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A Tissue-Mimicking Ultrasound Test Object Using Droplet Vaporization to Create Point Targets

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Abstract

Ultrasound test objects containing reference point targets could be useful for evaluating ultrasound systems and phase aberration correction methods. Polyacrylamide gels containing albumin-stabilized droplets (3.6 μm mean diameter) of dodecafluoropentane (DDFP) are being developed for this purpose. Perturbation by ultrasound causes spontaneous vaporization of the superheated droplets to form gas bubbles, a process termed acoustic droplet vaporization (ADV). The resulting bubbles (20 to 160 μm diameter) are small compared with acoustic wavelengths in diagnostic ultrasound and are theoretically suitable for use as point targets (phase errors $<20^\circ$ for typical f-numbers). Bubbles distributed throughout the material are convenient for determining the point spread function in an imaging plane or volume. Cooling the gel causes condensation of the DDFP droplets, which may be useful for storage. Studying ADV in such viscoelastic media could provide insight into potential bioeffects from rapid bubble formation.

I. Introduction

Although they have many applications in science and industry, polyacrylamide gels have been found to serve as suitable surrogates for biological soft tissues in terms of acoustic and thermal properties [1], [2]. The gels are easily made by combining deionized water, bis-acrylamide, tetramethylenediamine (TEMED), and ammonium persulphate (APS). The gel stiffness can be controlled by the volume fraction of acrylamide added; a higher percentage bis-acrylamide results in a stiffer gel. Accordingly, the speed of sound can also be controlled, and the range of speeds measured is close to that in tissue.

Acoustic droplet vaporization (ADV) [3] is the vaporization of superheated droplets to form gas bubbles through exposure to a mechanical perturbation from an ultrasound field. Here, the targets are albumin-stabilized dodecafluoropentane droplets (DDFP, C_5F_{12} , bulk boiling point 29°C), ranging from 1 to 20 μm in diameter with a mean of 3.6 μm (measured using a Coulter Counter, Multisizer, Beckman Coulter Inc., Fullerton, CA). When droplets are suspended in water, vaporization requires short ultrasound tone bursts with pressure thresholds greater than approximately 1 MPa peak negative pressure at frequencies of 3 MHz or higher [3]. Such vaporization at pressures lower than typical thresholds for significant lesion formation *in vivo* has many potential applications such as the *in situ* point targets presented here [4], drug delivery [5]–[12], vascular occlusion [13], [14], and high-intensity focused ultrasound (HIFU) assistance [15]. Depending on the application, acoustic

frequency and acoustic intensity must be chosen to avoid possible side effects from the rapid bubble formation [16].

The exploratory study presented here investigates the result after the perfluorocarbon droplets are added to polyacrylamide gels, and these droplets are vaporized to form small spherical gas bubbles for possible use as point targets for pulse-echo response and beam characterization. A review of some of the requirements for point targets is helpful in evaluating the role gas bubbles produced in a gel could play in ultrasound system characterization.

Ultrasonic beam and pulse-echo response profiles from single-element and array transducers can be characterized with point targets that scatter isotropically [17], [18]. However, there is a lack of reliable objects to accurately simulate point target sources. These targets should have specific and reproducible scattering characteristics, and would ideally be contained in a medium of tissue-mimicking (TM) or negligible ultrasound attenuation. The density, sound speed, and nonlinearity coefficient should be representative of human soft tissues. To determine spatial resolution, particularly lateral resolution, it was recommended to use a spherical tungsten carbide test object, which could be mounted on rods or wires in water [19]. This was written for A-mode, but could be duplicated in B-mode. Limitations were that the rod or wire should have a diameter no more than half that of the ball, and avoiding detrimental reverberations in the setup required careful positioning of the transducer relative to the target and mounting object.

A drawback of these tungsten carbide spheres regardless of the suspension mechanism is that their diameter is not small compared with the acoustic wavelength used in ultrasound (a 1.5-MHz center frequency acoustic wave in water has an approximate wavelength of 1 mm). The upper restriction on the allowable ball size for the apparent target to be acoustically small was established to be $d < 1.22\lambda F^2$, where d , λ , and F are target diameter, acoustic wavelength, and transducer f-number, respectively [19]. A lower bound of $d > 5 \text{ [mm/}\mu\text{s]}/f$ was placed on target size to minimize strong variations in the frequency dependence of target reflectivity for tungsten carbide in water [20], where f is the working frequency in megahertz and d is given in millimeters. For many common transducer configurations, meeting these criteria is impossible, thus making it necessary to find more suitable point targets. Furthermore, even with the imposed lower limit on target size, sharp variations in the scattering as a function of frequency are observed for steel spheres [21]. The upper limit of $d < 1.22\lambda F^2$ was an extremely liberal criterion as well. Much more stringent criteria on maximum target size are required to avoid phase cancellation effects across the aperture of the transducer under test [22], [23]. Some use has been made of solid particles embedded in TM material as point targets for subjective evaluation of diagnostic systems [24] improving the means of positioning, but producing noticeable distortions of the point spread function (PSF).

