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FOREWORD

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INTRODUCTION (excerpts from the original proposal)

Nature of the Problem

Mammography has proven to be reliable as a screening tool for breast cancer. However, the specificity of mammography for breast cancer may be as low as 10% as evidenced by the number of biopsies recommended compared to the number of cancers confirmed (Moskowitz and Gartside, 1982). Therefore, of significant health care benefit would be a method used in conjunction with mammography which could reduce the number of biopsies required while maintaining or improving survival rates. In terms of health care costs, Adler *et al.* (1990) estimated that more than half of the mammographic screening costs for breast cancer are the result of required biopsies or excisions due to low specificity. Again, an alternative method for establishing the type of lesion present would be of great benefit. Any improvement in early detection of breast cancer is clearly important as survival is significantly improved when cancers are detected in the 0.5 to 1 cm diameter size range (Axtel *et al*, 1976).

Background of Previous Work

Doppler ultrasound has been investigated and found some utility in the detection of cancer (Burns *et al*, 1982; Minasian and Bamber, 1982; Boyd *et al*, 1983) . Although the specificity has been high for cancer recognition, at 10 MHz frequencies used in these studies, the sensitivity of the technique has not and the use of other Doppler techniques have had mixed specificity and sensitivity results (Rubin *et al*, 1987; Adler *et al*, 1988; Jellins, 1988; Cosgrove *et al*, 1990; Adler *et al*, 1990). The advent of stable ultrasound contrast agents and the development of Doppler power mode imaging are clearly innovations which could improve the sensitivity of ultrasound techniques for cancer.

Abnormal accumulation of contrast during the arterial phase of contrast transit and a residual concentration of contrast agent in breast cancers has been observed with conventional angiography, but without exceptionally high specificity (Feldman *et al*, 1967; Kaushik *et al*, 1975; Sakki, 1974), with x-ray computed tomography (Chang *et al*, 1982) and with digital subtraction angiography (Flynn *et al.*, 1984). Gadolinium MRI is now looking quite positive as a means of discriminating likely breast cancers and even detecting mammographically occult malignancies (Harms, et al., 1993, Heywang-Kobrunner, et al., 1992). With the advent of ultrasound contrast, such contrast studies should now be possible. The desired IV administration of the agent however results in dilution of the contrast and the loss of a well resolved bolus. If such problems can be overcome, the prospect for ultrasound contrast detection of breast cancer would be greatly improved due to the increased signal strength from the smaller, more diagnostic vessels. Doppler power imaging has also demonstrated an improved signal to noise ratio over conventional color Doppler flow imaging. Images being made in this mode seem to indicate one can expect such a modality would improve on the sensitivity of ultrasound for small vessels.

Finally, recent work (Weidner *et al.*, 1991; Horak, 1992) concerning angiogenesis has placed renewed emphasis on the blood flow in the region of cancerous lesions. The potential of ultrasound techniques described in this proposal to measure regional perfusion suggests that information can be derived by noninvasive means using a relatively inexpensive imaging modality.

Purpose of Present Work

The present research is design to develop techniques for ultrasonic measurement of tissue perfusion in the breast. In combination with other information such as mammographic examination, the techniques proposed should have application in the detection of cancerous lesions or the monitoring of therapeutic interventions which affect the vascular flow of tumor tissue. The diagnostic specificity for cancer could be increased with these techniques leading to improved patient management while using an imaging modality which is generally less expensive than many alternatives.

Methods of Approach

This study examines the potential of three related Doppler techniques for measuring tissue perfusion. 1) Acoustic fields can be used to modulate a continuous infusion of bubble-based echocontrast agent to estimate wash in-wash out time courses for the agent. 2) The decorrelation time of the Doppler power signal can measure the regional perfusion based on the rate at which blood moves out of the Doppler sample volume. 3) The combination of Doppler signal power and velocity will be used to approximate the tissue perfusion where the Doppler signal power is normalized to that found in a large vessel near the region of interest. Development of these techniques will be through *ex vivo* and *in vivo* experimentation using simple and physiologically relevant flow phantom and animal studies. The latter two techniques described above will be examined in limited clinical trials within the time frame of this study.

DESCRIPTION OF RESEARCH PROGRESS

The following is a list of relevant publications during the past project year (June 1, 1996 to May 31, 1997) which have resulted from this work .

Peer Reviewed Journal Articles

Chen J-F, Fowlkes JB, Carson PL, Rubin JM, Adler RS: Auto-correlation of Integrated Power Doppler Signals and its Application, Ultrasound Med. Biol., 22, 1053-1057, 1996.

Chen J-F, Fowlkes JB, Carson PL, Rubin JM: Determination of scan-plane motion using speckle decorrelation: theoretical considerations and initial test, Int J Imaging Syst Technol, 8, 38-44, 1996.

Invited Presentations

Fowlkes JB (1996) Understanding the origins of nonlinear emissions from contrast agents, Invited lecture at the Symposium on Ultrasound and Microbubbles sponsored by the Japan Society of Ultrasound in Medicine, Sept. 27, 1996.

Fowlkes JB, Sirkin DW, Rhee R, Rubin JM, Carson PL (1997) Generation and detection of negative contrast boluses for use in blood flow studies, Invited lecture for the 2nd Thoraxcenter European Symposium on Ultrasound Contrast Imaging, Rotterdam, the Netherlands, Jan. 23-24, 1997.

Fowlkes JB (1997) Hot Topics in Medical Acoustics (Advanced Techniques in Ultrasound Contrast Agents), Invited lecture at the 133rd meeting of the Acoustical Society of America, June 15-20, 1997, J. Acoust. Soc. Am. 101 (5) pt.2, 3120.

