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Doppler ultrasound and other imaging modalities have been used to assess characteristics of vasculature associated with malignant breast masses. Specific to our institution, promising results have been achieved in discriminating benign from malignant masses using Doppler vascularity measures in conjunction with ultrasound grayscale features.

The purpose of this work is to develop a dual-transducer method to control the destruction and imaging of ultrasound contrast during 3D ultrasound scanning of suspicious breast masses. This method, which involves sequential scanning and co-registration of image volumes acquired during contrast refill, should provide mapping of vascularity around these masses and highlight the associated anatomic variation in mean transit time.

Experimental assessment of contrast agent life-span, destruction characteristics, and refill imaging had been previously undertaken in tube flow phantoms. These studies were refined and quantified in year two. In addition, a phantom kidney model has been tested under various flow conditions, and preliminary results between the dual-transducer method and standard interval imaging have been compared. Current limitations in the ultrasound machine have prevented patient evaluation to date, although these are close to being rectified and patient evaluation will be conducted in the latter part of year 3 and during a no-cost extension. Year two results are presented here.

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Table of Contents

Introduction

The overall objective of this project is to develop a 3D ultrasound contrast imaging system for characterizing suspicious breast masses. The originally proposed method uses a dual-transducer scheme to map mean blood transit time in three dimensions. The method requires a fraction of the time necessary to obtain similar information using other standard contrast imaging techniques, and it should provide information related to normal and anomalous vascular characteristics in and around suspicious masses. In addition, the technique should allow visualization of areas of slow flow and microvasculature, which cannot be detected with conventional Doppler imaging methods. It is hypothesized that these measures will enhance our ability to discriminate benign from malignant lesions as well as serve to increase our understanding of tumor biology in terms of vessel formation.

The scope of year two incorporated some deviation from the originally proposed schedule. For example: The mechanical apparatus was finished, complete with hardware and software interfaces; it was necessary to conduct unexpected flow and contrast characterization experiments using both the simple flow tube models and the kidney phantom; modification of the GE Logiq 9 to allow for cardiac-gating required more time and resources than expected; an alternative dual-sweep imaging scheme was designed and is under hardware and software development; and patient scans have been delayed until after more complete testing of the system has been performed. Given the delay in patient scanning, we are planning a no-cost extension to the project, which should allow its completion.

Body

Background:

Given that the following background text provides information regarding the impetus of the proposed work, it is essentially unchanged from our previous report. As mentioned in the original proposal and the year one report, previous studies by other investigators have demonstrated characteristics of vasculature associated with malignant breast masses. These have included thin-walled blood vessels, increased microvessel density, disordered neo-vascularization penetrating the mass, arteriovenous shunting, and a variety of characteristic Doppler ultrasound and histologic findings [Lee et al. 1996, Peters-Engl et al. 1998]. Some studies strongly suggest that flow velocity demonstrates significant correlation with tumor size [Peters-Engl et al. 1998] and that parameters such as vessel count and flow velocity display significant differences between malignant and benign lesions [Madjar et al. 1994]. A shortcoming of most of these trials has been the limitation of 2D images in assessing overall vascular morphology, density, and velocity distributions.

Given the limitation of 2D studies and the relative sparseness of breast vasculature, our group has investigated the utility of 3D breast imaging for several years. Recently published results [LeCarpentier et al. 1999] indicate that one of our Doppler vascularity measures, Speed Weighted pixel Density (SWD), is statistically different for benign versus malignant lesions and comparable to ultrasound grayscale (GS) evaluation. More recent work in a 38 patient pool suggests that multi-variable indices (which include both SWD and GS features) demonstrate good results in differentiating benign from malignant breast masses well beyond GS evaluation alone [Bhatti et al. 2000]. In a follow-up study (submitted and accepted for publication), the results of the initial 38 patients (18 benign, 20 malignant) were used to form a learning set (A), and multivariable indices were established using Bayesian discriminators. In Group A, 94% specificity was achieved for the SWD-Age-GS index at 100% sensitivity. Applying the same linear function to the second pool (B) resulted in 86% specificity at sensitivity of 100% [LeCarpentier et al. 2002]. The diagnostic performance of SWD in our second patient population strongly suggests the utility of vascular indices in the characterization of breast masses.

In addition to Doppler imaging, a number of investigators have performed extensive evaluation of ultrasound contrast agents in the evaluation of blood flow. Success of low-frame-rate imaging (termed "transient response imaging" or "interval imaging") is related to the "refill" of agent into tissue [Porter and Xie 1995, Porter et al. 1997]. Monitoring refilling has estimated the perfusion in tissue [Wei et al. 1998] and specific pulsing sequences such as "Flash Echo Imaging" (Toshiba Medical Systems) and "Power Pulse Inversion" (ATL/Phillips) have been developed on ultrasound scanners to obtain refill information. Studies at our institution [Fowlkes et al. 1998] have shown that it is possible to destroy contrast agent flow in arteries to produce interruptions with signal separation up to 30 dB. Similar interruptions allow downstream contrast agent to clear and the release of a short bolus by temporarily turning off the field [Rhee et al. 1998]. All of these methods rely on controlled destruction of contrast agents and subsequent reflow into tissue. Complications associated with such measurements in 3D are addressed in this work.