In considering small solid particles as point targets, it is important that acoustic scattering from solid targets usually only approaches that of a sphere with a scattering cross-sectional area equal to its physical (geometric) cross-section. That is, no more than the total acoustic energy incident upon its cross-sectional area is scattered. In contrast, a free gas bubble in the appropriate size range has greater scattering. The scattering cross-section for these two cases can be initially examined using a simple calculation of the nonrigid sphere for the gas bubble and a rigid sphere for the solid particle [25]. The results, normalized by the cross-sectional area of the targets, are plotted in Fig. 1 as a function of the wave number ($k = 2\pi/\lambda$) times the target radius a . An increase in ka can result from increasing ultrasound frequency or the target size. The markedly larger bubble scattering amplitude compared with the rigid sphere is evident for $ka < 1$. Psychoudakis *et al.* [22, Fig. 3] have shown by using

Rayleigh-Plesset simulations for $ka \ll 1$, that bubbles, as opposed to non-rigid spheres, retain a relative scattering cross-section of approximately 4. This factor motivates our selection in this paper of smaller bubbles rather than rigid spheres. It should also be mentioned that, above the bubble resonance, shown in Fig. 1 for a free bubble at $ka \sim 0.012$, there are no sharp variations in the bubble scattering, unlike that from real solid particles for $0.2 < ka < 10$. For comparison, the normalized scattering cross-section is also shown for a tungsten carbide sphere. This calculation is based on the solution from [26] using parameters for tungsten carbide [27]. Note that the scattering for this material is very close to that of the ideal rigid sphere up to $ka \sim 6$, where shear wave interactions produce sharp resonances. The use of small solid particles as surrogates for point targets is considered in the asymptotic limit for the scattering from the rigid sphere because as ka approaches 0, the frequency dependence is f^4 . This frequency dependence is the same as that for the non-rigid sphere (bubble), but it occurs only at very small bubble sizes. If one really wants to measure the PSF of an ultrasound system for small, individual solid targets with their f^4 frequency dependence, one must use very small solid targets in an environment with very low acoustic noise so that the weak scattering can be seen. However, the frequency dependence for the backscatter cross-section from most tissue internal structures (excluding blood) is approximately f^1 to f^2 , or even f^0 for large, specular reflectors [28]. Thus, the flat portion of bubble scattering curve above $ka = 0.1$ has a good frequency response for measuring imaging system resolution as it is likely to manifest *in vivo*. It is important to remember that the scattering from the bubble is assumed to be linear, and therefore the acoustic pressure must be kept relatively low to avoid nonlinear response by the bubble. Note that for the flat portions of the curves in Fig. 1, scattered power increases as the unnormalized backscattering cross-section, i.e., as diameter (or ka), squared. Other applications of bubble point targets are considered in Section IV.

Given this scattering behavior, gas bubbles distributed in polyacrylamide gels have the potential to act as spherical point target scatterers, which could be useful in evaluating ultrasound system performance, as well as testing phase aberration correction methods. Also, as the bubble concentration contained in the gel is easily controllable, it may be an ideal medium to study contrast agent scattering behavior. Studies on the behavior of contrast agents in varying acoustic pressure fields are impeded by the difficulty of isolating scattering from single bubbles [29]. To demonstrate their potential applications, bubbles with diameters ranging from 20 to 160 μm were created in polyacrylamide gels by vaporizing perfluorocarbon droplets using ultrasound. This paper presents initial experiences in constructing these gel phantoms and illustrates some physical properties of the bubbles. Scattering of bubbles was compared with that of solid spheres to verify their feasibility as point targets for pulse-echo response and beam characterization, and the PSFs of single-element and array transducers were determined experimentally and analyzed.

II. Materials and Methods

A. Gel Phantom Preparation

The acrylamide gels were made from a 30% (19:1) bisacrylamide (BA) stock solution (all chemicals were purchased from Sigma Chemicals, St. Louis, MO), further diluted with deionized water to concentrations of 15%, 10%, and 6% BA by volume. Changing BA concentration yields different gel stiffness, which can be tuned to mimic soft or hard tissue structures or vessels. After the mixture was prepared for the desired quantity, it was poured into a mold and placed in a vacuum chamber to degas at 3.8 kPa until boiling ceased. Next, in-house-prepared DDFP droplets (see [3] for details) were added to the solution, followed by the two cross-linking agents, TEMED and APS, at concentrations of 1 and 5 $\mu\text{L/mL}$, respectively. The concentration of droplets added depended on the intended application (further detailed in following sections), and quantities were based on the concentration of

droplets in the stock solution in terms of 10^7 droplets per milliliter [3]. The solution was then stirred gently to ensure that gas was not introduced into the liquid. The gel began to stiffen within minutes of the final step, and was fully set within a couple of hours. The droplets were then ready to be vaporized, forming spherical bubbles within the gel. During storage, the gel surfaces exposed to air were covered with a layer of water to prevent desiccation.

B. Bubble Sizing

Determination of bubble sizes in the acrylamide gels was accomplished using digital microscopy and subsequent image processing. The gels were examined using a Nikon optical microscope (SMZ-U, Melville, NY), and the images recorded digitally with a charge-coupled device (CCD) camera (HR200-CMT, Diagnostic Instruments Inc., Sterling Heights, MI) with a resolution of approximately 1.3 pixels per micrometer, based on calibration measurements with a micrometer scale. The bubble sizes were calculated using manual edge tracing and a script written in Matlab (The MathWorks Inc., Natick, MA) to determine the bubble perimeter and corresponding radius.

C. Pulse-Echo Response and Point Spread Functions

For the pulse-echo response and PSF measurements, a sparse population of droplets (concentration approximately 1 droplet/mL of gel) was embedded in 15% acrylamide gels and vaporized just before the experiment with a 10-MHz linear array transducer, $MI = 1.2$ (mechanical index = peak negative pressure [MPa] / $\sqrt{\text{frequency [MHz]}}$). For comparison purposes, two tungsten carbide spheres of diameters 500 and 580 μm (20 times larger than the mean bubble size for that gel stiffness) were embedded in a separate gel sample. This was achieved by pouring only half the gel volume into a container and adding the corresponding amount of cross-linking initiator. After the gel began to stiffen but not fully settle (about 2 min), the spheres were placed on top of the initial layer, and the remainder of the gel was then poured in and cross-linker added. Speed of sounds for 6, 10, and 15% gel were measured as 1525, 1545, and 1569 m/s, respectively; acoustic impedances were measured as 1.54, 1.58, and 1.63 MRayl, respectively [2]. Speed of sound and acoustic impedance are close to the values for human soft tissue (1540 m/s and 1.5 MRayl). The gel blocks were then placed in a water tank with degassed and heated (37°C) deionized water. Measurements were conducted with 3.5- and 7.5-MHz nominal frequency, spherically focused transducers (A-series, Panametrics Inc., Waltham, MA). A pulser/receiver (model 5900PR, Panametrics Inc.) in pulse-echo mode was used with a pulse repetition frequency (PRF) of 200 Hz, and the echo was recorded from an oscilloscope via LabVIEW (National Instruments, Austin, TX), with further data processing performed in Matlab.

