Imaging the destruction of individual ultrasound contrast microbubbles with diagnostic ultrasound

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Abstract: Ultrasound imaging of ultrasound contrast agent fragmentation in a water bath was performed with the color Doppler mode of the HDI 5000 (Phillips Ultrasound). A highly diluted suspension of ultrasound contrast microbubbles (Optison®) was injected into the water bath such that individual microbubbles passed through the image plane every few seconds. Decorrelation of the signal, along with the appearance of multiple signals, suggests that single microbubble fragmentation was observed, with daughter bubbles being formed from the original microbubbles, depending on the applied acoustic pressure.

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Ultrasound contrast agents (UCA), micron-sized stabilized bubbles, can enhance the contrast of blood relative to background tissue. Common applications in diagnostic ultrasound involve low Mechanical Index (MI) imaging, so that the UCAs remain intact, and high-MI imaging, which utilizes the destruction properties of UCAs to form an image. Several imaging techniques use both high-MI and low-MI to monitor the transition from oscillation to destruction of UCA bubbles.[1,2]

Of particular interest is the threshold for which UCA destruction occurs. Several studies have been performed to measure the destruction threshold of UCA clusters under various conditions.[3–6] However, there is anecdotal evidence that the actual destruction threshold is much lower than this work suggests. Therefore, the first step in measuring an accurate threshold with diagnostic ultrasound systems is to image the destruction of *individual* UCAs subjected to actual diagnostic ultrasound pulses.

Diagnostic ultrasound has previously been used in an attempt to image individual ultrasound contrast microbubbles.[7,8] While individual bubbles can apparently be discerned within a field of bubbles, the field of view still contains many echogenic objects, and the detailed evolution of individual objects cannot be obtained. We take a different approach by injecting individual contrast microbubbles into a water tank, and image them with a Philips Ultrasound HDI 5000 diagnostic ultrasound system with a phased array used for adult cardiac scanning (P4-2 probe). Thus, *we are able to observe the evolution of individual bubbles*. For this study we used a 2D Color Flow Doppler mode (2 MHz center frequency, ≈6 cycles). The present work serves as a precursor to a more careful measurement approach of microbubble destruction thresholds under diagnostic ultrasound conditions.

The experiment setup is straightforward. A diluted Optison® solution (calculated to be on the order of 10^5/ml) was injected into a rectangular water tank (3.5×3.5 cm cross-sectional area, filled to height of 4 cm) using a syringe pump (rate≈10 ml/h) and a 0.5-mm-i.d. tube. The exit tip of the tube was near the edge but within the imaging field of view of the scanner (Fig. 1). Ejected microbubbles passed through the entire field of view of the scanner. A VCR connected to the HDI 5000 was used to record the video from HDI 5000 for postprocessing.

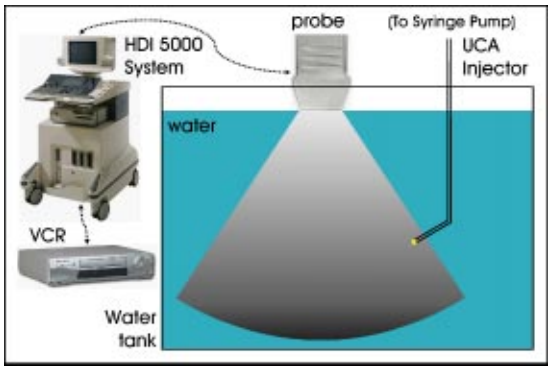

Fig. 1. Experiment setup.

A sample of the raw video images is included (Mm. 1). In order to enhance the images, the videos were digitized and postprocessed in two steps: first, background subtraction was performed by taking a video frame before the bubbles were injected, and subtracting it from all subsequent video frames. Background noise is relatively stationary and is removed from the video after this procedure. This is a necessary step as the use of a water bath results in a highly reverberant environment which results in multiple reflections and image artifacts. Background subtraction significantly enhanced the processed images. Second, threshold contrast filtering was used to enhance the microbubble images. Specifically, we use the MATLAB software package (The Math Works Inc.) to change the upper threshold to enhance the video.

Mm. 1. Guan video file (1.4 Mb). This is a file of type "mov".