Book Chapters (which included topics related to this project)

Fowlkes JB and Hwang EY, "Echo-Contrast Agents - What Are The Risks?" in Safety of Diagnostic Ultrasound, S Barnett and G Kossoff, eds. from the series Progress in Obstetric and Gynecological Sonography, A Kurjak, ed., Parthenon Publishing, UK.

Abstracts and Proceedings

Rubin JM , Fowlkes JB, Adler RS, Carson PL (1996) Normalization and Decorrelation of Doppler Power to Estimate Tissue Perfusion , 1996 Annual Meeting of the American Association of Physicists in Medicine, Medical Physics, Vol 23, No 6, p 1109.

Rubin JM, Bude RO, Fowlkes JB, Adler RS (1996) Cumulative Power Distribution Function: Technique for Definition of a Stable Intravascular Point for Normalizing Fractional Moving

Blood Volume Estimates with Power Doppler US, 1996 Annual Meeting of the Radiological Society of North America, Dec.1-6, Chicago, IL, Radiology 201(P), 153.

Rhee RT, Fowlkes JB, Sirkin DW, Rubin JM, Carson PL (1997) In Vitro Investigations: Negative Contrast Bolus Generation for Use in Blood Flow Studies, nd Ultrasound Contrast Media Research in Radiology Applications, Quantitation & Instrumentation, Feb 7-9, 1997, Wyndham Emerald Plaza Hotel, San Diego, CA.

Fowlkes JB, Sirkin DW, Rhee R, Rubin JM, Carson PL (1997) In Vivo Interruption of Contrast Agents for Temporally Short Arterial Bolus Production, (Procs., AIUM 39th Annual Conv., Mar. 17-20) J. Ultras. in Med., 16:S1, S36.

Fowlkes JB, Moskalik A, Rhee R, Rubin JM, Adler RS, Carson PL (1997) Decorrelation Imaging of Contrast Agents for Flow Detection, (Procs., AIUM 39th Annual Conv., Mar. 17-20) J. Ultras. in Med., 16:S1, S22.

As is indicated above, this research project is divided into three components. Progress in each of these areas will now be discussed in turn. Two of the research areas have been combined in this writing. This method of relating the progress information is chosen for presentation purposes in this report given the considerable interaction between the different aspects of the project.

Contrast Manipulation

One of the most significant issues facing successful contrast manipulation *in vivo* was the acoustic intensity required to produce reliable interruptions. In our previous experimentation, we used acoustic fields comprised of long bursts of continuous wave (CW) ultrasound. In order to obtained substantial interruption of the contrast agent flows, the acoustic intensity required reached a level where significant bioeffects due to heating could be expected. Therefore, during this past year, we have concentrated on methods to reduce the acoustic intensity. The results of our *ex vivo* efforts have reduced the acoustic field to a level that is **within the FDA limits for diagnostic ultrasound.** This is very important to the long-term clinical viability of any of the interruption techniques.

Methods

Experimental System

The experimental setup is diagrammed in Figure 1. A single pass flow system was used to maintain a fairly constant level of contrast agent in the 2.1 mm dia tube of 4-tube rubber flow tube phantom. The four sizes of channels through the phantom can be used in the future to determine if there exist a variation with vessel diameter. The contrast agent circulated was MRX-115 (ImaR$_X$ Pharmaceuticals, Tucson AZ) where the base concentration of the agent (10^9 bubbles/ml) was diluted 1:20,000 in saline. The source reservoir was a 200 ml graduated cylinder whose contents were pumped through the phantom with a peristaltic pump (Masterflex, Cole Parmer, Chicago, IL). The solution was used for two passes before being replaced to insure that the scattering from the contrast agent remained constant during the experiments. Due to the quick draining of this reservoir, bubble settling was not an issue. Flow velocity was assumed to be parabolic in profile, and yielded an average velocity of 9.45 cm/s (19 cm/s peak center velocity). The entire phantom was submerged in a tank of filtered, degassed water to allow coupling of the transducers.

The interruption transducer was powered by an ENI 240L (Rochester, NY) amplifier whose input waveform was gated through computer control of a Wavetek Model 164 (San Diego,

CA) operating at 2.25 MHz and attenuated for fine amplitude control using an Alan Attenuator Model 50TX82.5 (not shown in Fig. 1). The transducer (Harisonic Model HI-0232-P, 2.0" dia., f# 1.5 focused element, Stamford, CT) had a -6 dB beamwidth of 1.52 mm and a calibrated efficiency at the focus of 0.196 bar/Volt for peak rarefactional pressure. Calibration was performed in a water tank using a Marconi PVDF coplanar membrane hydrophone (Chelmsford, Essex, UK). The transducer focus was placed in the center of the flow tube using a pulse-echo technique to identify the positions of the near and far walls of the tube. The pulse parameters used in these experiments are the significant change from previous experiments. Rather than using the continuous wave bursts of 0.5 - 2.0 seconds as before, a sequence of higher amplitude short bursts were used. Each burst was only 20 cycles in duration and was repeated with a pulse repetition frequency (PRF) of 0.75 - 6.0 kHz for a period of 0.5 - 2.0 seconds. The range in peak rarefactional pressure (PRP) used was 0.6 - 1.2 MPa. At a frequency of 2.25 MHz, this corresponds to mechanical indices (MI) of 0.4 - 0.8 which are well within the recommended limits for diagnostic ultrasound. In addition, the calculated I_{SPTA} and I_{SPPA} values were also in the range of those commonly used in diagnostic imaging systems.