Pulse-echo responses for both the microbubble and tungsten carbide spheres were obtained by centering the transducers on the targets, which were placed approximately 2.8 mm past the axial geometric focus to obtain an approximately planar acoustic wave field, and recording the received RF waveform. The PSFs of the transducers were also measured with both targets and compared with the theoretical PSF at that depth for focused radiators. To find the PSF, a LabVIEW-controlled automated stepper motor (Parker-Daedal, Irwin, PA) was used to scan the transducers over the target, with pulse-echo measurements made at 0.1-mm intervals. The maximum echo amplitude was extracted from the data at each position. Care was taken in all measurements to assure that the targets were located at the same axial depth from the transducer, with similar amounts of overlying gel.

Finally, to demonstrate their functionality for calibrating ultrasound imaging systems, the PSF of a GE Logic700 probe (GE Medical Healthcare, Milwaukee, WI) was measured using ADV-transitioned droplets in gel. For the measurement, a phantom containing the vaporized

droplets was scanned using a motorized translation stage to position an M12 linear matrix array (GE Medical Healthcare) operated at 11 MHz center frequency. The transmit focal zone of the transducer was set as close as possible to the point target of interest, and the scanner was set to maximum zoom, resulting in pixel sizes of 0.055×0.055 mm in the digital B-mode image. Image volumes of 100 frames with a frame spacing of 0.1 mm were obtained. Axial, lateral, and elevational cross-sections through the pixel with maximum brightness were extracted, decompressed and normalized. Spline-interpolation was used to enhance the spatial sampling of the cross-sections before determining the full-width at half-maximum (FWHM).

D. ADV Pressure Threshold Versus Gel Stiffness

The experimental setup, as illustrated in Fig. 2, was used to determine at what sound pressure amplitude ADV occurs in gels of varying stiffness. A 3.5-MHz single-element transducer (A-series, Panametrics Inc.) was used to create bubbles in gels containing high number densities of droplets, while a 10-MHz diagnostic scanner (VST series, Dasonics, Milpitas, CA) was positioned above the focal point of the single-element transducer to record the backscatter at low power. Because of the impedance mismatch between gas and gel, an increase in detected backscatter indicates the formation of gas bubbles in the gel. A function generator waveform (3314A, Hewlett Packard, Palo Alto, CA) was amplified (240L, ENI, Rochester, NY) and used to drive the ADV transducer. Tone bursts with a PRF of 500 Hz and 13 cycles per burst were applied.

III. Results

A. Bubble Properties in Acrylamide Gel Phantoms

Fig. 3(a) shows a microscope image of a $4.6 \times 3.75 \times 1$ mm block of 15% gel containing droplets immediately after the right half was exposed to an ultrasound field with an MI = 0.8 (Dasonics VST system using a 10-MHz linear array), causing ADV and the formation of spherical gas bubbles. Note that, although the entire volume shown contained a large concentration of droplets, bubbles were only created on the side exposed to ultrasound. In these images, the droplet concentration was approximately 100 droplets/mL based on 0.1 mL of the pure droplet solution ($\sim 10^7$ droplets per milliliter) being diluted to 1/10 of the initial concentration, and then adding 100 μ L of the diluted droplet solution to 100 mL of gel. There did not appear to be a time restriction as to when the droplets must be initially vaporized after the gel was made. The droplets were stable and could be stored in the gel before vaporization for a period of weeks. (No specific long-term storage studies have been performed.)

After 3 d, the gel block shows a higher number density of small bubbles [Fig. 3(b) compared with Fig. 3(a)]. The size distribution is becoming increasingly bimodal, likely because of Oswald ripening.

The initial size distribution of the gas bubbles in various gels as measured immediately after ADV is given in Fig. 4. Not surprisingly, the distribution was dependent on gel stiffness, with mean bubble diameters of 37, 40, and 80 μ m for the 15%, 10%, and 6% gels, respectively. The total size range produced was 10 to 160 μ m, which closely fits the range necessary for bubbles to be considered linear isotropic scatterers (30 to 120 μ m for frequencies less than 8 MHz [24]). The diameters of bubbles in 15% and 10% gels spanned a narrower diameter range of 20 to 60 μ m, making them theoretically suitable for phase aberration corrections over the full 1 to 15 MHz bandwidth of general-purpose diagnostic imaging.

When a gel containing vaporized droplets was left at room temperature, some bubbles began to expand because of the inward diffusion of air from the surrounding gel. Because perfluorocarbon has both a low solubility and diffusion coefficient, it might not diffuse out of the bubbles rapidly. However, because the Laplace pressure inside a bubble is inversely proportional to the radius ($2\sigma/r$, where σ is the interfacial tension between the perfluorocarbon gas interior and acrylamide gel and r is the bubble radius), smaller bubbles were at higher pressures, facilitating perfluorocarbon diffusion from them outward into the gel. Therefore, the size distribution shifted as the small bubbles disappeared and the larger ones took on gas, resulting in a population that included some bubbles larger than the maximum diameter criterion of 120 μm established for point target scatterers. The onset of gas diffusion seemed to occur immediately, but the bubble growth rates depended on the ambient temperature, droplet concentration, and gel stiffness, and varied from hours to days. Faster growth occurred at higher temperature, higher bubble concentration, and lower gel stiffness. Ultimately the gel tended to fail, causing the bubbles to become non-spherical as pictured in Fig. 3(b), then to disappear completely as the perfluorocarbon and ambient gases gradually diffuse out [Fig. 3(c)].

