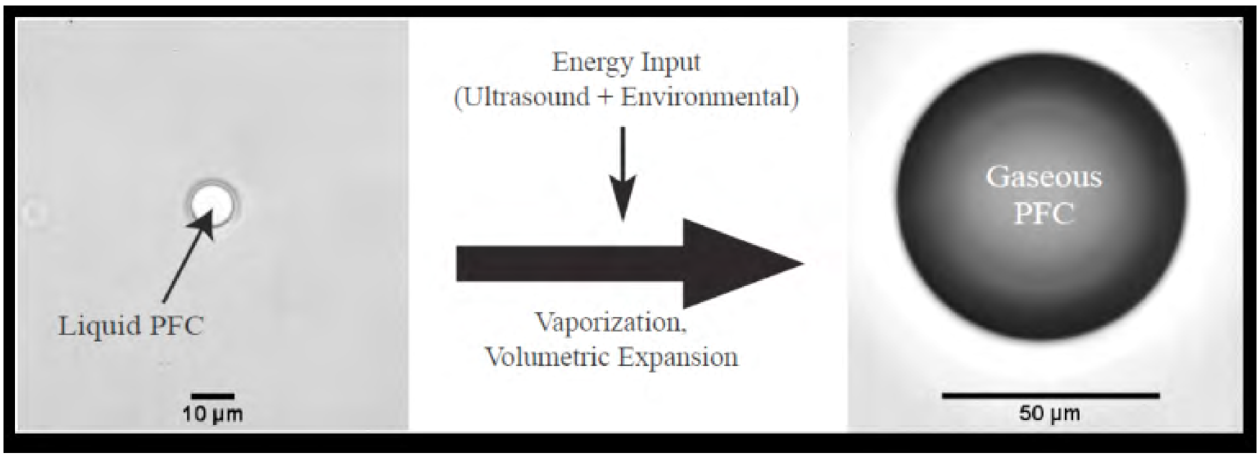
Reference: Bullitt 2009, Gessner 2012

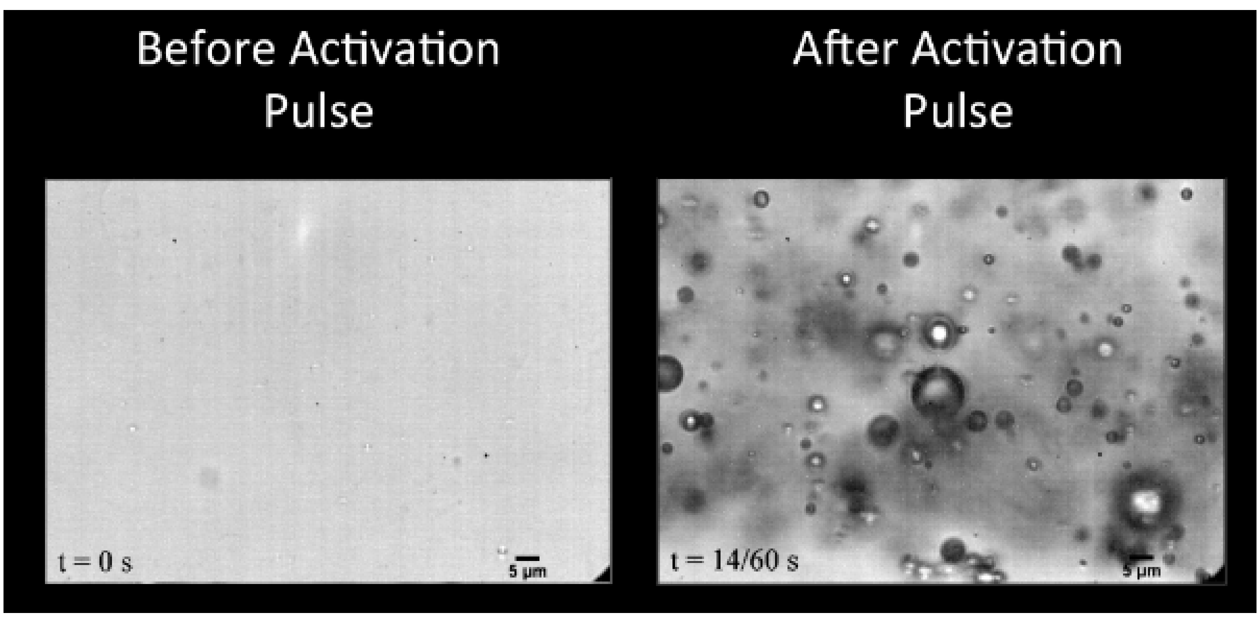
Notes

Ultrasonic Activatable Nanoparticles

Ultrasonic Activatable Nanoparticles:

- Liquid perfluorocarbon core
- Lipid or polymer shell
- Tipped to gaseous state by ultrasound