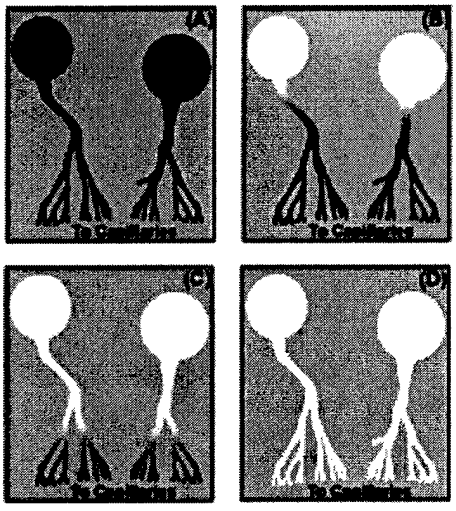

Figure1. Schematic representation of ultrasound contrast refill. An ultrasound beam is used to destroy contrast agent in all vessels in the imaging plane (A). The larger vessels quickly refill (B) and feed the smaller arteries and arterioles with fresh contrast (C & D). Over time, capillary refill can be visualized.

Figure 1 shows a general schematic of contrast disruption and refill. An ultrasound beam is used to destroy contrast agent in all vessels in the imaging

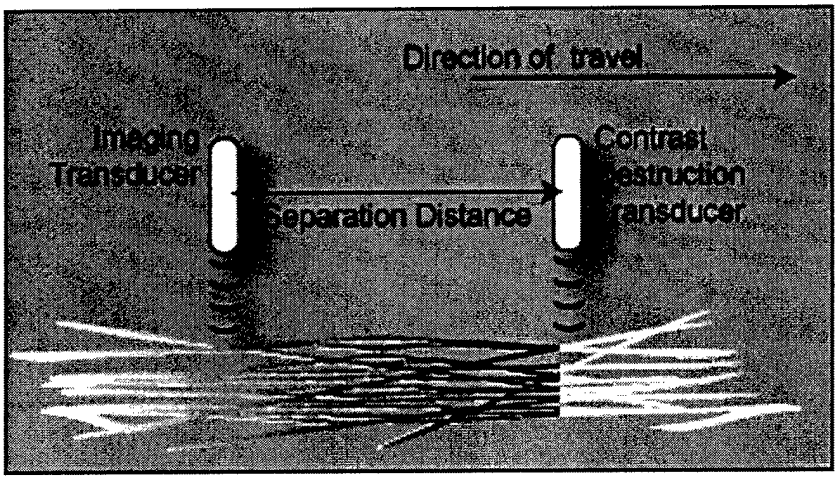

Figure 2. Schematic of dual-transducer method or monitoring capillary refill. The high intensity transducer is used to destroy contrast and create a zero-contrast-enhanced wavefront. The low intensity imaging transducer follows behind at some fixed time (distance). By sequentially scanning the same region using different delays, a refill-time map can be constructed for the volume.

plane. The larger vessels with significant volume flow and high flow rates would quickly refill. The volumes of interest, however, are slower flow in the capillary bed. As the arterioles are filled, the contrast can be visualized, and eventually capillary refill will be seen. Figure 2 depicts the dual-transducer imaging scheme. For the sake of discussion, consider the case of a patient under constant drip infusion of ultrasound contrast agent. At steady state, the imaged blood is 100% contrast enhanced. By translating an ultrasound transducer transmitting a sequence of high-intensity pulses, a wavefront of maximally broken contrast or "zero-contrast-enhanced" tissue is formed. Although the figure shows vessels virtually flowing in the same direction for simplicity, a model will be developed to describe the more "real-world" scenario of isotropically distributed flow into and out of the particular volume of interest. The second transducer, which arrives at the same location at time 2, images the partially refilled volume. This process can be repeated multiple times using different delay settings between contrast destruction and imaging to estimate refill rates for every region in the overall imaged volume.

