Disruption of Contrast Agents for Monitoring Blood Flow

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Abstract: An experimental system is being developed for controlling the flow of ultrasound contrast agent to create abrupt changes in contrast levels in tissues. Such changes can be used to monitor blood flow through bolus passage and to identify specific feeder vessels. Focused ultrasound (2.25 MHz) has been used to interrupt flow of the contrast agent MRX-115 (ImaRx Pharmaceuticals, Tucson AZ) in a tube (2.1 mm id., average velocity of 9.45 cm/s) and in vivo using short bursts 20 cycles in duration with a pulse repetition frequency (PRF) of 0.75 - 6.0 kHz. Peak rarefactional pressures (PRP) for effective disruption of contrast agent were only 0.6 - 1.2 MPa. This corresponds to mechanical indices (MI) of 0.4 - 0.8 and intensity values which are well within the recommended limits for diagnostic ultrasound. Up to 90% of contrast agent signal was eliminated and positive boluses were produced by turning the field off and on. Similar results were achieved with in vivo in a rabbit model. Therefore the potential exists to use common diagnostic ultrasound to produce contrast disruption suitable for short bolus production without arterial catheterization.

INTRODUCTION

The use of bolus contrast has in the past provided a means of tissue perfusion measurement especially when used with arterial injections. Unfortunately such injections are invasive and alternative methods are clearly desired. It is the goal of this research to acoustically manipulate the flow of intravenously injected ultrasound contrast agent to achieve the temporal resolution of bolus passage normally only possible with arterial administration. 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. Additionally, myocardial perfusion has long been a desired quantitative measure and other many applications could benefit from a convenient, relatively noninvasive perfusion measurement technique.

MATERIALS AND METHODS

The initial experimental setup used a single pass flow system to maintain a fairly constant level of contrast agent in the 2.1 mm id tube of rubber flow phantom. The contrast agent (MRX-115, ImaRx Pharmaceuticals Inc. Tucson, AZ, diluted 1:50,000 in saline) was pumped through the phantom with a peristaltic pump (Masterflex, Cole Parmer, Chicago, IL). An in-line bubble trap served as a flow capacitor to remove the pulsatility of the pump. 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 two transducers.

The first transducer (Harisonic Model HI-0232-P transducer (2.0" dia., # 1.5 focused element, Stamford, CT)) was focused in the center of the flow tube. To stop the flow of the contrast agent, a sequence of short bursts only 20 cycles in duration was repeated with a pulse repetition frequency (PRF) of 0.75 - 6.0 kHz. This signal eliminates the contrast agent from the flow. Then the field is turned off momentarily for a period of 0.5 - 2.0 seconds. This released a bolus of agent which flowed downstream. The range in peak rarefactional pressure (PRP) used for contrast disruption 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 IsPTA and IsPPA values were also in the range of those commonly used in diagnostic imaging systems.

All imaging and data collection was done with a second transducer located downstream (Diasonics Spectra VST ultrasound imaging scanner (Diasonics Inc., Milpitas, CA)). Using this system, b-mode and color flow images were obtained and Doppler spectra were recorded from the center of the tube. Each spectrum from the Diasonics was integrated over frequencies using AVS software (Advanced Visual Systems, Waltham, MA) to give a high temporal resolution measure of Doppler power. The pixel intensities in the Diasonics spectra which are normally on a logarithmic scale were linearized prior to integration. We generated a cumulative power Doppler (integral over time of the power Doppler record) and then fit it with three connected line segments (the integral of an ideal positive square bolus). From the fitted experimental data we determined the bolus signal to noise ratio (SNR) of the Doppler power by comparing the slopes of the line segments, the bolus delay, and the bolus duration.
Initial animal trials were designed to demonstrate the reproducibility of the contrast interruption process. Adult female New Zealand albino rabbits, 2-4 kg, were anesthetized with xylazine (Rompun) (10 mg/kg s.c.) and ketamine (50 mg/kg i.m.) and anesthesia maintain by isofluorane inhalation. Fur on selected sites was removed with clippers and depilatory lotion. MRX115 contrast agent (ImaRx Pharmaceutical Corp., Tucson, AZ) was administered through the ear vein catheter as a diluted solution (4% vol/vol in saline), infused for up to 10 min at 0.5 ml/min. A 2.25 MHz, 19 mm dia. planar transducer (Picker Ultrasound, Cleveland, OH) used to disrupt the contrast agent was attached in line with a 5 MHz linear array (Diasonics). This combination transducer assembly was coupled directly to the skin lower groin. This arrangement provided targeting of the 2.25 MHz transducer on the femoral artery and provided immediate confirmation its effect on the contrast agent. A second imaging array (10 MHz Diasonics linear) monitored the bolus passage to a distal position in the rabbit leg. Doppler spectra were collected and processed in a similar fashion to those described above.

RESULTS AND DISCUSSION

Experiments performed in the flow phantom and in vivo for a variety of pulse parameters indicate that a wide range of values will provide interruption in contrast agent flow. In all cases the duration of the interruption measured immediately downstream is slightly higher than the off-time of the acoustic field used to produce the bolus. The degree to which the contrast agent was disrupted by the field did vary with some acoustic parameters. The reduction in Doppler power during the on-time of the acoustic field increased with increasing amplitude and PRF although the values used were within diagnostic limits. The SNR ranged from 25-30 dB for the acoustic parameters tested. Figure 1 shows the integrated Doppler power during the passage of a contrast bolus produced by a 1.0 sec interruption in the applied acoustic field. Note the sharp increase and decrease in signal over just a few cardiac cycles (approximately 1.5 seconds). Use of the cumulative integrated Doppler power makes fitting the experimental results in an automated fashion relatively easy as seen in Fig. 2 even in the presence of pulsatility.

The results of this initial work suggest that acoustic manipulation of ultrasound contrast can produce a relatively short bolus of contrast. The acoustic fields required are within the range of those used in diagnostic ultrasound in terms of MI, ISPAP, and ISPAT. Contact scanning and imaging can be used to guide and confirm the production of the bolus and in the future can be used to measure the input function to the tissue downstream and the bolus can be detected at downstream locations. Further studies will be required to compare this technique to other tissue perfusion measurements.

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