Reference: Sheeran 2011

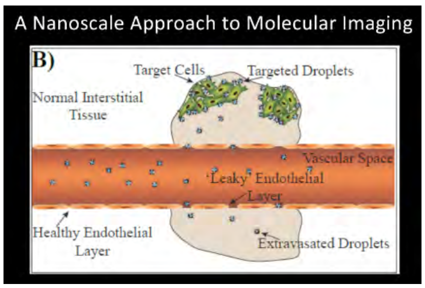
Notes

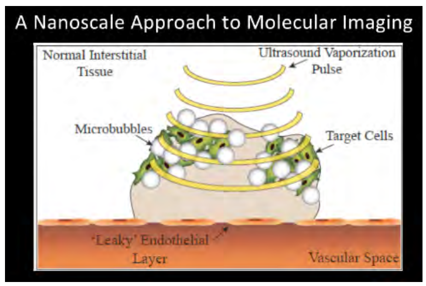
Ultrasonic Activatable Nanoparticles

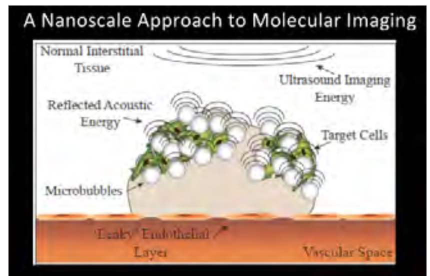
Ultrasonic Activatable Nanoparticles:

- Applications:
  - Vascular Occlusion
  - Cavitation Agents
  - Extravascular Diagnostics