The Diasonics Spectra VST Scanner (Milpitas, CA) with 5 MHz linear array probe was placed 10 cm downstream to monitor the interruption and was sufficiently far such that interference would not be seen on the scanner screen when the interruption transducer was fired. The Diasonics transmit power was adjusted to its lowest (-8 dB) setting when collecting data to avoid disruption of bubbles due to data collecting diagnostic transducer. The pulsed Doppler mode was used to collect data that could be quantitatively analyzed later. The Doppler sample volume was placed in the center of the phantom tube to obtain spectra from the highest flow velocity region. The computer controlled both the firing of the interruption transducer and the freeze control of the Diasonics through a serial connection to the scanner. This allowed repeated collection of Doppler data with fixed delays after firing the interruption transducer. Figure 2A shows a typical result for the recorded Doppler spectrum when the negative bolus passes through the Doppler sample volume. Note that the field parameters for the acoustic exposure are quite low in terms of the MI and for the intensities at this lower duty factor of 1.3 % (PRF = 1.5 kHz).

Data Analysis

The resulting Doppler data was analyzed using the new techniques described in the last year's report. Namely, the stored Doppler spectra were processed on a Digital Equipment Corporation Alpha workstation and then tabulated on an Apple Macintosh computer. Each spectrum from the Diasonics was integrated over all frequencies using AVS software (Advanced Visual Systems, Waltham, MA) to give a time record of power Doppler (Rubin et al. 1994, Rubin et al. 1995). Since the pixel intensities in the Diasonics spectra are on a logarithmic scale ("logarithmically compressed" data), these values had to be linearized prior to integration. Figure 2B is the representative interruption of Fig. 2A where the relative absence of integrated Doppler power (ordinate) occurs at a specific time and with a specific duration recorded along the abscissa. Using the software package Matlab (The MathWorks, Inc., Natick, MA), we generate a cumulative power Doppler (integral over time of the power Doppler record) and then fit it with three connected line segments (the integral of a notch or negative pulse). Figure 3 is result of this process corresponding to the integrated Doppler power shown in Fig. 2B. Note that the fit of the cumulative distribution is quite good and yields 5 parameters related to the negative bolus: the contrast level before during and after the bolus (given by the slopes of the 3 line segments), and the times at which the bolus begins and ends. This is the information that will in the future be used to make washin-washout measures in tumor tissue.

Results and Discussion

Experiments have been performed for a variety of pulse parameters and the results indicate that a wide range of values will provide interruptions in the flow of contrast agent. Figures 4 and 5

show some of the results of these experiments. In Figure 4, the duration of the contrast interruption is plotted as a function of the peak rarefactional pressure in the applied waveform. Figure 4A shows the results when a 2.0 second duration burst sequence is applied which results in approximately the same interruption duration. There is a slight trend toward longer interruptions at the higher acoustic pressures. The interruption is quite reproducible under these condition where the error bars represent the standard error of the mean. Note also that very little dependence on PRF is seen in the almost one order of magnitude range tested. Figure 4B shows the results for a variety of burst sequence durations (0.5, 1.0, 2.0 sec). In all cases the duration of the interruption measured downstream is slightly higher than the burst sequence. However, in each case there was very little PRF or acoustic amplitude dependence over the range of values tested.

The degree to which the contrast agent was disrupted by the field did vary with some acoustic parameters. As shown in Figure 5, the amount of signal reduction (meaning the ratio of the integrated Doppler signal averaged during the bolus passage to that measure prior to the interruption) was affected by the amplitude of the acoustic field. Figure 5A shows the result for a 1.0 sec burst sequence duration where it is noted that signal reduction increases with increasing acoustic pressure. Figure 5B shows the result for a 2.0 sec burst sequence in which the reduction effect appears to saturate at the higher amplitudes. Although the rate at which pulses are being applied is the same as that for Figure 5A, the degree to which the contrast agent can be disrupted is greater as the duration of the applied field increases. This change for shorter burst sequences results from the finite time for the contrast signal amplitude to increase and decrease in response to the application and elimination of the interruption field upstream. The onset of the negative bolus is not instantaneous such that the slope of the leading and trailing edge of the bolus is dependent on the acoustic amplitude applied. When averaged over the duration of the bolus, the contributions from these edges become a greater fraction of the whole bolus for short interruptions and therefore the average signal reduction is not as great. It remains the case that higher amplitudes are desirable since these will produce sharper edges to the interruption bolus and thus greater temporal resolution for flow measurements. The fact that there is little PRF dependence would imply that the contrast agent is being disrupted by the first bursts it encounters. Therefore the PRF will probably become important as the velocity of the flow increases because the requirement will be that all bubbles flowing into the focal zone must be destroyed and the faster these move into the beam, the faster bursts must be applied. This factor will be tested in subsequent experiments.

Decorrelation Techniques and Combination Blood Flow Measurements

The personnel originally hired to work on this portion of the project took a position in industry and left the project with a vacancy which was rather difficult to fill. However we have now had the good fortune to hire Dr. Theresa Tuthill to fulfill this role. Dr. Tuthill received her Ph.D. from the University of Rochester where she worked in ultrasound and more specifically on tissue characterization. In the process of doing her work she developed a considerable expertise in the factors controlling speckle. It is the decorrelation of the speckle pattern which is the core of our flow detection technique and therefore she is well suited to the purposes of this project. Due to this personnel dilemma, progress in this area has not been as strong as desired but we anticipate being able to return to schedule quickly given Dr. Tuthill's background on the subject. There were a few advances that were made during this period and those are outlined below.