Specific Tasks:

In the originally proposal document, the approved statement of work included the five major tasks listed below:

Task 1 (months 1-6): Model input function of contrast agent destruction:

(a) Generate mathematical flow model

(b) Measure beam profile

(c) Incorporate various profiles, flow, and scan rates

Task 2 (months 3-12): Assemble and test mechanical imaging scan system:

(a) Design and construct mechanical translation system

(b) Design and test electrical interface

(c) Design and test interface software

Task 3 (months 13-24): Design and perform experimental assessment of imaging system design:

(a) Evaluate performance on strict flow tube models

(b) Evaluate performance on kidney phantom

(c) Evaluate 3 point method of refill curve modelling

Task 4 (months 1-24): Develop and assess visualization and quantification software:

(a) Verify flow model

(b) Develop regional mapping software (*can start as soon as the project begins)

(c) Develop and evaluate parametric histogram visualization scheme

Task 5 (months 13-36): Assess system and 3D imaging software on small patient population:

(a) Recruit patients

(b) Perform scans

(c) Evaluate refill maps and parameterize

(d) Test discriminators

Task 6 (months 30-36): Overall data analysis and write-up

In this second year, we believe we have remained within the overall approved statement of work with some minor unavoidable modifications. As in the first year, the scope of year two again includes some logical rearrangement of tasks from the original proposal. Notably, in terms of the mechanical scanning apparatus itself (Figure 3), it was modified to perform its function more smoothly, and the electrical and software interfaces were developed and tested. In addition, the tube-flow experiments initially demonstrated somewhat unexpected results, and an unanticipated investigation of contrast destruction zone characteristics became necessary. Accounting for a destruction zone wider than anticipated, the imaged tube flow appeared to correspond reasonably well with theoretical flow profiles.

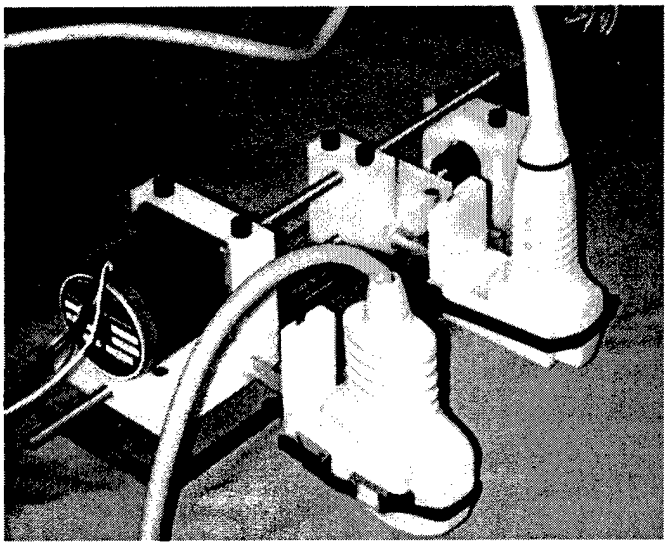

Figure 3. DualTransducer Scanning Apparatus. Two stepper motors (3.5 and 1.2 Amps) control the contrast destruction transducer from the Toshiba PowerVision 8000 and the imaging transducer attached to the GE Logiq 9. Software control was acheived using a portable computer and a custom made LabView interface.

In more complex experiments, the logistics of dehydrating and rehydrating a harvested kidney phantom were initially problematic. After reliably dehydrating/rehydrating this particular phantom over time, flow characteristics were still initially inconsistent. After a series of experiments, these inconsistencies appeared to be primarily due to excessive contrast concentrations, which we hypothesize has unpredictable effects on microvascular flow. Low contrast concentrations, while potentially more difficult to visualize, yielded results more consistent with theoretical flow predictions, although extensive test is still pending.

Algorithms for parametric imaging of the 3D volume are still in development. These are basically to show refill rate "maps" throughout the entire volume. What is still under investigation is the determination of region-of-interest (ROI) or "kernel" size and criteria for regions of "insufficient data." These blanked out regions would typically correspond to where there is very little flow and inadequate signal-to-noise ratio to produce a reliable refill curve (and hence a reliable value for refill rate). The visualization scheme will continue into the final stages of the project.

As for assessing the device on a patient population, we consider such an investigation premature due to the factors noted above. There were other unanticipated issues in this regard as well:

(1) The experimental protocol for the patient study requires that the ultrasound machine be cardiac-gated for the comparative Doppler studies. This was not possible at the end of year two. In previous studies, R-wave detection was performed in software, and the GE Logiq 700 was triggered via an external foot switch control. Given new hardware used for the current project, it was more straightforward to perform R-wave detection using hardware, which has been designed, built, and tested. We have additionally upgraded to a GE Logiq 9, whose default configuration does not include external triggering of any kind. Nonetheless, in collaboration with GE, external triggering has been made available and has been tested under a variety of conditions necessary for most acquisition modes. Unfortunately, at the time of this writing, triggered acquisition in Doppler mode at rates as slow as average heart rates remains problematic. Specifically, the cine buffer needs to be saved frame by frame after triggered acquisition.