Example: Molecular Imaging





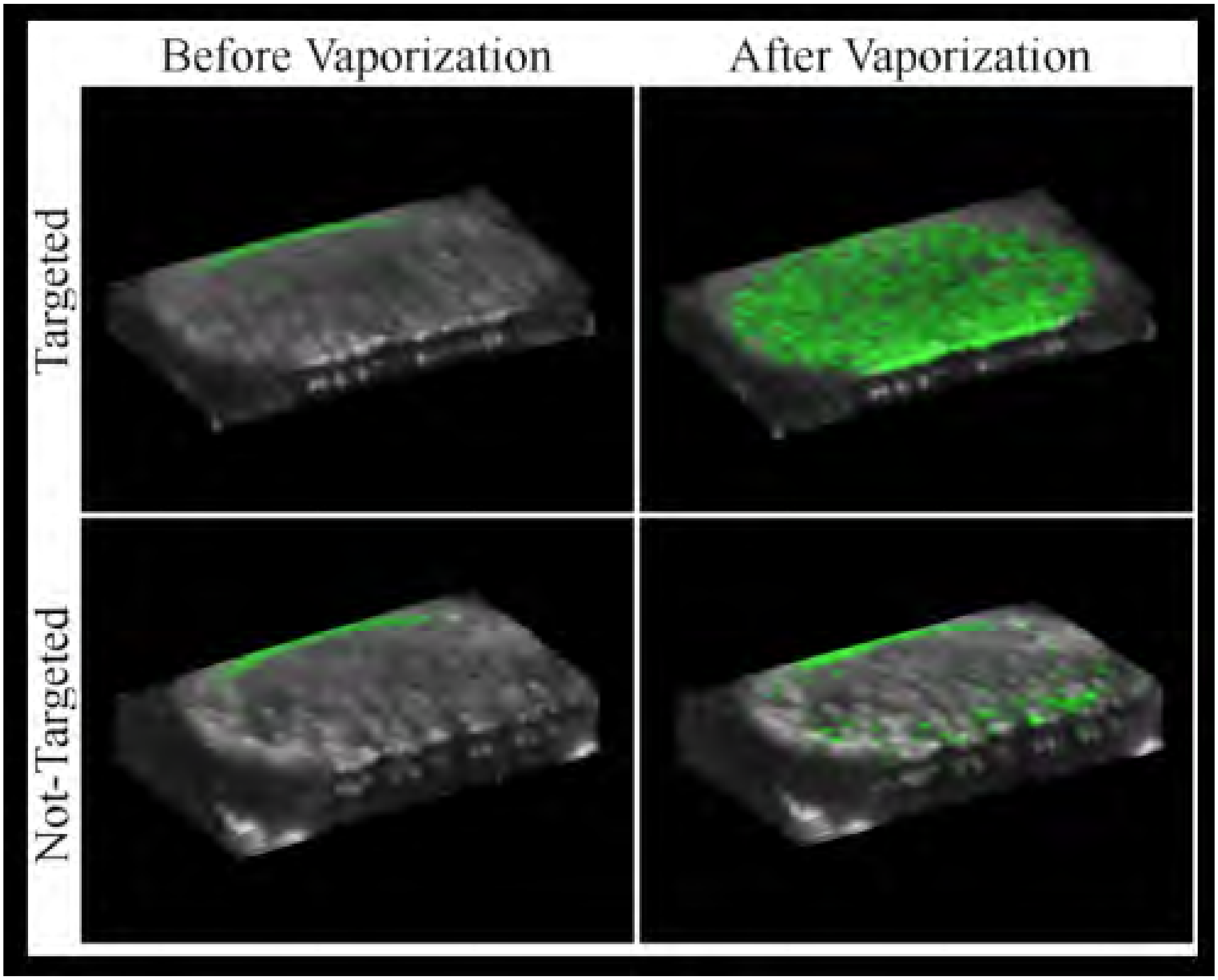


Reference: Sheeran 2011, Sheeran 2012

Notes

Ultrasonic Activatable Nanoparticles

Example: Molecular Imaging

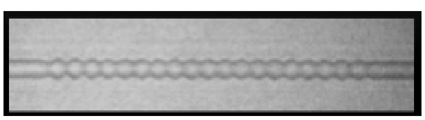


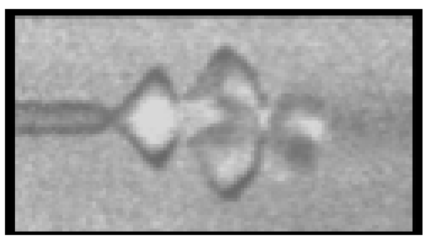
Reference: Sheeran 2012

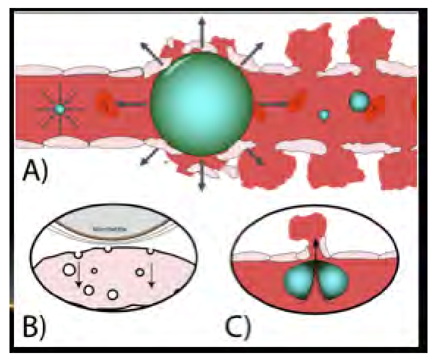
Notes

Biological Effects

- Interaction between ultrasound and microbubbles
- Increased thermal energy conversion
- Mechanical stimulation of biological membranes
  - Microstreaming
  - High pressure and temperatures
- Cavitation (violent expand/collapse)
  - Shock waves
  - Microbubble jetting
  - High pressures and temperatures
  - Free radical formation







Reference: Quaia 2005

Notes

Biological Effects

- Mild
  - Reversible Capillary Permeability Changes
  - Reversible Cell Membrane Permeability
  - Small Temperature Changes
- Strong
  - Capillary Rupture
  - Tissue Ablation
  - Cell Death

Reference: Quaia 2005

Notes

Biological Effects

- Drug delivery - can be achieved LOCALLY with focused ultrasound and microbubbles
- Enhanced blood brain barrier permeability
- Enhanced capillary permeability
- Increased cellular delivery through cell membrane permeability
  - Have been shown to significantly enhance local drug and gene delivery, and corresponding therapeutic response
- Improved thermal ablation (requires less delivered power with microbubbles reduces thermal damage to healthy tissues)

Reference: Quaia 2005

Notes

Microbubble Clearance

- Microbubbles are vascular agents
- Phagocytosis in the liver and spleen
- Gas is expelled through the lungs
- Shell content is eliminated by the kidney and liverl
- Phospholipids enter normal metabolism
- Typical circulation half life ∼5 to 15 minutes

Reference: Quaia 2005

Notes

Safety Concerns

- 1994 Albunex (albumin shell air core)
- 1997 Optison (albumin shell perfluorocarbon core)
- 1994 Definity (lipid shell perfluorocarbon core)
- 2007 Blackbox Warning - Microbubbles may cause fatalities
- Extensive Investigative Studies
- >1 Million administered doses
- Most frequent adverse reactions are mild
- Headache: 5%, Nausea: 4%, Flushing: 4%, Dizziness: 3%
- Uncommon arrhythmias, hyper/hypotension, neurologic and anaphylactoid reactions

Procedure	Mortality
Contrast Echo	1:145,000 (SonoVue) 1:500,000 (Definity)
Myocardial Scintigraphy	1:10,000
Exercise ECG	1:2,500 (or AMI)
Coronary arteriography	1:1,000

Reference: Quaia 2005, optisonimaging.com

Notes

Safety Concerns

Blackbox remains, but contraindications to contrast agents restored to the original labeling

- Contraindications:
- Right-to-left, bi-directional, or transient right-to-left cardiac shunts
- Hypersensitivity to perflutren, to blood, blood products, or albumin
- Intra-arterial injection
- 30 minute observation period recommended for patients with...
- Pulmonary hypertension (undefined)
- Unstable cardiopulmonary conditions
- Ultrasound contrast agents are extremely safe with a low incidence of side effects
- They are not nephrotoxic or cardiotoxic
- Incidence of hypersensitivity or allergic events appears much lower than current X-ray or MR contrast agents
- As in all clinical procedures, physicians should balance potential clinical benefits against the theoretical possibility of associated adverse bioeffects in humans

Reference: Quaia 2005, http://www.fda.gov

Notes

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