Factors influencing dual-frequency ultrasound

J.G. Swan[1], J. C. Wilbur[2], T. L. Beach[2], D. A. Knaus[2], S. D. Phillips[2], P. J. Magari[2], and J. C. Buckey[1]

[1]Geisel School of Medicine at Dartmouth College, Lebanon, NH, [2]Creare, Inc., Hanover, NH USA.

Introduction

•Studies have shown that microbubbles may exist normally in tissue and that their numbers can be changed by exercise and other interventions

•Using dual frequency ultrasound (DFU) we have detected signals consistent with microbubbles after exercise

•Since no “gold standard” comparison exists for these in-vivo measurements, characterizing the factors that influence DFU measurements is essential

•We have performed experiments to characterize the factors that could influence DFU microbubble measurements

Question

What is the sensitivity, and stability of DFU measurements?

What confounding factors could influence the measurements?

Dual Frequency Ultrasound

•Bubbles behave nonlinearly when resonating.

•Dual-Frequency Ultrasound (DFU) involves “pumping” bubbles at their resonant frequency and “imaging” the bubbles using a second frequency (Figure 1).

•When bubbles of resonant size are present, mixing (sum and difference) signals are produced.

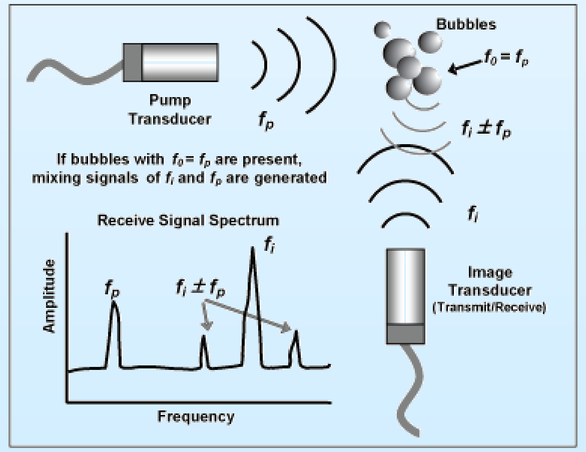

Figure 1. Dual-frequency ultrasound looks for the nonlinear mixing of two different ultrasound frequencies to detect and size resonating bubbles.

Methods

•Lipid-stabilized microspheres (Definity™) were used as a nonlinear source when needed

•All experiments were performed in a water-filled aquarium to allow for optimal sound conduction

•Water was clean and debubbled/degassed

•The transducers and targets were held in a stable configuration via a custom built holder

DFU Resolution

What is the resolution (bubbles/mL) that can be detected using DFU?

•DFU can detect 3 microbubbles/mL (Figure 2)

•Modeling predicts this is a hard physical limit below this the inherent nonlinearity of the host fluid masks the microbubble nonlinear contribution (Figure 3)

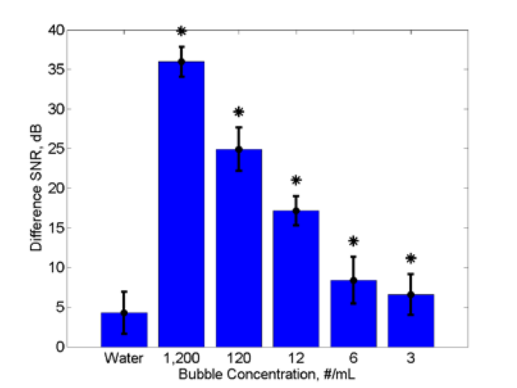

Figure 2. Bubble detection resolution

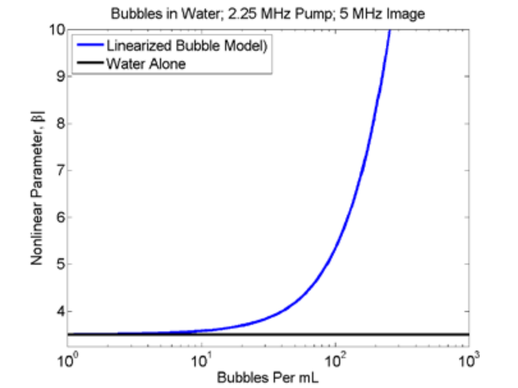

Figure 3. Modeling of bubble detection limit

Effect of Temperature

Due to the positive relationship of temperature on sound, will a change in medium temperature effect DFU?

•Temperature was increased from 22°C to 27°C over 2 hours

•The difference signal changed with temperature (r^2=0.18), although the change was small (Figure 4)

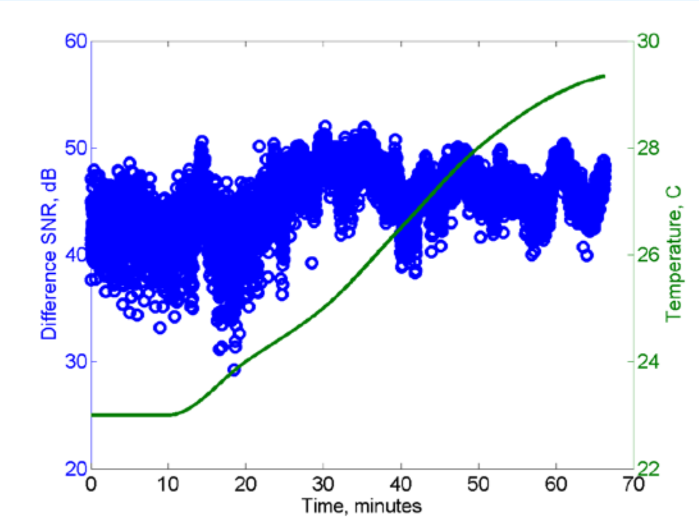

Figure 4. Effect of temperature on difference signal

Optimal Driving Pressure Settings

What driving pressure produces the greatest SNR?