To verify that bubbles in 15% acrylamide gels were stable for a suitable duration of time to determine the PSF of a transducer, the growth of three different bubbles was monitored over the course of several hours, as shown in Fig. 5. The bubble diameters were relatively constant over 8 h, with low standard deviations of 1.7, 3.4, and 2.6 μm , respectively, for each of the representative bubbles numbered 1, 2, and 3. They also remained spherical and small compared with wavelength, showing that the bubbles were acceptable point targets in 15% gel, even for high-frequency transducers.

Another interesting feature of these perfluorocarbon bubbles in gels is that upon cooling (18 h, 5°C), they condense again into droplets that could be vaporized later. This property could potentially be a storage mechanism for gel phantoms to prevent bubble growth. The size distribution of the bubbles changed when droplets were vaporized a second time as shown in Fig. 6. This figure compares the initial size distribution of bubbles from one ADV application to those created from droplets that had been condensed after the previous ADV process, then vaporized again by exposure to ultrasound and immediately sized. The elapsed time after ADV, temperature, and ambient gas content for the first and second bubble sizings were similar.

As summarized in Table I, the mean diameter of re-vaporized bubbles increased by 23% in the 10% gel, and 15% in the 6% gel, and the standard deviation for the 10% gel broadened appreciably. However, even with this increased size range, <6% of the re-vaporized bubbles formed in the 10% gel were over 70 μm ; of these bubbles, none were larger than 120 μm , so they were still theoretically suitable for point target scatterers at both high and low diagnostic frequencies. None of the re-vaporized bubbles in the 6% gel were under 70 μm in diameter; however, only 4% were greater than 120 μm , making them useable as point targets at frequencies below 8 MHz only. Though no quantitative data on the subject was taken, by observation, the droplet-to-bubble conversion efficiency was similar for the initial and re-vaporized droplets. Remarkable, however, is the observation that the bubbles resulting from re-vaporized droplet emulsion showed only one-half the standard deviation of the initial bubble distribution.

During droplet production, albumin is required to prevent coalescence. Without a shell, droplets coalesce rapidly while in physical contact with each other. However, once incorporated into the gel phantom, they are spatially separated by the gel matrix and can therefore no longer coalesce. Surface active agents, such as the here employed bovine serum albumin, lower surface tension. As a consequence, the Laplace pressure will be lowered too.

This in turn will increase the likelihood of vaporization. Removing the shell increases surface tension and Laplace pressure, therefore the likelihood of vaporization will decrease. Neither increase nor decrease of ADV threshold must be an easily measurable phase-transition threshold shift. Bulk materials can superheat and supercool. For boiling and condensation, seeds are required to process at the transition temperature and pressure. Sequestering of a material in small, non-communicating compartments shifts the phase-transition point, because as each compartment requires a seed.

B. Pulse-Echo Response

The waveforms and frequency responses of the scattering from bubble and tungsten carbide targets are shown in Fig. 7. Fig. 7(a) shows that the pulse-echo response for the 3.5-MHz transducer for the bubble, ball, and steel plate (left column from top to bottom, respectively) were similar, but in the case of the 7.5-MHz transducer (right column) the waveform from the ball differed from that of the bubble and steel plate in that it was a longer signal with post-target oscillations. This effect, reproduced qualitatively with another sphere and several bubbles, indicates a frequency dependence in the larger metal sphere scatterers that was not present in the bubbles. No diffraction correction was applied to attempt to match the normalized spectra between the two transducers.

The vibrations introduced by the solid-ball target are more clearly visible in Fig. 7(b), where the frequency spectra from the point targets have been plotted to a 12-dB pulse-echo transducer transfer-function bandwidth, and normalized with respect to the steel plate response to eliminate artifacts inherent to the transducer. It is apparent that the bubble has a fairly flat profile for all frequencies measured, whereas the response from the ball, though similar, shows a dip in backscatter at approximately 6 MHz. This dip can be observed in simulations using Faran's theory [26] for a tungsten sphere of 680 μm diameter inside a fluid with the mass density and speed of sound of the gel matrix used here. A sphere of the size used in the experiment (580 μm) showed a dip at 6.6 MHz. The amplitude response for the bubble is, as expected, lower in amplitude because its radius is 20 $\times$ smaller than that of the ball.

C. Point Spread Functions

The theoretical PSF curves for a focused single-element transducer were computed to validate the experimental data. This was done using

$$\text{Directivity} = \left[\frac{2}{z} J_1(z) \right]^2 \quad (1)$$

$$z = \frac{2\pi f}{c} a \sin \theta, \quad (2)$$

taken from O'Neil's paper on the theory of focusing radiators [30]. Fig. 8 illustrates the associated geometry. The right side of (1) has been squared to account for the transmit/receive mode of the transducer. In the equations, $J_1(z)$ is a spherical Bessel function of the first order, a is the radius of the transducer aperture, f is the working frequency, and c is the sound speed in the medium. O'Neil's assumptions that the transducer diameter is large relative to both the wavelength and depth of the concave surface are valid for our situation.