Alternative Methods for Quantifying Decorrelation

In conjunction with Dr. Adler, an alternative description of the decorrelation process in ultrasound images has been developed. A kinetic equation for the received pressure amplitude and its corresponding correlation function has been derived which takes the form of a Langevin type equation. The coefficients are defined in terms of both physical and ultrasonic system parameters which can be measured and stored for future use in the velocity estimate. The decorrelation rate is then measure which depends on particle velocity, angle of insonation and the voxel geometry and

may be expressed as a two-time correlation function involving the random particle fluxes passing through a voxel. The connection between the rate of decorrelation in pressure amplitude and power mode decorrelation has been derived and thus the technique is applicable to both methods which are being investigated in flow experiments, namely, contrast agent imaged in b-mode and power mode Doppler with or without contrast agent. Two simple examples are considered, an asymmetric and spherically symmetric voxel, both of which demonstrate that the decorrelation rate scales linearly with the magnitude of the particle velocity. In the case of a spherically symmetric Gaussian voxel, the formulation suggests that acquiring flow data at near-orthogonal angles of insonation relative to the direction of flow may be advantageous. This is the area where normal Doppler methods for estimating flow fail. Therefore there may be considerable advantages to the technique. A manuscript on this effort has been submitted to IEEE Transactions on Medical Imaging.

Other Efforts

In addition, two publications have appeared during this past year, as indicated above, which relate to the decorrelation topic. The first paper, published in *Ultrasound in Medicine and Biology*, addresses some issues associated with the decorrelation in power mode Doppler. It was designed to specifically target the use of power Doppler and develop the theoretical basis for decorrelation in the measurement of flow velocity. The second paper is a description of the *Image-Based Registration (IBaR)* technique which was developed in part through efforts on this project. The technique has the potential to eliminate the need for position monitoring devices currently necessary for acquiring 2D images to create 3D ultrasound images. This could have a significant impact on the increasing interest in 3D ultrasound by reducing the cost and eliminating a considerable inconvenience associated with current 3D acquisition devices. This paper appeared in a special ultrasound issue of The *International Journal of Imaging System Technology* .

FUTURE PLANS

We are presently working on arrangements for *in vivo* demonstration of the short burst interruption of contrast agents. These experiments are designed to demonstrate that the low amplitude techniques are as effective as those we have used in the past. At that point we will be in an excellent position to test both the contrast interruption and decorrelation flow measurement techniques in the animal model. We expect some of these results to be available within the next few months. There are some areas for futher investigation in terms of the acoustic field for interruption. Now that the acoustic amplitude has been greatly reduced for contrast interruption, the potential exists to produce positive boluses of contrast by applying the acoustic field sufficiently long to washout downstream contrast and subsequently release a short bolus of agent by momentarily turning off the field. The passage of a positive bolus may be easier to detect against the constant tissue signal. In addition, the contrast agent in an entire area could be eliminated rapidly with a relatively low amplitude field as indicated by the transient response imaging techniques now being investigated for contrast agents. So far, we have used focused ultrasound transducers. Using an unfocused planar transducer, whole capillary beds can be "wiped" of bubbles to measure the tissue space characteristics. We do not know the lower bound in amplitude for effective contrast agent disruption.

CONCLUSIONS

The research that we have conducted thus far places us a a good position to succeed in our origin goal to demonstrate the utility of contrast interruption in the measurement of blood flow. Although it is clear that we are behind in some aspects of the project as pointed out in last year's review, we feel that our recent results greatly improve the potential for the technique to be clinically viable. Without a reduction in the applied acoustic field, even a successful demonstration of a

blood flow measurement would not have meant that the technique could be used clinically. It is our intention to make every effort during the coming year to achieve the goal of *in vivo* demonstration of both the contrast manipulation and decorrelation-based techniques as originally described. Both the research to date and the additional personnel recently hired are strides forward and have renewed our excitement in this work. We look forward to the coming year.

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FIGURE CAPTIONS

Figure. 1. Diagram of the experimental set-up used in the burst sequence experiments for contrast interruption.

Figure 2. Sample of a single interruption: (A) Doppler spectrum measure on the Diasonics Scanner. (B) Corresponding integrated power Doppler. The acoustic field parameters for this example are: MI = 0.784, PRP = 1.176 MPa, I_{SPPA} = 46.10 W/cm, I_{SATA} = 599.2 mW/cm

Figure 3. Cumulative integration technique applied to the data of Fig. 2. The measured curve is simply the cumulative sum over time of the integrated Doppler power in Fig. 2B. The calculated curve is from the mathematical model which assumes an idealized rectangular interruption (infinitely steep leading and trailing edge). Note that for this case the two curves are in close agreement.

Figure 4. Duration of the contrast interruption as a function of the acoustic pressure for a variety of PRFs. (A) For the case of 2.0 sec duration of burst sequence applied upstream. Error bars represent the standard error (B) For the cases of 2.0, 1.0, 0.5 sec duration.

Figure 5 Reduction in Doppler power during bolus passage as a function of the acoustic pressure for a variety of PRFs. (A) For the case of 1.0 sec duration of burst sequence applied upstream. (B) For the cases of 2.0 sec duration.