(2) After extensive laboratory experience, it has become apparent that the use of two distinct transducers clinically is unrealistic. The apparatus itself is large and cumbersome, and a second ultrasound machine in the scan room would be a less than appealing scenario from both the operator and patient perspective. We have devised an alternative "dual-sweep" imaging scheme which should mimic the originally proposed method. In this case, the same transducer acts as the destructive transducer on the first sweep, then returns home before imaging the second sweep. Initial tests on an available single transducer positioning system

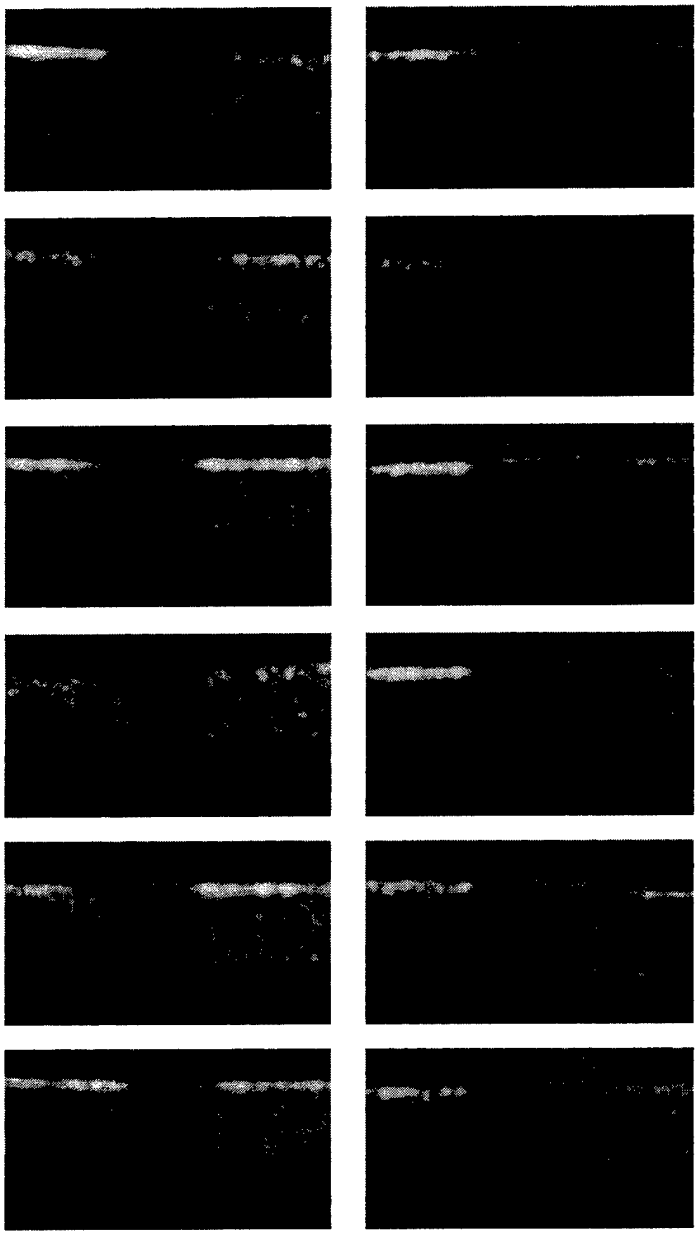

Figure 4. Visualization of contrast disruption zones. A Toshiba PowerVision 8000 with a 3.75 MHz curvilinear array was used to was used disrupt dilute contrast in a 6.35 mm diameter tube cross-section. Power levels were varied from P2 to P16, and number of pulses were varied from 1 to 10. The lateral section of the tube was imaged with a GE Logiq 9 and a 7L array at 1% acoustic output. The images shown are representative of the data collection at 1, 2, 3, 4, 5, and 10 pulses: (Left) disruption at P6 shows no discernible zone at 1 and 2 pulses, and (Right) disruption at P12 shows nearly constant zone width regardless of the number of pulses. More quantitative results are shown in Figure 5.

have indicated translation speeds of at least 10 mm/sec; so for a 40 mm region of interest, the corresponding minimum delay between destruction and imaging (travel time of 40 mm out and back) would be at least as short as 8 seconds. The system may in fact be faster. Our current dual-transducer system has a minimum transducer spacing of 45 mm and a maximum translation speed of 7 mm/sec and is thus able to perform a destruction-imaging sequence with a delay as short as 45/7 = 6.4 seconds. The performance of the two systems appears comparable.
Interface/controller software for the alternative system is currently underway.

Given these considerations, we have not yet expended resources for the patient study and are planning a no-cost extension. Essentially this means that much activity originally scheduled for months 20-36 will be performed during months 30 through the no-cost extension period.