Figure 2(a) (and associated video Mm. 2) shows the destruction of a UCA bubble at MI=0.41 (measured peak negative pressure 0.54 MPa) after the processing procedures of background subtraction and contrast enhancement. The UCA bubble travels from top-left to the bottom-right in the screen after it is injected, where the injector is located near the top-left corner. The apparent distortion of the microbubble is due mostly to the internal temporal and spatial averaging of the HDI 5000. Thus, a micron-sized bubble can look much larger, and not spherical. In addition, the minimum size of a target in the image is determined by the spatial resolution of the imaging system, which in turn is a function of the bandwidth and beamwidth of the

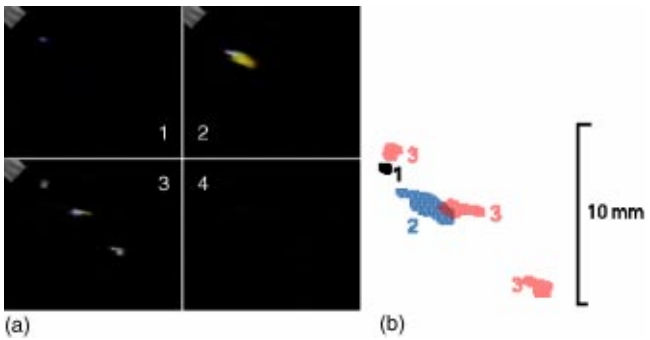

Fig. 2. (a) An Optison® microbubble ejected from the tip of a needle (approximate size and location shown in upper left) fragments into multiple daughters. The MI is 0.41 (peak negative pressure 0.54 MPa). (b) The position and outline of the blobs is traced from (a). Sizes and shapes are influenced by the temporal and spatial averaging of the machine.

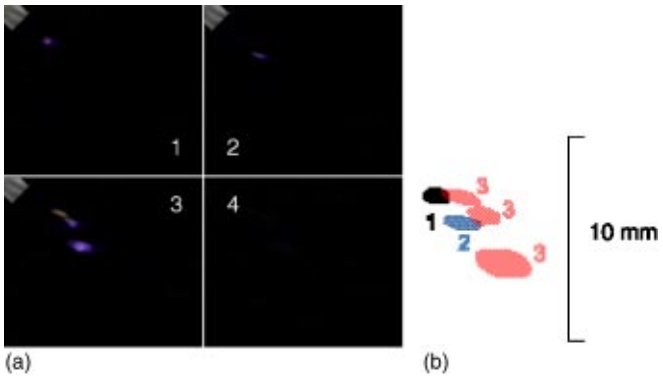

Fig. 3. (a) The fragmentation and dissolution of an Optison microbubble at an MI of 0.58 (peak negative pressure 0.72 MPa). (b) The positions and shapes are traced from the data in (a).

transmitted pulse. This is especially evident in Fig. 2, where we examine the destruction of individual contrast microbubbles subjected to color Doppler pulses from the HDI 5000.

We note that the actual frame rate of the imaging system (16 Hz) is not equal to the video system (about 29 Hz). In some cases, the video will capture two identical images from the imaging system. An example of this artifact image is shown in Mm. 2. Artifacts are not seen in the other videos.

Mm. 2. Guan video file (44 kb). This is a file of type "mov".

The image labeled 1 in Fig. 2(a) corresponds to a microbubble soon after exiting the needle tip. Frames 2–4 are the subsequent images from the HDI 5000. Image 2 appears to show Doppler signals that are the result of pulse-to-pulse decorrelation, due in part to the destruction of the microbubble. In 3, there appears to be three separate fragments. In 4, the fragments have dissolved. No further echogenic objects are observed in subsequent frames, indicating that these daughter bubbles have apparently dissolved. Decorrelation signals from moving (but intact) microbubbles would show the bubble traversing the field of view over 700 ms, not a complete loss of signal. This set of images suggests that the bubble and daughters dissolve in less than 200 ms (16 Hz frame rate$\times\sim$3 frames). In Fig. 2(b), we trace the shape and positions of the images of the UCA bubble and daughter bubbles from each frame, as an overlay image to show the relationship between the original bubble and the daughter bubbles.