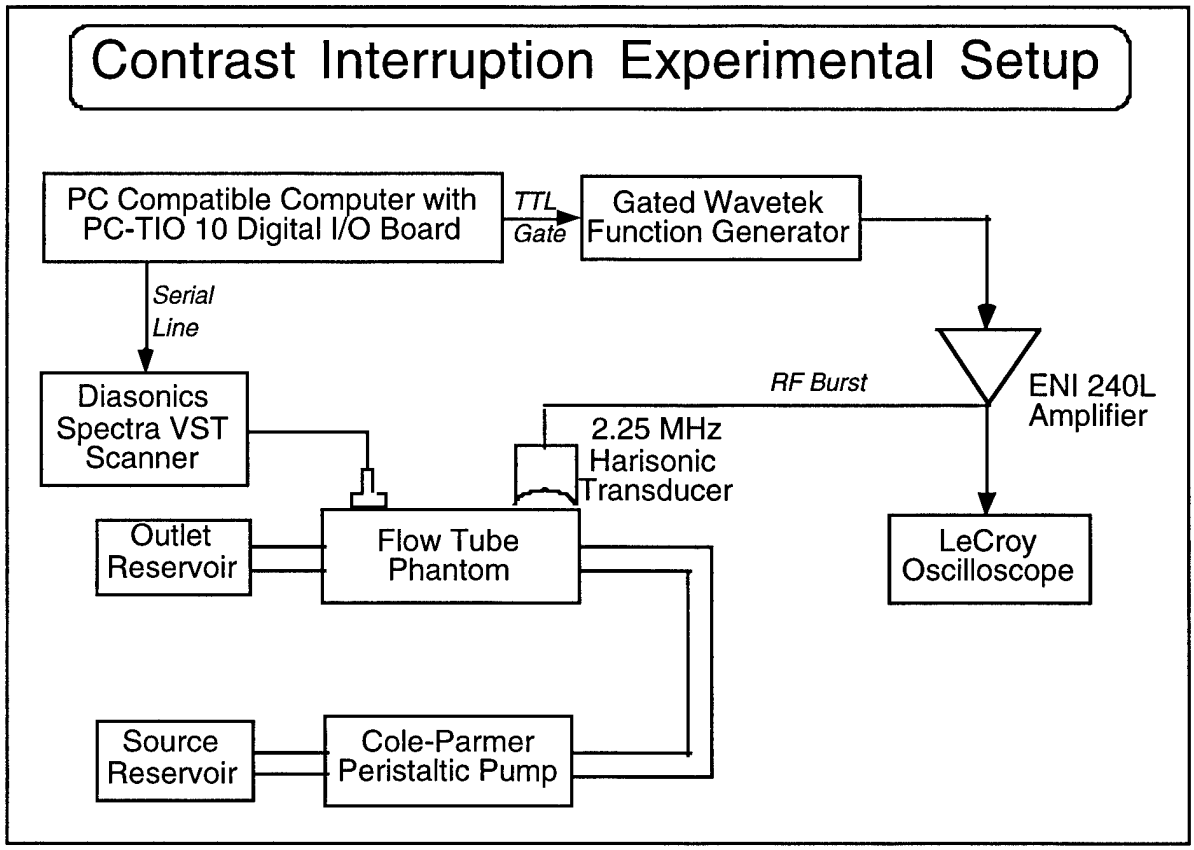
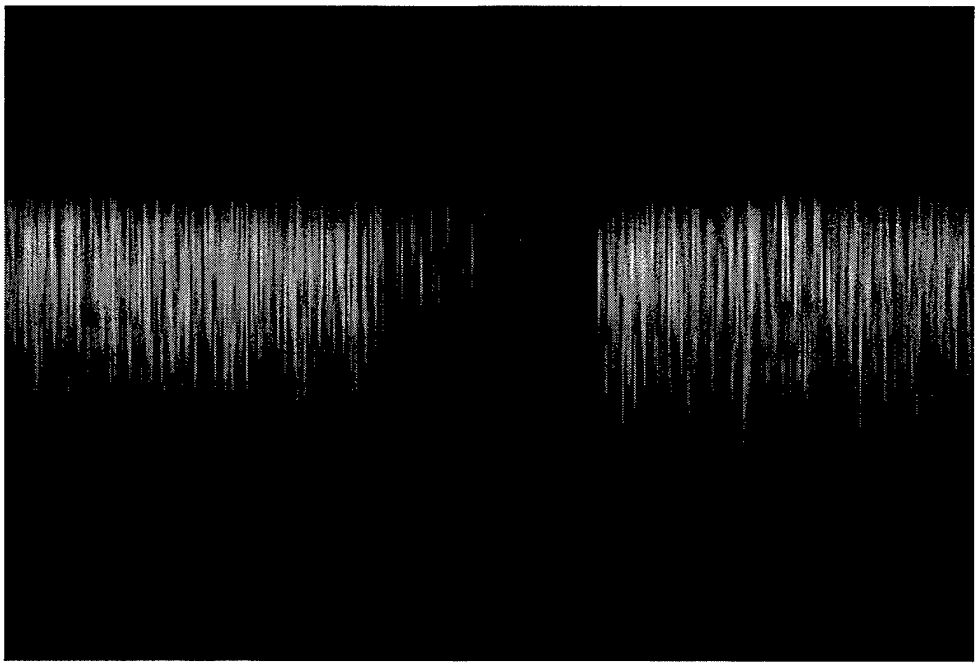

Contrast Interruption Experimental Setup
PC Compatible Computer with PC-TIO 10 Digital I/O Board
TTL Gate
Gated Wavetek Function Generator
Serial Line
RF Burst
ENI 240L Amplifier
Diasonics Spectra VST Scanner
2.25 MHz Harisonic Transducer
Outlet Reservoir
Flow Tube Phantom
LeCroy Oscilloscope
Source Reservoir
Cole-Parmer Peristaltic Pump