Results:

A laboratory set-up and interface software was developed to implement the dual-transducer method described in the introduction. The apparatus shown in Figure 3 was

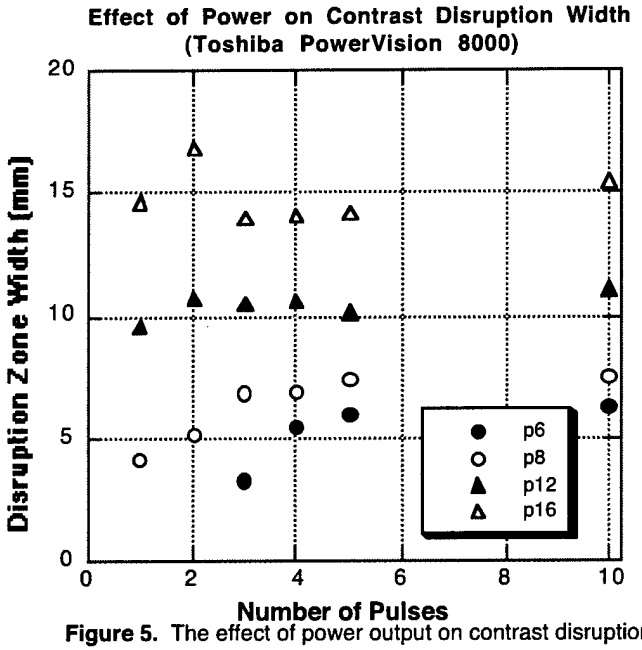

Figure 5. The effect of power output on contrast disruption zone width. Disruption zone widths were estimated from the image data acquired as described in Figure 4 and the text. At power levels below P6, a disruption zone could not be achieved. At P12 and above, 1 pulse was essentially as effective as 10. At P6, 4 pulses are required to reach near steady state, while still minimizing the width of the disruption zone. At the transducer translation speeds and frame rates used for tube flow experiments (see Figure 6 and the text), P6 was deemed an appropriate choice.

used to translate the transducer pair at a constant rate. The distance between the two transducers was varied, and destructive/imaging sequences were performed over a 6.35 mm flow tube.

Various experimental results in tube-flow experiments showed inconsistencies between expected (i.e. theoretical) profiles and those obtained experimentally. This was particularly evident in where the onset of the parabolic flow started. As such, we investigated the characteristics of the disruption zone, which was initially assumed to start at the position of the disruptive transducer. Figures 4 and 5 demonstrate the results of this investigation. As highlighted in the figures, the width of the disruption zone is significant. As such, the power output for the disruptive transducer in subsequent experiments was selected to minimize the width of the disruption zone while still ensuring complete contrast disruption.

Parabolic flow profiles are expected in slow tube flow scenarios. Laminar, viscous fluid flow velocity (V) through a straight, circular tube has a well-known parabolic velocity profile as a function of radial distance (r) from the center given by

$$V(r) = Vmax \bullet (1 - (r/R)^2)$$

where $Vmax$ is the peak velocity and R is the tube radius. If one were to take a "snapshot" of the flow pattern at any given moment, this pure parabolic profile would be seen. In the case of the dual-transducer method, however, each slice is actually acquired at a different time, hence creating a "time-dilated" parabola upon imaging. If one solves for the position (distance from the starting point, d) of the parabola "front" as a function of time, the expression is simply

$$d(t,r) = t \bullet V(r).$$

Substituting the previous equation and solving for *r* yields

$$r = R \bullet \mathrm{sqrt}(1 - d/t \bullet Vmax).$$

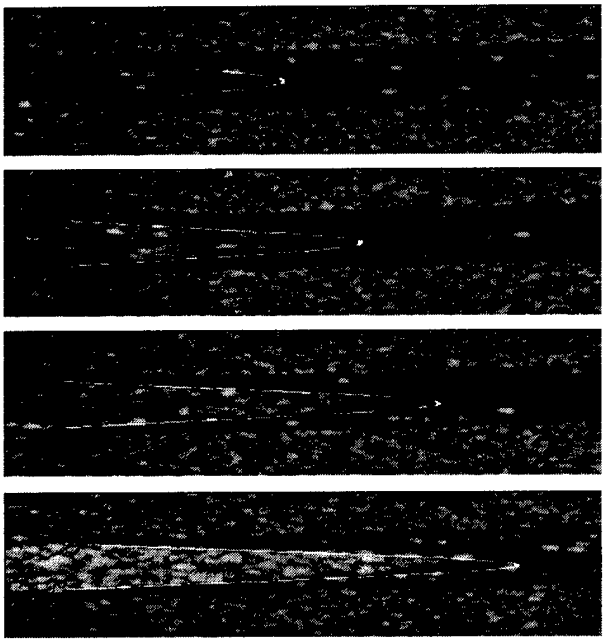

Figure 6. Comparison of contrast profiles in a tube with theoretical "time-dilated" parabolic flow profiles. The imaging transducer (GE 7L) traversed the tube at 6 mm/s and an image was acquired every 317 microns. The image volume was subsequently reconstructed, and the coronal slices in the figure were extracted (at 7.5, 10, 12.5, and 15 second delay times between transducers. In this particular case, the flow velocity was 0.04 ml/sec in a 6.35 mm diameter tube (average velocity = 1.25 mm/sec, peak velocity Vp = 2.5 mm/sec). Thus the imaging transducer was travelling at 2.4 times the peak flow velocity in the tube. As described in the text, the time-dilated parabolas have the form

