

Particle-Stabilized Bubbles for Enhanced Organ Ultrasound Imaging

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IODIPAMIDE ETHYL ESTER (IDE) particles previously have been shown to be effective in enhancing ultrasound backscatter images of the liver.^{1,2} The theoretical backscatter for solid particles can be determined from the long wavelength approximation for scattering from an inhomogeneity in a fluid medium. The scattering cross section—a function of the difference in compressibility and density between the particles and the surrounding fluid—is proportional to frequency to the fourth power and to the scatter radius to the sixth power.³ Although actual particle diameter must be limited to approximately 3 μm or less, to pass freely through the smallest capillaries, the effective scattering radius can be much larger due to concentration of the particles in the Kupffer cells and the observed higher concentration of particles in Kupffer cells located closer to the portal triads than the central veins.⁴ These dimensions all are smaller than the ultrasound wavelength, so the wave interacts with particles having a larger effective scattering radius homogeneously distributed throughout the normal liver. Liver lesions, however, having few, if any, phagocytic cells are not enhanced by the particles and appear as dark holes on the ultrasound image.

Although IDE particles do enhance ultrasound liver im-

ages, the backscatter enhancement is not as large as can be obtained with gaseous bubbles which have compressibility and densities which are orders-of-magnitude different from liver tissue.³ Developing a bubble contrast agent which can survive passage through the lungs and heart has been a considerable challenge.

Recently, we have developed a modified IDE particle suspension which contains air trapped within the otherwise solid IDE matrix. The purpose of this study was to evaluate the ultrasound enhancement potential of these new bubble/particles compared with standard IDE particles.

Methods

IDE and Rabbit Liver Preparations

The preparation of the new bubble/particles involves a modification of the method for preparing solid, dense IDE particles which has been described elsewhere.¹ For the in vitro studies, the particles were suspended in a bovine plasma-distilled water (1:1) solution and placed in a small plastic pipette.

In the animal studies, New Zealand White rabbits (Hazelton Laboratories), weighing 2–4 kg, were anesthetized, and injected intravenously with a 8–10 mL (depending on weight) IDE suspension (final concentration of approximately 100 mg/mL) at a rate of 1 mL/minute. The rabbits were scanned periodically using a clinical scanner.

Backscatter

A pulse echo technique was used to determine relative backscatter. A wideband, 10 MHz center frequency, Panametrics transducer (1.3 cm diameter, 5 cm focus), driven by a JSR Pulser, was used to obtain rf scan lines. For the in vitro measurements, the mean backscatter (root mean square, RMS) was computed for 8 uncorrelated scan lines, each corresponding to 4 mm in length.

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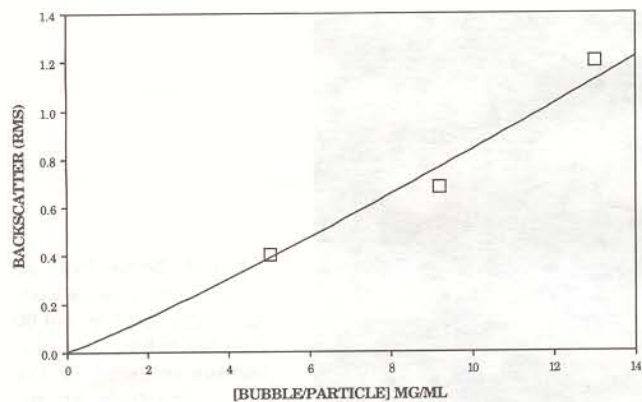


Fig. 1. Raw backscatter values (RMS) of bubble/particle suspensions plotted as a function of the concentration of these particles in the suspensions. The data indicate a linear relationship between backscatter and concentration.

Results

In vitro analysis of the new bubble/particle suspensions reveals that backscatter increases linearly with concentration as shown in Figure 1.

In vitro analysis of the bubble/particle suspension and a standard IDE particle suspension after mixing with bovine plasma reveals a much higher backscatter from the bubble/particle agent than from the old standard particle agent as shown in Figure 2. Moreover, these data demonstrate that the high echogenicity of the bubble/particles is sustained for hours after mixing with bovine plasma.