Figure 1



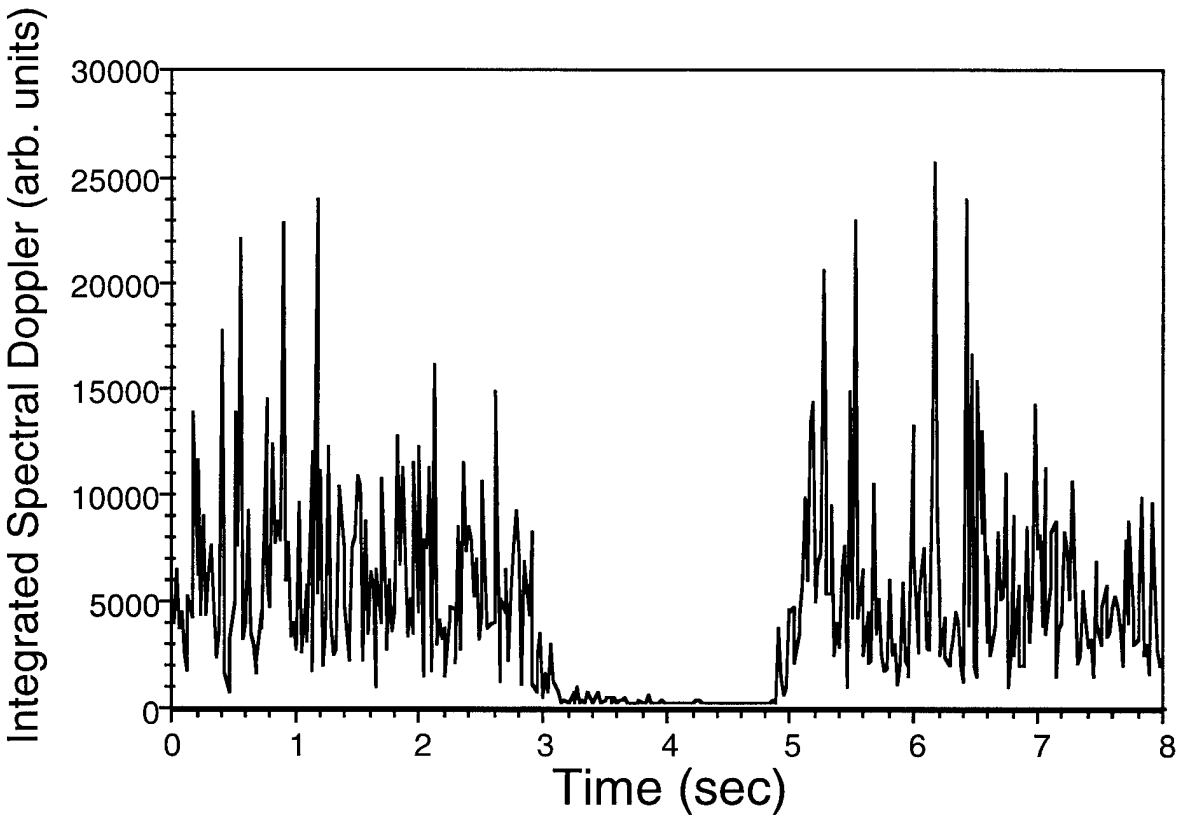
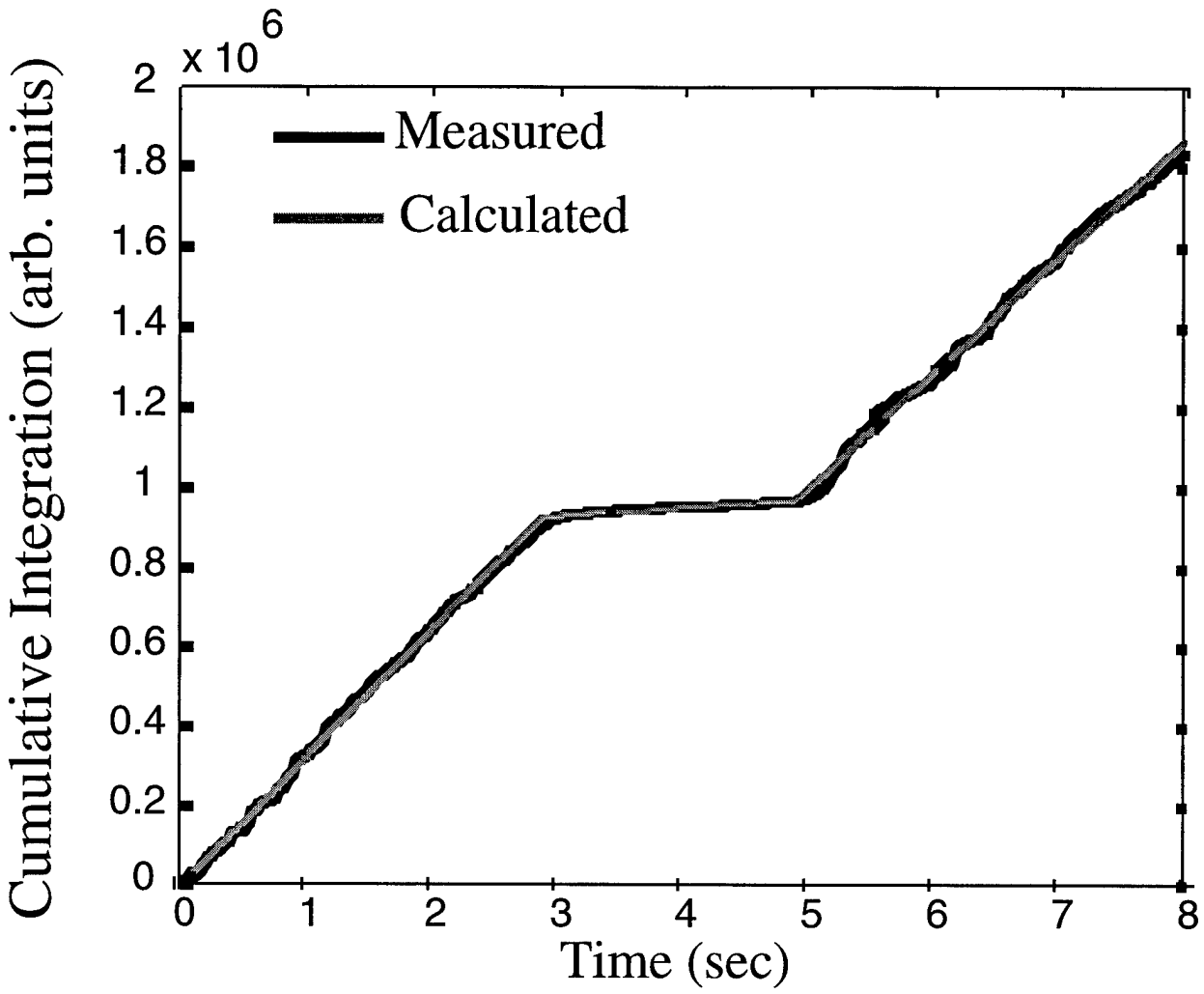