$$r = R \bullet \mathrm{sqrt}(1 - d/tVmax),$$

where *r* is profile radius (or the "thickness" of the parabaloid) at a given *d* (distance from the start position along the tube axis), *R* is tube radius, and *Vmax* is the maximum velocity (i.e. at the center of the tube). The starting point of the contrast destruction zone was determined from the know starting position of the destructive transducer (Toshiba 3.75 MHz curvilinear array) and its known destruction zone width, in this case roughly 6 mm. The contrast profiles imaged correspond reasonably well with the theoretical profiles. The discrepancies at the center (i.e. the tips of the parabolas) may well be due to contrast destruction by the imaging transducer itself as a result of the profile providing very little overlying attenuation at the center tip as well as the fact that the center of the tube is exposed to the ultrasound beam for the greatest amount of time. (See the text and Figure 7.)

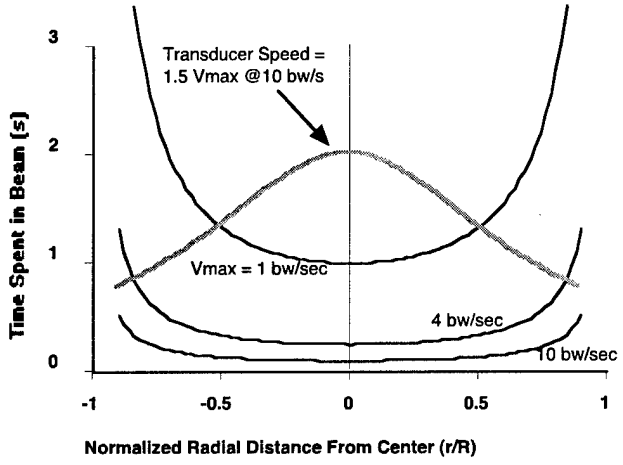

Figure 7. Simplified model of time spent in the ultrasound beam. Flow speeds are represented in units of "beam-widths" per second for normalization. Flow velocity (V) as a function of radial distance (r) from the center is considered parabolic [$V(r) = Vmax \bullet (1 - (r/R)^2)$ where Vmax is the peak velocity and R is the tube radius]. With a stationary transducer, the fluid closest to the tube wall is exposed to the beam for the longest period of time, and these exposure durations decrease with increased flow velocity as shown by the three curves representing Vmax at1 bw/sec, 4 bw/sec, and 10 bw/sec. The thicker shaded curve represents what happens as the transducer is translated along the axis of the tube at a speed higher than the maximum flow velocity. In this case, where Vmax was set to 10 bw/sec and the transducer speed was set to 1.5 times Vmax, the maximum exposure to the beam occurs at the center of the tube. This may help explain the center peak cut-off of the flow profiles shown in Figure 6. That is, the contrast may be exposed to sufficient pulses in the center to break the bubbles at higher flow velocities. This effect is compounded by the fact that there is also less overlying attenuation due to the flow profile shape.

Time-dilated parabolas of this form were calculated and super-imposed over experimental results and are presented in Figure 6. Note the good agreement between the parabolic front and