An important question is whether or not this video (and those that follow) represents the images of a single bubble, and if so, whether or not it began as a shelled microbubble. To answer these questions, we rely on our previous research: The technique of injecting a single microbubble into a water vessel[9] was validated with injections into a slightly more viscous gel, whereby individual microbubbles could be imaged. Because of the viscosity of the gel, the bubble could be "trapped" and imaged with a microscope. Although the resolution of the microscope was not sufficient to provide good measurements of its ambient size, it was sufficient to show that only a single bubble was present. If the bubble were not shelled, it would have dissolved during this time. Thus, we are confident that our technique can in fact deliver a single microbubble. Nonetheless, there is always the possibility that two or more bubbles can be "stuck" together. We offer only that our experiments are consistent with other experiments we have performed which show that the bubble appears to be a single bubble. We have observed cases where multiple signals were measured near the injector tip, indicating that multiple bubbles were injected at the same time. However, these signals are relatively rare.

Figure 3 illustrates another example of UCA bubble's destruction with higher acoustic pressure. This time we increased the MI to 0.58 (measured peak negative pressure 0.72 MPa; video Mm. 3). The images are similar to those from Fig. 2: After being injected into the water,

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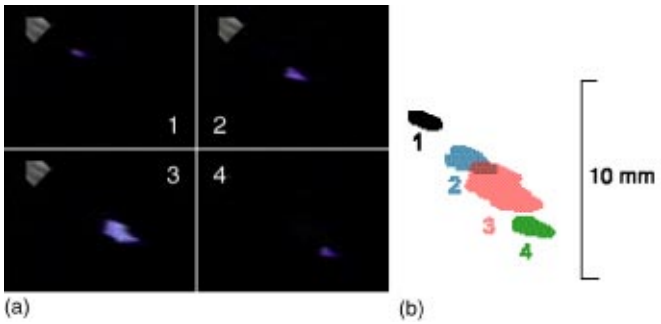

Fig. 4. (a) The fragmentation and dissolution of an Optison microbubble at an MI of 0.60 (peak negative pressure 0.74 MPa). (b) The positions and shape from the data in (a).

the microbubble is fragmented into three daughter microbubbles. After fragmentation, the daughter microbubbles disappear, with no further images observed. Again, the apparent distortion is an artifact of the imager processing. We only performed background subtraction and contrast enhancement.

Mm. 3. Guan video file (44 kb). This is a file of type "mov".

Another video of a destruction event is shown in Fig. 4, for a MI of 0.6 (0.74 MPa; video Mm. 4). In this particular case, we do not observe a fragmentation into multiple (separate) daughter microbubbles. Instead, we observe an apparent signal growth from images 1 to 3, followed by a subsequent loss of signal. By frame 5 (not shown) and beyond, no bubble is observed. Because of the spatial and temporal averaging that occurs with the scanner, it is difficult to quantify these data. The microbubble shell can be destroyed. The unshelled microbubble can undergo large oscillations (in frames 2 and 3) before dissolution. It may also be that the bubble has fragmented into two or more pieces, but that they remain close to each other, so that the individual daughter microbubbles cannot be resolved.

Mm. 4. Guan video file (40 kb). This is a file of type "mov".

The data shown here are representative of the types of data we have observed, but does not encompass all the different destruction features. In many cases, especially at higher MI, we observe the signal from a single bubble in frame 1, and thereafter, no signal can be detected, suggesting that the bubble was completely destroyed soon after exiting the needle tip (<62 ms). Finally, we point out that our observations are made along the scan plane. Bubble movement out of the plane is not considered. We do not believe it is important because bubble ejection was along the scan plane, and destruction occurred in less than four pulses. However, longer pulse studies would need to account for bubble motion out of the plane due to flow patterns.

In conclusion, we presented evidence of imaging the destruction of a single UCA bubble using the color Doppler mode of an HDI 5000 diagnostic ultrasound system at an MI range from 0.41 to 0.60 (measured peak negative pressure range 0.54–0.74 MPa). Features such as fragmentation and bubble dissolution from pulse to pulse were observed. The ability to measure bubble destruction with diagnostic imaging systems is necessary in order to quantify destruction thresholds of various bubbles under a variety of imaging conditions. In addition, an enhanced ability to image individual UCA bubbles would help both contrast-assisted diagnostic imaging and targeted drug delivery applications.

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