Figure 2A (top) and 2B (bottom)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Time (sec)

Figure 3

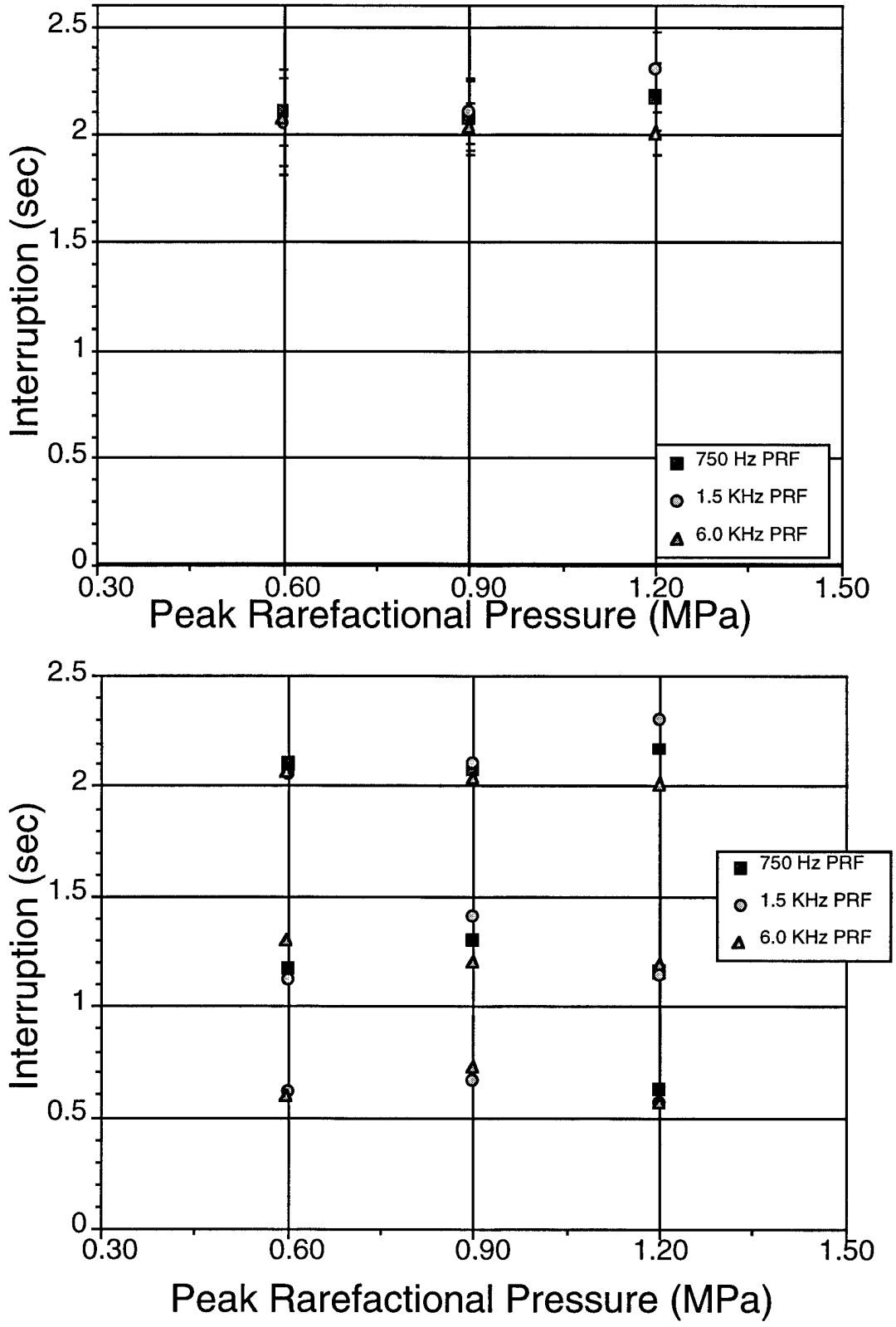
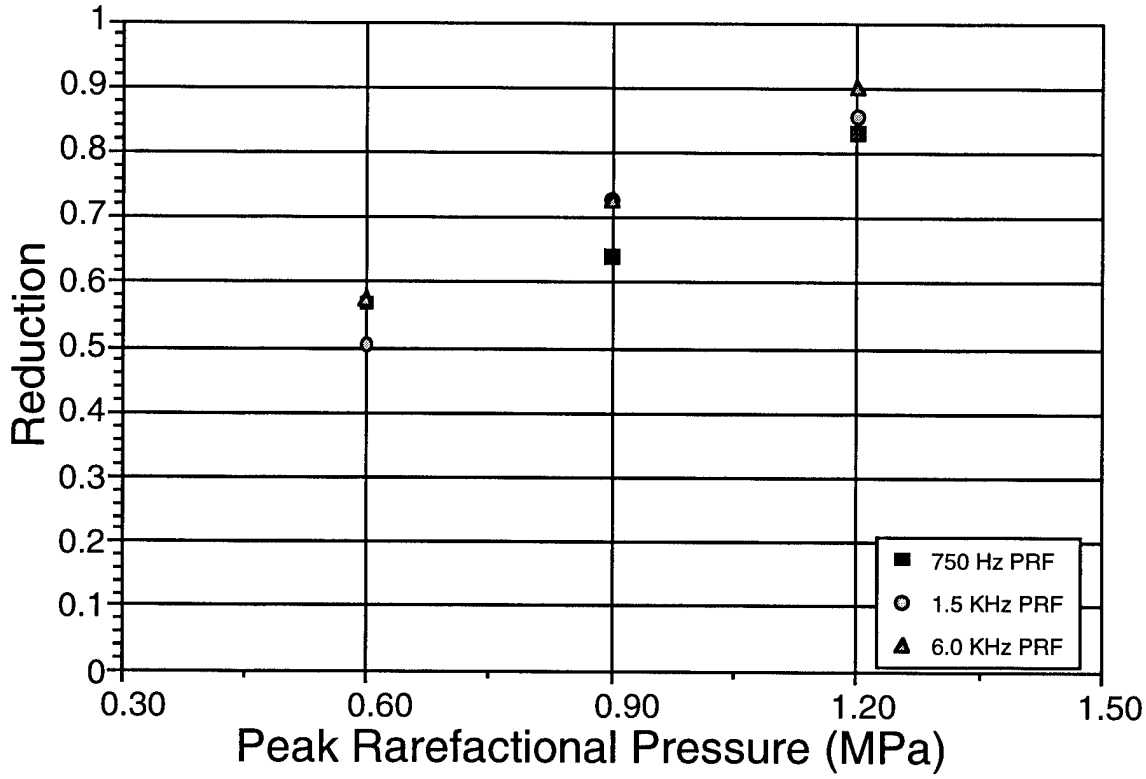