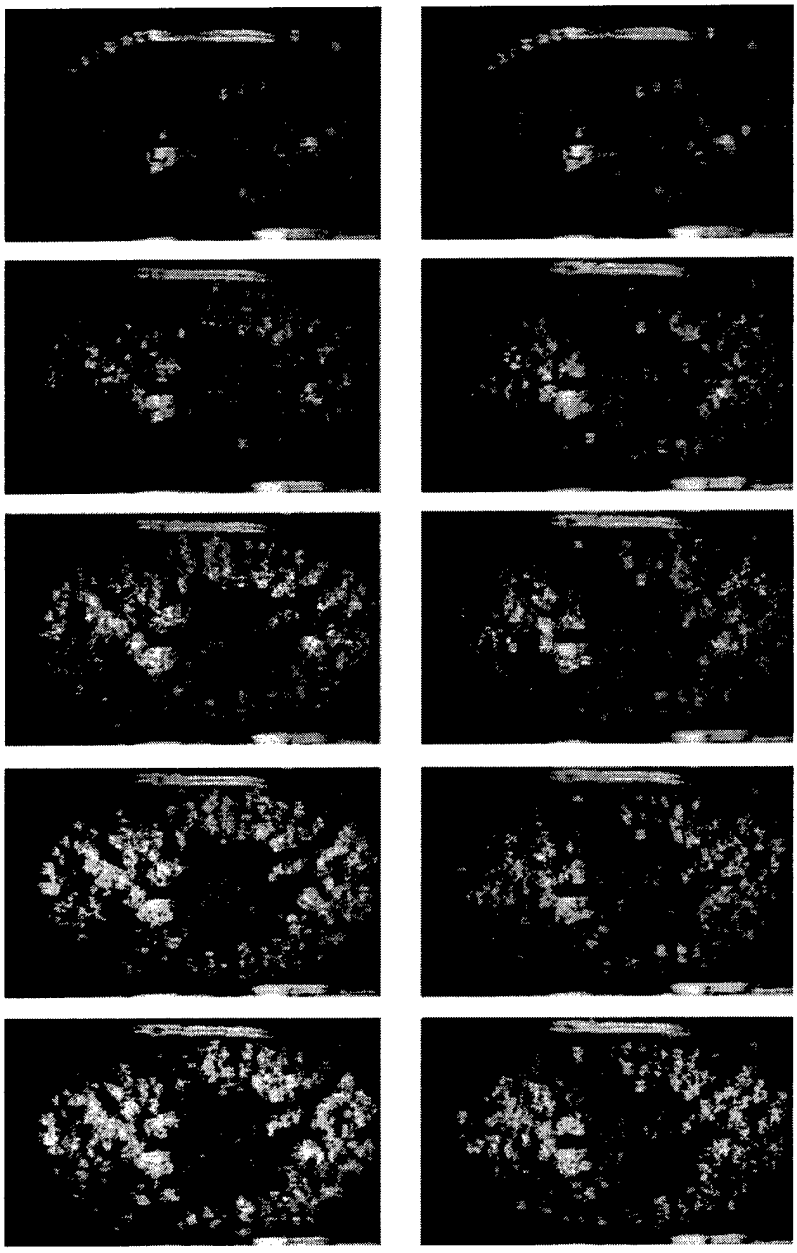

Figure 8. Contrast refill in a porcine kidney phantom. In this case, dilute contrast was slowly infused into a porcine kidney phantom at a rate of 0.05 ml/sec. From top to bottom, images represent refill at times 0 (empty), 20, 40, 60, and 120 seconds: (left) images generated using the dual-transducer method described in the text, and (right) images generated using interval-imaging. In both cases, steady refill can be seen. Note that the dual-transducer method generated an entire volume of images at each refill time, whereas a selected slice plane was chosen for the interval-imaging scenario for comparison. The slightly lower intensity of the interval-imaging sequence may be due to the age of the contrast. A 20x20 pixel region (at approximately 10 o'clock in the images) was selected to evaluate refill characteristics more quantitatively (see Figure 9). Incidentally, dual-transducer image volumes were also collected at refill times 180 and 240 seconds.

the theoretical line. At the peak, discrepancies between theory and measured results may be explained by the simple model presented in Figure 7.

Extensive studies were performed on fixed porcine kidney phantoms as described by Holmes and others [Holmes et al. 1984]. Initially, the logistics of dehydrating and rehydrating these kidneys were problematic. After overcoming these difficulties, a flow system was assembled and tested. The stability of contrast agent (Definity) was also problematic given the relatively long (20-30 minute) experimental protocol due to contrast exposure to atmosphere, suspension (stirring) issues, and various pumping parameters. These were stabilized and subsequent experiments yielded the preliminary results presented in Figures 8 and 9. Comparative results between the dual-transducer method and current interval-imaging techniques show good correlation between trends in both. Nonetheless, the differences in these results are curious. Inherent differences in the two techniques may explain

the absolute differences in refill curves shown in Figure 9. These are currently under investigation.

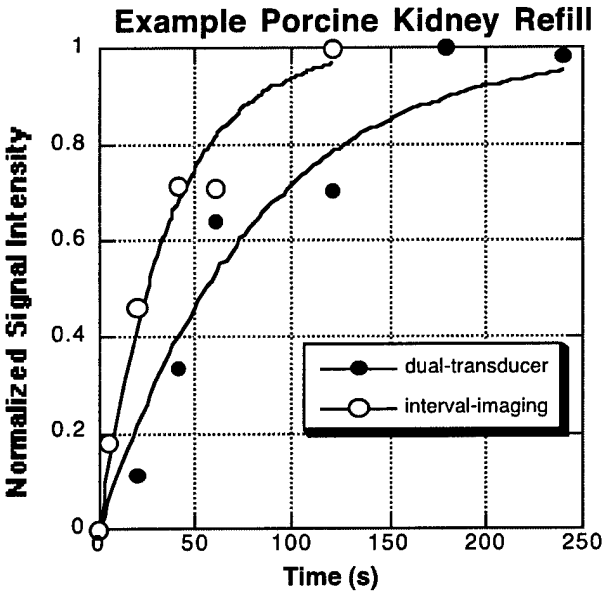

Figure 9. Refill curves for a selected region in a porcine kidney phantom. The selected region was a 20x20 pixel region at approximately 10 o'clock in the images shown in Figure 8. Image data were log decompressed to provide signal intensities which were normalized to their maximum values. The data were fit to the smooth exponential curves shown (a shape somewhat arbitrarily chosen). Since refill characteristics were unknown *a priori* for this preliminary comparison, the interval-imaging acquisition was unfortunately stopped earlier than what would have been optimal. Nonetheless, both the dual-transducer and interval-imaging methods display reasonable refill characteristics. Under ongoing investigation are reproducibility studies, trends as a function of flow rate, and differences between dual transducer and interval-imaging results.