Because these measurements were made over short distances with respect to the transducer diameter and point target depth, it can be assumed that θ was very small, and the

approximation that $\sin(\theta) \approx \tan(\theta) = x/d$ is valid, where d is the point target depth. Substituting (1) into (2) and using the small angle approximation yields

$$\text{Directivity} = \left[\frac{c}{\pi f a x} J_1 \left(\frac{2\pi f a x}{c d} \right) \right]^2. \quad (3)$$

Fig. 9 shows the experimental PSFs, plotted with (3) for an ideal PSF with the same parameters as those used for the measurements. Registration- and transmission-based sound speed estimations found c to be 1530 m/s at room temperature in 15% acrylamide gels [31]. Fig. 9(a) is the 3.5-MHz case; Fig. 9(b) is the 7.5-MHz case. The agreement between theory and experiment is excellent for the 3.5-MHz case, whereas for the 7.5-MHz case, the theoretical PSF is narrower, and the curve measured over the tungsten carbide sphere shows bulges on its sides. These irregularities in the PSF profile may be due to the complex resonant behavior of the tungsten carbide sphere, as revealed with the 7.5 MHz transducer in Fig. 7. Although one would expect the measured PSF over the tungsten carbide sphere to be broad because that particular target was about 350 μm , which is not small compared with the acoustic wavelength at 7.5 MHz of 200 μm , one would, however, expect the PSF from the bubble to be more accurate.

There are a few possible explanations for the good agreement between the bubble and tungsten carbide sphere curves. One possible explanation is that the bubble was approximately the same size as the ball at the time of the measurements; this is not impossible, because the bubbles were found to grow because of gas diffusion. However, these results were repeatable for PSFs measured on different bubbles, in different gels, and at different times after vaporization, and all measurements were made well within the period monitored for bubble growth (Fig. 5) for which they were found to be stable. Thus, it is highly unlikely that all of the measurements were conducted on the same size bubble, or that the bubbles grew to be as large as the ball target within the time needed to make the measurement. A more likely explanation for the discrepancy between measurement and theory for the 7.5-MHz curves is that the transducer beamwidth was larger than the apparent target size. Fig. 10 shows the frequency spectra of the transducers as measured from a steel plate at the same focal depth as the point targets of interest. The bandwidth for the 3.5-MHz transducer is fairly narrow, whereas the 7.5-MHz transducer spectrum spans the lower frequencies. This was not taken into account for the ideal case and would contribute to a broadened PSF. Furthermore, the focusing of the transducers was accomplished by lenses rather than the piezo-ceramic elements themselves. This reduces surface displacement amplitude at the lens periphery, effectively narrowing the transmit aperture and resulting in a broader measured PSF. This effect should be more pronounced at higher frequencies because of larger signal attenuation.

A similar analysis was conducted for the M12 linear array operating at 11 MHz. The lateral, elevational, and axial PSF measurements over a bubble at a depth of 23.5 mm are shown in Fig. 11. As expected, the elevational profile is wider than the lateral and axial profiles.

For comparison with a simplified ideal PSF of the transducer over a point target, the theoretical elevational PSF for a perfect isotropic scatterer was calculated assuming a planar, rectangular aperture. Once again, the small angle approximation for the sine function was valid. Thus, the ideal pulse-echo PSF for a rectangular transducer is given by

$$\text{rect}_L(x) \xrightarrow{F} \left[L \text{sinc} \left\{ \frac{\pi L f}{c} \left(\frac{x}{\text{depth}} \right) \right\} \right]^2 \quad (4)$$

for the geometry shown in Fig. 12, where L is the transducer width and the other variables are as before.

Fig. 13 compares the measured PSF for a microbubble in the gel at depth of 31.1 mm to that of a perfect isotropic scatterer (4) at the same distance from the transducer. The ideal curve is narrower than the experimental, which may be due to transducer characteristics not accounted for in the calculations, such as the elevational focal length and the existence of an expanding aperture design. The array was a 1.25-dimensional array with a small number of rows in the elevational direction. Only the central rows are used for the short focal lengths and those rows have a mechanical length with shorter focal lengths than the other rows [32]. However, the full available aperture was assumed for both in the calculations. Fig. 13 shows good agreement, considering the expected narrower beam resulting from the transducer characteristics.

The good agreement of experimental and theoretical PSF profiles shown in Figs. 9 and 13 suggests that the microbubbles created in the acrylamide gel have the dynamic range to serve as point target scatterers and that the bubbles could be used with reasonable convenience to evaluate ultrasound system performance.

D. ADV Threshold in Gels of Varying Stiffness

It has been found that the vaporization threshold for ADV varies with gel stiffness as indicated by the results plotted in Fig. 14, where the vertical axis is the linearized backscatter amplitude from the bubbles and the horizontal axis is the pressure applied by the transducer. The threshold for ADV in the 15% and 10% gels is approximately 2 MPa (measured using methods described in [3]), whereas the threshold in the 6% gel is approximately 1.8 MPa ($\sim 100 \text{ W/cm}^2$). These are in the range of the threshold of droplet vaporization in water [16], which is shown by the gray box in the figure, although the stiffer gels are near the higher end of the range of water threshold values. The graph also shows that the ADV or large bubble creation efficiency was higher in the 6% gels than the 15% and 10%. This is indicated by the steep initial slope in the 6% curve, which levels off almost immediately after ADV first occurred, whereas the backscatter from the 15% and 10% gels increased gradually with the applied pressure. These results imply that ADV or large bubble creation may be somewhat more difficult in areas of dense tissue or confining walls such as the microcirculation. However, applying the necessary pressure amplitude for droplet transition in these situations without damaging overlying tissue is still probably not a problem, because pressure thresholds for the generation of notable bubbles in tissue *in vivo* occur at intensities greater than 3000 W/cm^2 [33], [34], or 30 times higher than the 1.8 MPa (100 W/cm^2) threshold (Fig. 14). In addition, thresholds for ADV in water with less-focused fields were even lower [3]. Therefore, one can expect to vaporize these droplets well before reaching the threshold for spontaneous cavitation in tissue.