Figure 4A (top) and 4B (bottom)



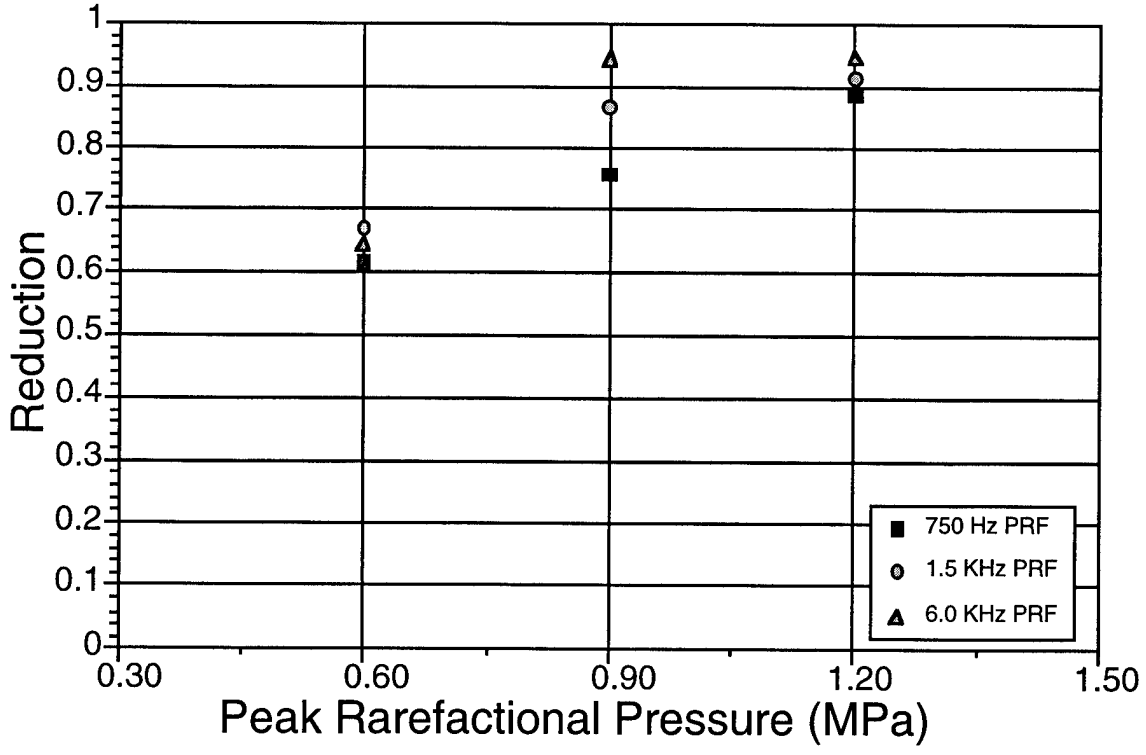


Figure 5A (top) and 5B (bottom)

ABSTRACT

Mammography has proven to be reliable as a screening tool for breast cancer. However, the specificity of mammography for breast cancer may be as low as 10% as evidenced by the number of biopsies recommended compared to the number of cancers confirmed (Moskowitz and Gartside, 1982). The present research is design to aid diagnosis by developing techniques for ultrasonic measurement of tissue perfusion including ultrasound contrast agent interruption for more effective washin/washout studies, decorrelation techniques and combination of Doppler power and velocity information for perfusion-like measures.

One of the largest questions concerning the future success of the contrast interruption techniques has initial been addressed, namely, the required acoustic amplitude has been reduced to levels in the operating range of diagnostic ultrasound scanners. A series of experiments have been conducted in aqueous media to measure the negative bolus parameters resulting from short bursts of the ultrasound applied at specific pulse repetition frequencies. Even though the acoustic field is reduced in peak rarefactional pressure and intensity, it appears to as effective as previously used continuous wave fields. This significantly improves the prospects for clinical application.

Decorrelation techniques are presently being adapted for *in vivo* application in the presence of soft tissue motion and are showing promise in the detection of small vessel flow.