•Driving force (kPa) is pressure per unit area

•Increasing the driving force increases mixing signal but also increases noise and the risk of disrupting the the bubble population (destroying or translating bubbles)

•In water, a source pressures of 16 kPa resulted in the greatest separation between a positive and negative control while source pressures of 8 kPa resulted in a near-zero difference signal for negative controls (Figure 5)

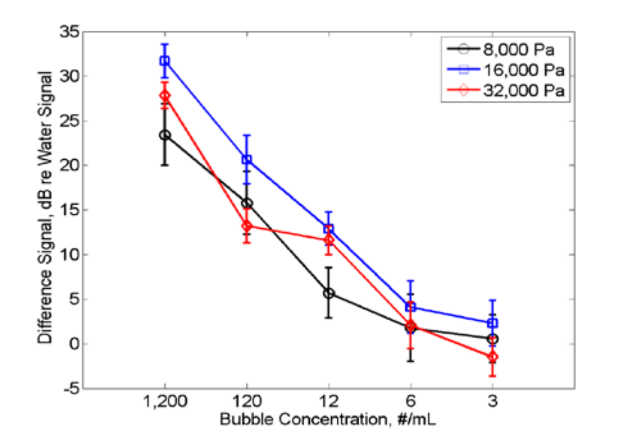

Figure 5. Effect of driving pressure

Optimal Pump/Image Settings

What pump/image frequencies produces the greatest SNR?

•Changing frequency changes the bubble size detected

•For detecting Definity™ the optimal pump frequency is 1.25 MHz and the image frequency is 4 MHz. The optimal frequencies may be different for DCS-related microbubbles (Figure 6)

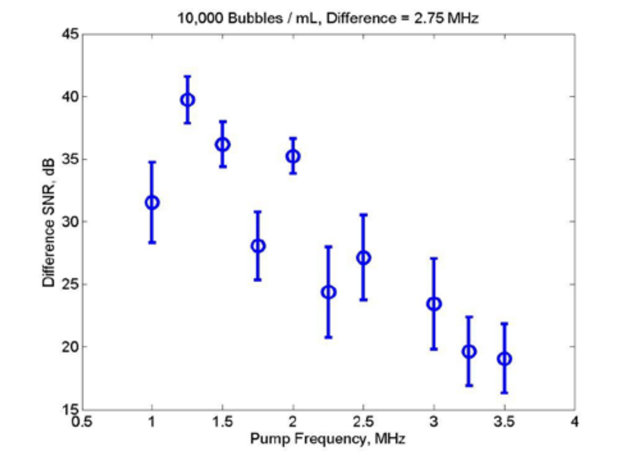

Figure 6. Effect of frequency on difference signal

Effect of Tissue Composition (B/A)

What is the effect of changing the sound medium (B/A) on returned signal?

•As ultrasound at two different frequencies co-propagates, nonlinearity in the host medium can also lead to the generation of nonlinear difference signals

•These signals may confuse those returned from microbubbles

•The confounding signals increase with acoustic pressure, co-propagation distance, and the nonlinearity of the medium (B/A)

•While difficult to model exactly for all but he simplest geometries, we can estimate the contribution of an effective one-dimensional co-propagation distance. For typical geometries used in this work, this distance is 0.25 – 2 cm. Modeling and experiments show that source pressures above 8kPa are more likely to generate these signals (Figure 7)

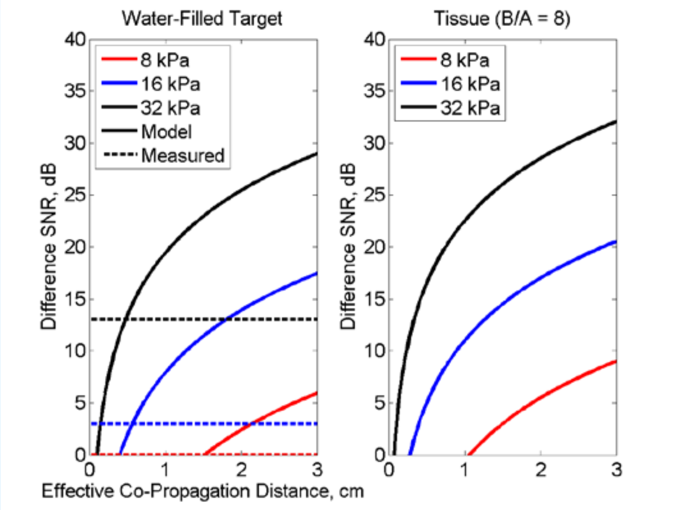

Figure 7. Effect of B/A and co-propagation

Discussion

•DFU is highly sensitive to lipid-stabilized microspheres

•Temperature is positively correlated to returned signals but this change is minimal and occurs outside the normal range of exercise-induced muscle temperature change

•In water, the optimal power level is 16kPa. Larger pressures may be needed in tissue due to greater attenuation.

•The optimal pump/image setting was found to be pump = 1.25 Mhz and image = 4 MHz

•Settings need to be modified based on the characteristics of the tissue to be monitored

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