IV. Discussion

A. Phase Aberration Correction and Simulation Imaging

If the measurement of a point spread function of a transducer to precisely simulate that transducer's response to a tissue imaging situation is desired, the full amplitude and phase as a function of frequency or full pulse response for the planned pulse must be measured as a function of position in space. Then, scattering from multiple elements in the tissue can be summed coherently with the appropriate phase and frequency response, assuming the frequency response of the surrogate point target is known. From Fig. 1, it appears that the region between $ka \sim 0.03$ to 1 for scattering from bubbles is quite appropriate in terms of its

frequency dependence. Note that acoustic pressure amplitudes must be kept relatively low to avoid nonlinear scattering by even the larger bubbles.

Gas bubbles a few micrometers in radius, or microbubbles, are known to be effective scatterers at ultrasound frequencies. What appear to be single, transpulmonary microbubble contrast agents can often be seen *in vivo* with ultrasound imaging systems in cases of modest attenuation of the sound by tissues between the bubble and transducer. This is made possible by the relatively large scattering from bubbles at resonance, as seen from the resonance in each curve of Fig. 1. For the lower diagnostic frequency range, this resonance usually occurs in bubbles that are several micrometers in diameter, by far the strongest individual scatterers that can pass through the pulmonary vasculature. Although such resonant scattering is strong, it is weaker than the linear scattering from much larger microbubbles, those greater than 30 μm in diameter, for example (see Fig. 1 and consider the unnormalized scattering cross-section). Thus, in addition to our direct experience, it can be reasoned that the backscatter amplitudes of bubbles created by ADV *in vivo* should generally be easily detected among the relatively strong contrast agent scatterers in cerebral tissues [35]. It is understood that part of the benefit to using resonant bubbles is the nonlinear scattering serving to distinguish bubble scattering from tissue. Although bubble nonlinearity provides increased signal compared with background, the acoustic response is also more complex and will have to be studied further to determine if such signals are suitable for PSF measurements.

Simulations conducted by modeling gas bubbles as non-rigid spheres show that for spherical bubbles of a reasonable range of diameters, the phase variation across a transducer array at typical diagnostic frequencies is within 20° of that from a perfect isotropic scatterer at the location of the bubble [24] as diagrammed in Fig. 15. Theoretically, this should hold for bubble diameters ranging from 30 to 120 μm for transducer frequencies lower than 8 MHz, and 30 to 70 μm for 8 to 15 MHz frequencies.

For use of microbubbles for aberration correction in flow imaging and therapy, the essentially spherical sound front radiating from a microbubble allows simple and accurate correction of phase and amplitude errors caused by aberrations in the tissue. Typical aberrations caused by tissue can be as large as 180° out of phase, so an error of 20° frequently represents a nearly 10-fold improvement. More importantly, for many types of targets, anatomic sites, and types of signal processing, there is an ambiguity in which the phase error, $\Delta\phi$, can exceed $\pm 180^\circ$; i.e., $\Delta\phi = N \times 180^\circ + \Delta\phi_0$, where $\Delta\phi_0$ is the observed phase shift and N is an unknown integer.

B. Bioeffects and Tissue Characterization Studies

ADV in viscoelastic materials such as acrylamide gel may provide insight on potential bioeffects of rapid bubble formation, which should be known before ADV can be approved for clinical diagnostic or therapeutic applications. For example, it was observed that some gels ruptured on the periphery of the gas bubbles after ADV. It is not certain whether rupture occurred at the moment of vaporization or during subsequent growth caused by gas diffusion. However the onset of elliptical bubble shapes occurred after a significant period of time, indicating that planar fracture probably occurred well after ADV and often after cooling and condensation of the bubble and revaporization of the droplet. If the appropriate material properties of the gel were quantified, observations of bubble size and gel failure could be utilized to develop and verify theories on the mechanical forces involved in the process of ADV and subsequent bubble expansion. With this information, one could predict the effects of droplet vaporization on the surrounding tissue, and thus help avoid potential consequences of ADV such as vessel wall damage, or suggest whether this process would be better suited to destroying tumor tissue locally rather than occluding flow. The resulting

theories could also lay the groundwork for use of ADV to measure mechanical properties of tissues, or to systematically study and optimize the acoustic exposure regimes leading to ADV in dense tissue or restrictive flow channels.

V. Summary

ADV of perfluorocarbon droplets embedded in acrylamide gels forms spherical gas bubbles, a phenomenon which could prove useful in applications such as evaluating ultrasound system performance or conducting bioeffect studies of ADV. The bubble diameter range varies with the gel stiffness, the entire distribution being 10 to 160 μm upon initial vaporization. Because the bubbles are small compared with the wavelengths of ultrasound diagnostic transducers, this size range makes them theoretically suitable for use as point target scatterers with phase errors of less than 20° . Upon cooling the gel, the bubbles condense into droplets and can be vaporized again later. This is a potential mechanism for gel phantom storage; however, the mean bubble diameter may increase upon subsequent vaporization.

As discussed in the introduction, initial theoretical studies [22] have shown that spherical bubbles can be suitable as point target scatterers. This paper provided initial verification of these results by comparing pulse-echo responses of single element transducers from microbubbles, tungsten carbide spheres, and flat plate reflectors. The FFT of the RF waveform from the solid spheres showed a frequency-dependent reverberation which was not present for the bubbles, indicating that the microbubbles were more ideal for use as spherical point targets than some of the best materials currently being used. Smaller tungsten carbide spheres could be employed in the future at the expense of considerable signal loss.