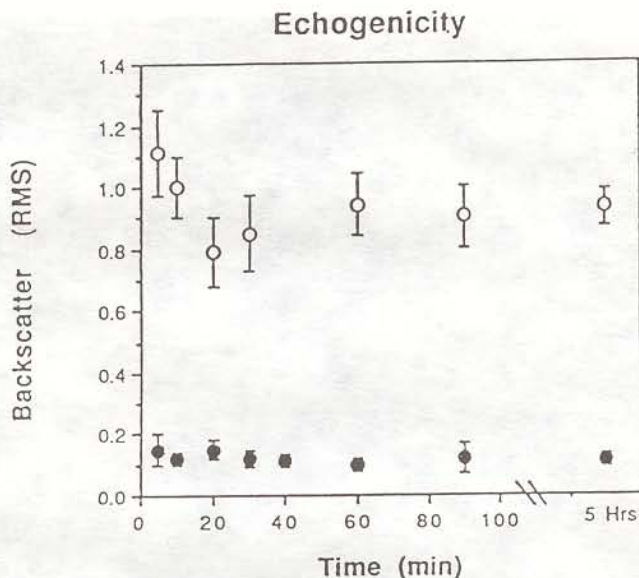


Fig. 2. Raw backscatter values (RMS) of bubble/particles and standard IDE particles mixed with bovine plasma plotted as a function of time after mixing. Note the high echogenicity of the bubble/particle suspensions compared with standard IDE particle suspensions. Also note the sustained high backscatter observed with the bubble/particle agent even after mixing with plasma.

B-scan images of a rabbit liver with and without the bubble-IDE particles are shown in Figures 3 and 4. These images were obtained from a 5.0 MHz Acuson scanner with all settings held absolutely constant over a 120 minute ex-

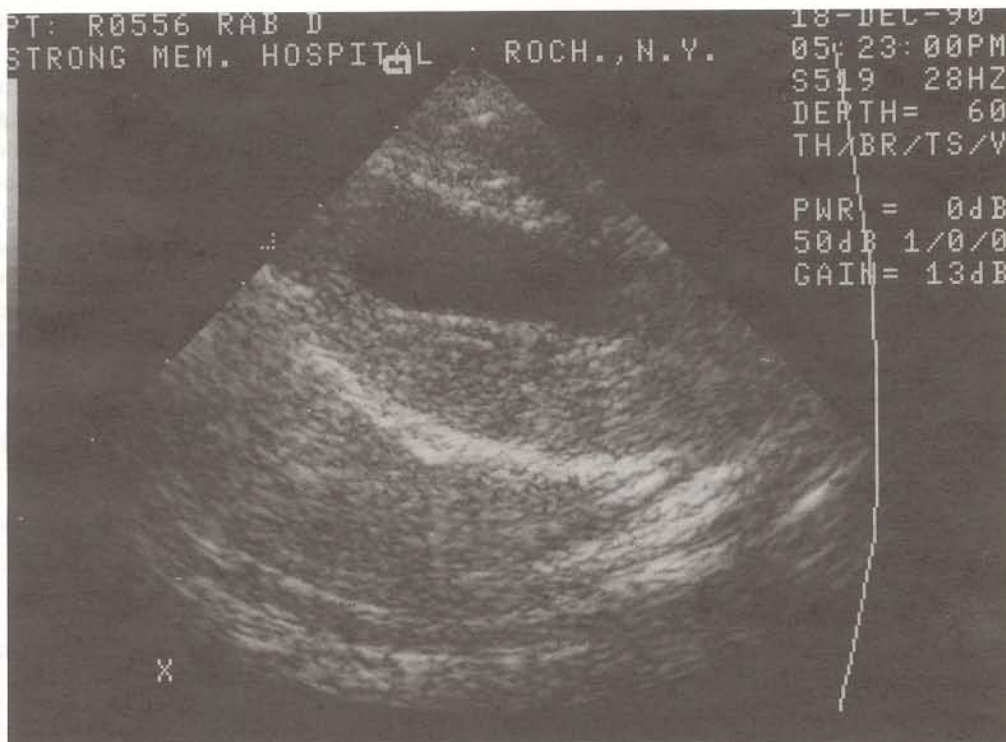


Fig. 3. B-scan image at 5 MHz of normal rabbit liver with gall bladder before infusion of the bubble-IDE contrast agent.