Key Research Accomplishments

- Completed modifications to experimental set-up and software interface to mechanical scanning apparatus. The latest addition to the software allows external triggering of the ultrasound machine for more reliable time-position recording.
- Performed extensive flow-tube experiments to determine reasonableness of dual-transducer method in the simplest case.
- Quantified contrast "destruction zone" as a function of transducer output and number of pulses (Figures 4 and 5).

- Correlated measured tube flow profiles with theoretical profiles, accounting for destruction zone characteristics (Figure 6).
- Reasonably explained contrast variation in tube flow (at the center "peaks") with simplified model of "time spent" in ultrasound beam (Figure 7 and text).
- Worked out logistics of reproducibly obtaining a fixed kidney phantom model and developed appropriate experimental pumping interface.
- Performed extensive contrast stability studies in optimizing the experimental approach to imaging contrast over long periods of time (i.e. over 20 minutes). This optimization is ongoing.
- Acquired preliminary 3D results for contrast refill analysis in fixed porcine kidney. Refill characteristics of the kidney were compared for the dual-transducer versus the interval-imaging mode, and parametric studies are currently underway (Figures 8 and 9).
- Began development of software controller interface code for adjusting patient protocol to a dual-sweep method.
- Initiated parametric visualization software development and identified areas requiring further investigation. Software development is still ongoing.

Reportable Outcomes

The following was presented during the second year of the proposed research:

LeCarpentier GL, Chen NG, Fowlkes JB, Carson PL: A New Dual-Transducer Method of Three-Dimensional Ultrasound Contrast Agent Imaging of Vascularity. (proceedings of the 10th Congress of the World Federation for Ultrasound in Medicine and Biology) Ultrasound in Medicine and Biology, 2003, 29(5S): S53.

Conclusions

Careful attention must be paid to beam width and disruption characteristics when assessing flow visualization *in vitro*. Nonetheless, our preliminary results suggest that slow flow can be visualized and tracked at contrast agent concentrations relevant to clinical practice. As a modification of interval imaging, the dual-transducer technique provides vascular refill information highly correlated to interval imaging, while drastically reducing imaging time required for a 3D volume. The technique may provide measures of tissue perfusion and refill

characteristics which are unobtainable with current Doppler methods, although our recent Doppler analysis methods are well suited to contrast agent imaging quantification and breast mass characterization. Given the correlation of neo-vascularization and breast tumor growth, this imaging method has the potential of detecting anomalies and enhancing our understanding of changes in microvasculature at early stages of tumor development.

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Appendix

The following abstract was presented at the AIUM-hosted 10th Congress of the World Federation for Ultrasound in Medicine and Biology (Ultrasound in Medicine and Biology, 2003, 29(5S): S53):

A New Dual-Transducer Method Of 3D Ultrasound Contrast Agent Imaging of Vascularity

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Objective: Although promising results have been achieved in assessing benign from malignant masses in the breast, prostate, and other organs using Doppler ultrasound (US), certain limitations remain. Of particular interest is slow flow and small vessel imaging in 3D. The purpose of this work is to develop a dual-transducer (DT) method of controlling the destruction and imaging of US contrast in 3D, aimed specifically at imaging vascular anomalies in these suspicious masses.

Methods: To date, all experimental procedures have been performed on flow phantoms. As controls, contrast (Definity) flows at various speeds and concentration were imaged laterally in a tube phantom using a GE Logic 9 in a contrast imaging mode (GE9). In the DT scenario, cross sectional images were acquired along the tube, and sequential scanning of image volumes acquired during contrast refill was performed. A Toshiba PowerVision 8000 (TPV) was used to destructively sweep the region and create a contrast-cleared front in the volume. The GE9 transducer followed behind that of the TPV and imaged continuously. The transducers were set various distances apart while both swept the region on a mounted and controlled motor system. The sweep speed was held constant such that the distances between the destruction and imaging transducers would correspond to particular times during refill. Sequential image volumes were reconstructed from the GE9 data sets.

Results: Contrast agent concentrations less than 4:10000 were linearly related to signal intensity in a 6 mm tube. In the control sets, the expected 2D parabolic evolution of the flow profile was seen. The DT images did not suffer the 2D limitation, and image planes reconstructed as slices along the tube displayed striking clarity and clear definition of flow profile information.

Conclusions: Preliminary results suggest that slow flow can be visualized and tracked in 3D, and the DT technique may provide measures of tissue refill characteristics unobtainable with current Doppler methods. Given the correlation of neo-vascularization and tumor growth, this imaging method has the potential of detecting and enhancing understanding of changes in microvasculature at early stages of tumor development.