A potentially convenient method for measuring the PSF of single-element and diagnostic linear-array transducers employing ADV-created bubbles in polyacrylamide gels was illustrated. For the 3.5-MHz single-element transducer, the measured PSF was in good agreement with theory, and in the case of the 7.5-MHz transducer, the use of a microbubble target eliminated profile irregularities caused by reverberations when the metal sphere was used. The discrepancy between the measured and narrower theoretical PSF curves for the 7.5-MHz transducer most likely indicates that the beamwidth was wider than the target diameter at depth, a result of its broad frequency spectrum and associated differential attenuation from the focusing lens. Though the measured PSF for the diagnostic array transducer was wider than calculated, the curves agree rather well considering that the effective aperture on the commercial array was probably smaller than that used in the calculation, and a complex lens probably changed the focus.

Finally, there is a potential for bioeffect studies using viscoelastic materials such as polyacrylamide gels to determine the consequences of ADV. Initial studies show that in stiffer gels, more pressure was needed to vaporize droplets or produce large gas bubbles, and the conversion/creation efficiency was lower, indicating that this process in dense tissues or restrictive vasculature may be more difficult than in soft tissue or large vessels. In the future, it would be useful to quantify the stiffness of the gels, so that by observing bubble size or gel failure, knowledge could be gained regarding the stress that ADV-transitioned droplets exert on surrounding tissue.

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Biographies

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Oliver D. Kripfgans (S'00) was born in 1969 in Saarbrücken, Germany. He received his Diplom degree in physics from the University of Saarbrücken in 1996. During his graduate studies (1989–1996), he was a research assistant in the Department of Ultrasound at the Fraunhofer Institute for Biomedical Engineering, St. Ingbert, Germany. His work included industrial as well as biomedical ultrasound, mostly related to microbubble detection and characterization. Dr. Kripfgans's doctoral work (Ph.D. 2002) in the Applied Physics Program at the University of Michigan, Ann Arbor, included the interaction of microbubbles and microdroplets with ultrasound, therapeutic, and diagnostic ultrasound as well as acoustic material properties and acoustic sensors. Post-doctoral training included Doppler and 3-D ultrasound signal processing and associated pre-clinical research. Since 2003, Dr. Kripfgans has been a faculty member in the Department of Radiology at the University of Michigan, working on 2-D CMUT ultrasound arrays, 3-D B-mode imaging, 3-D color Doppler, and bubble generation and drug delivery via acoustic droplet vaporization. Dr. Kripfgans is a member of the Deutsche Physikalische Gesellschaft (DAGA), the Acoustical Society of America, and of the IEEE.

Jochen Krücker (S'01–M'04) received the Diplom degree in physics from the Rheinische Friedrich-Wilhelms-Universität in Bonn, Germany, in 1997 and the Ph.D. degree in applied physics from the University of Michigan in 2003. From 1995 to 1997, he worked as a research assistant for TIMUG e.V. in Bonn, developing a fiber-optic ultrasound hydrophone. In 1997 and 1998, he visited the ultrasound group of the Basic Radiological Sciences Division at the University of Michigan, where he worked toward his Ph.D. degree from 1998 to 2002. In 2003, he worked as a postdoctoral fellow in the Department of Radiology at the University of Michigan, conducting research in ultrasound image registration and breast imaging. He joined Philips Research North America in November 2003, working as an on-site clinical scientist at the NIH Clinical Center in Bethesda, MD. He has been leading collaborative research projects with Philips, NIH, and other partners in the area of interventional image guidance and procedure planning. His current research interests include multi-modality imaging and navigation technologies for minimally invasive liver and prostate procedures.

Paul L. Carson (M'74) received the B.S. degree from the Colorado College, Colorado Springs, CO, and the M.S. and Ph.D. degrees from the University of Arizona, Tucson, AZ, in 1969 and 1971, all in physics. From 1971 to 1981, he served in the Department of Radiology at the University of Colorado Medical Center, Denver. Since 1981, he has served as associate professor, professor, and BRS Collegiate Professor in the Department of Radiology, and as a professor of Biomedical Engineering and member of the Applied Physics faculty, University of Michigan, Ann Arbor, MI. He was Director of Basic Radiological Sciences in Radiology from 1981 to 2008. His responsibilities have been in research, clinical support, and teaching of radiological sciences. Research interests include medical ultrasound (quantitative imaging, functional imaging, equipment performance, safety, new or improved diagnostic and therapeutic instrumentation and applications including microbubble creation in body fluids *in vivo*), combined breast X-ray tomosynthesis/ultrasound, microwave, and photoacoustic tomography. Dr. Carson is a fellow, past vice president, and J. H. Holms Basic Science Pioneer Award Recipient of the American Institute of Ultrasound in Medicine and is a fellow, past president, and 2008 Coolidge Award Recipient of the American Association of Physicists in Medicine. He is a fellow of the Acoustical Society of America, the American College of Radiology, and the American Institute of Medical and Biomedical Engineering.

J. Brian Fowlkes (M'94) is a Professor of Radiology and Professor of Biomedical Engineering. He is currently directing and conducting research in medical ultrasound including the use of gas bubbles for diagnostic and therapeutic applications. His work includes studies of ultrasound contrast agents for monitoring tissue perfusion, acoustic droplet vaporization for bubble production in cancer therapy and phase aberration correction, effects of gas bubbles in high-intensity ultrasound and volume flow estimation for ultrasonic imaging. Dr. Fowlkes received his B.S. degree in physics from the University of Central Arkansas in 1983, and his M.S. and Ph.D. degrees from the University of Mississippi in 1986 and 1988, respectively, both in physics. Dr. Fowlkes is a fellow of the American Institute of Ultrasound in Medicine and has served as Secretary and as a member of its Board of Governors. He also received the AIUM Presidential Recognition Award for outstanding contributions and service to the expanding future of ultrasound in medicine. As a member of the Acoustical Society of America, Dr. Fowlkes has served on the Physical Acoustics Technical Committee and the Medical Acoustics and Bioresponse to Vibration Technical Committee. As a member of the IEEE, he has worked with the IEEE I&M Society Technical Committee on Imaging Systems. Dr. Fowlkes is a fellow of the American Institute of Medical and Biomedical Engineering and the Acoustical Society of America.