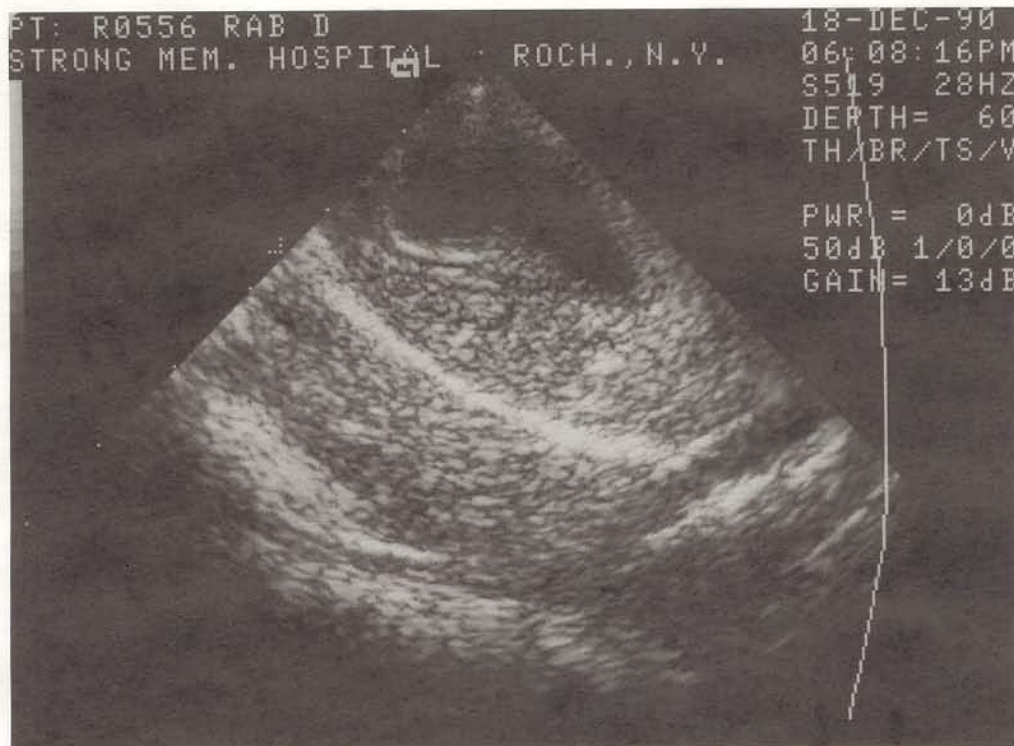


Fig. 4. Same liver as Figure 3 and same constant gain settings, but 60 minutes following intravenous infusion of the bubble/particle agent. Note the enhancement of the parenchymal echogenicity was observed up to 120 minutes.

amination period. The injected dose of the bubble-IDE agent was approximately 250 mg IDE/kg body weight. Liver echogenicity following IV administration of the bubble/particle agent is markedly enhanced compared with the pre-contrast image.

Discussion

When IDE is added to normal liver, the resulting increase in backscatter depends on the particle size and dose administered but can be approximately a 3-dB increase in echo strength for 1.2- μ m particles at 200–300 mg IDE/kg body weight. An increase of 3dB is comparable to other backscatter variations which have been utilized in tissue characterization such as those associated with myocardial tissue.⁶ Furthermore, 3dB is a significant enhancement in regards to the lesion detection problem for fully developed speckle.^{7,8}

When gas is stabilized in modified IDE particles, the resulting particle-bubble agent has high echogenicity compared to standard IDE and has long stability in vitro and in vivo. This sustained high echogenicity obviously is critical to achieve organ enhancement after the agent has passed through the lungs and heart. Further investigation is required to explain this difference. The long-term stable echogenicity of the bubble/particle in bovine plasma (Fig. 2) is markedly different from other agents, such as Alunex[®], with a reported in vitro half-life measured in seconds.⁹

Preliminary results in rabbits demonstrate that the stabi-

lized, echogenic gas can be delivered to the Kupffer cells of the liver, raising the backscatter well above the levels obtained with standard IDE. Improving liver lesion detection by enhanced ultrasound may now be possible. Defining the sensitivity and specificity of this new agent will be the subject of future investigations.

These new bubble/particles produce enhanced ultrasound backscatter as a result of the air trapped within otherwise solid IDE particles. This IDE matrix provides the stability for sustained echogenicity. Since the entrapped gas is confined in a solid matrix, the echogenicity may be less than would be expected from a "free" gas bubble. Nonetheless, the backscatter enhancement appears to be quite adequate to improve detection of liver lesions.

In addition, the IDE matrix is still capable of enhancing CT images of the liver by virtue of the iodine in the matrix. These new bubble/particles, therefore, have the potential to be a multi-modality imaging agent.

Acknowledgment

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