Fig. 1.

Normalized underwater scattering cross-sections for three sphere types. The rigid and non-rigid spheres are idealized models; the latter corresponds to the response of a bubble [25]. The tungsten carbide sphere (calculated using [26]) is an example of a nearly rigid sphere where the response closely follows that of the idealized model of the rigid sphere except for sharp resonances at higher ka values. In contrast, note the large range of ka ($ka > 0.1$) over which the bubble response is relatively flat or changing slowly and predictably, making it a good selection as a point target scatterer.

Fig. 2. Setup used to detect ADV threshold of droplets in acrylamide gels. Embedded droplets were transitioned with a 3.5-MHz single-element transducer, and monitored with a linear array at low acoustic power operating through the gel block from above.

Fig. 3.

Acrylamide gel blocks containing high concentrations of perfluorocarbon droplets. (a) Right side of gel exposed to a 10-MHz linear array, $MI = 1.2$, resulting in ADV and microbubble formation. Image taken 1 h post-ADV, size 4.6×3.75 mm. (b) After 3 d, gas diffusion caused by Laplace pressure and gel failure leads to large and non-circular bubbles, respectively. Oswald ripening was also observed, in which large bubbles increase in size at the expense of small bubbles shrinking. Image size 9.5×7.2 mm. (c) Cooled for 18 h at 5°C , all gas eventually diffuses from bubbles and gel failure is more clearly evident. Image size 9.5×7.2 mm.

Fig. 4.

Initial size distribution of bubbles in gels of varying stiffness is small compared with typical ultrasound acoustic wavelengths. The diameter range for 15 and 10% gels makes them suitable for phase aberration corrections. The numbers of bubbles sampled for 15, 10, and 6% gels were 100, 118, and 206, respectively.

Fig. 5. Bubble diameter versus time for droplets vaporized in 15% acrylamide gels. The bubbles remained spherical and small compared with wavelength over the eight-hour period monitored, showing suitability of ADV in gels as point targets.

Fig. 6.

Comparison of initial bubble size distributions to that for bubbles formed after the gel had been cooled to reform the droplets and the droplets were vaporized again. Results are shown for two different gels (10 and 6% formulations).

Fig. 7.

(a) RF waveform of backscatter from bubble and ball point targets using single-element transducers. (Top to bottom) Responses of bubble, ball, and plate, respectively. The left column is the response of 3.5-MHz transducer and the right is the response of 7.5-MHz transducer. Note the post-target vibrations in the ball's response for the 7.5-MHz transducer that were not apparent in the bubble's response. (b) Frequency spectra for (top) bubble and (bottom) ball point targets. Each response is normalized to the response from the plate and the 12-dB pulse-echo transducer transfer-function bandwidth is in bold. For both transducers used, the bottom figure clearly shows a sharp dip in backscatter at 6 MHz in the ball's response that is not apparent in the bubble response.

Fig. 8. Geometry of focused spherical transducer relative to point target and associate directivity function. Reprinted with permission from [30]. Copyright 1949, Acoustical Society of America.

Fig. 9.

Comparison of measured and theoretical lateral PSFs taken over microbubbles and tungsten carbide sphere for (a) 3.5-MHz and (b) 7.5-MHz spherically focused transducers.

Experiment and theory are in good agreement for the 3.5-MHz case, but not for the 7.5-MHz case.

Fig. 10. Comparison of (a) 3.5-MHz and (b) 7.5-MHz spherically focused transducer frequency spectra as measured from steel plate. The 7.5-MHz spectrum has broader bandwidth, which could contribute to the broader PSFs measured over the bubbles and tungsten carbide sphere.

Fig. 11.
Point spread function of M12 linear array of the GE Logiq 700 over microbubble at depth of 23.5 mm.

Fig. 12. Geometry for ideal PSF calculation for rectangular transducer over microbubble at depth.

Fig. 13.
Theoretical versus measured elevational PSF at depth 31.1 mm for rectangular transducer.
Variance in curves may be due to elevational focusing or existence of expanding aperture.

Fig. 14.

Echogenicity versus peak applied pressure reveals that the vaporization threshold for droplets varies with gel stiffness; increased echogenicity indicates increase in droplet transition. ADV in 6% gels occurs at ~1.8 MPa peak applied pressure and at ~2 MPa in 10% and 15% gels. The gray region demarks the threshold ($\pm$ one standard deviation) for droplet vaporization in water as previously determined [16].

Fig. 15. Phase front for a bubble scatterer compared with that of a spherical wave, showing the phase error $\Delta\phi$ at scattering angle θ . Reprinted with permission from [23].

TABLE I

Statistical Data for Bubble Diameters in 10 and 6% Gels Upon Initial Vaporization and Subsequent Cooling/Re-Vaporization.

	10% Gel		6% Gel	
	Initial	Re-vaporized	Initial	Re-vaporized
Mean (μm)	39.6	48.9	85.1	97.9
Minimum (μm)	25.5	31.9	35	76.5
Maximum (μm)	57.4	111.5	162.5	137
Standard deviation	5.5	13.8	22.6	10.7
Number sampled	118	170	206	137