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Transmitted Ultrasound Pressure Variation in Micro Blood Vessel Phantoms

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Abstract

Silica, cellulose, and polymethylmethacrylate tubes with inner diameters of ten to a few hundred microns are commonly used as blood vessel phantoms in *in vitro* studies of microbubble or nanodroplet behavior during insonation. However, a detailed investigation of the ultrasonic fields within these micro-tubes has not yet been performed. This technical note provides a theoretical analysis of the ultrasonic fields within micro-tubes. Numerical results show that for the same tube material, the interaction between the micro-tube and megaHertz-frequency ultrasound may vary drastically with incident frequency, tube diameter, and wall thickness. For 10 MHz ultrasonic insonation of a polymethylmethacrylate (PMMA) tube with an inner diameter of 195 μm and an outer diameter of 260 μm , the peak pressure within the tube can be up to 300% of incident pressure amplitude. However, using 1 MHz ultrasound and a silica tube with an inner diameter of 12 μm and an outer diameter of 50 μm , the peak pressure within the tube is only 12% of the incident pressure amplitude, and correspondingly the spatial-average-time-average intensity within the tube is only 1% of the incident intensity.

Keywords

ultrasound contrast agents; blood vessel phantoms; transmitted ultrasound pressure; pressure variation

Introduction

Preliminary investigations of ultrasound-mediated drug and gene delivery using microbubble contrast agents have shown great promise (Mitragotri 2005; Stride and Saffari 2003; Tartis et al. 2006; Unger et al. 2004). After arriving at target sites, the microbubbles can locally release a drug or gene. In these applications, insonation with a transmission frequency of 1 to 10 MHz is expected to deflect and fragment drug carriers such as perfluorocarbon microbubbles in small blood vessels (Bekeredjian et al. 2005; Stride and Saffari 2003). Due to the difficulties inherent in optically imaging *in vivo* vascular beds, micro-tubes made of silica (Sassaroli and Hynynen 2006), cellulose, polymethylmethacrylate (PMMA) (Caskey et al. 2006), or similar materials have been widely used as blood vessel phantoms for *in vitro* experiments. These micro-tubes typically have inner diameters ranging from ten to a few hundred microns (Caskey et al. 2006; Sassaroli and Hynynen 2006). In order to understand the behavior of drug carriers within

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micro-tubes exposed to ultrasound, it is necessary to know the ultrasonic fields within these micro-tubes. However, even the smallest ultrasonic hydrophones are on the order of 0.1 mm in diameter, which makes it impossible to spatially map the ultrasonic fields within these micro-tubes directly. The scattering of acoustic waves by a cylindrical tube and the radiation pressure on the tube have been studied extensively for five decades (Borovikov and Veksler 1985; Doolittle and Uberall 1966; Guo 1993; Hasegawa et al. 1993). Thompson et al have also studied intraluminal ultrasound intensity in millimeter-sized vessels (Thompson and Aldis 1996; Thompson et al. 2004a; Thompson et al. 2004b). Recently, theoretical and experimental analyses have indicated that micro-tube boundaries can substantially change bubble oscillation in small tubes (Caskey et al. 2006; Ory et al. 2000; Qin and Ferrara 2006; Qin et al. 2006; Sassaroli and Hynynen 2006; Yuan et al. 1999).

A theoretical analysis of the ultrasonic fields within elastic fluid-loaded cylindrical micro-tubes, as described here, will facilitate the investigation of the response of microbubbles, nanodroplets, and other particles within micro-tubes. Because the focal length of the ultrasound transducers used in most *in vitro* experiments is one or two orders of magnitude larger than the micro-tube diameter, in this technical note we have approximated the incident ultrasonic waves as harmonic plane waves. The tube is treated as an infinite elastic tube filled with and submerged in liquid, as is typical of the experimental conditions in many studies. In our analysis, the classical elastic wave equations in the liquid and tube were solved independently as in (Gaunard and Brill 1984). A numerical code was developed, numerical analysis was performed, and the significant results are summarized here.

Theoretical Analysis

Consider an isotropic elastic cylindrical tube of outer radius a and inner radius b that vibrates in response to an incident harmonic plane wave. Let the axis of the tube coincide with the z axis of a cylindrical coordinate system (r, θ, z) and let the incident wave propagate toward the tube in the $\theta=0$ direction. We assume that the tube has an infinite length and that the liquids inside (indexed by $j=3$) and outside (indexed by $j=1$) are inviscid with densities of ρ_3 and

ρ_1 , respectively. Solving the linear wave equation in the inviscid fluid ($\nabla^2 p_j = \frac{1}{c_j^2} \ddot{p}_j, j=1,3$), the well-known expressions for the total pressure outside the tube, p_1 , and acoustic pressure within the tube, p_3 , are:

$$\begin{aligned} p_1 &= p_0 e^{-i\omega t} \sum_{n=0}^{\infty} \varepsilon_n i^n \left[J_n(k_1 r) + a_n H_n^{(1)}(k_1 r) \right] \cos n\theta, \\ p_3 &= \frac{\rho_3}{\rho_1} p_0 e^{-i\omega t} \sum_{n=0}^{\infty} \varepsilon_n i^n g_n J_n(k_3 r) \cos n\theta, \end{aligned} \quad (1)$$

where ε_n is the Neumann symbol, a_n and g_n are constants, p_0 is the amplitude of incident pressure wave p_i , ω is the angular frequency, t is the time parameter, $i = \sqrt{-1}$, $k_j = \omega/c_j$ ($j=1$ or 3) is the wave number in the liquid, c_j ($j=1$ or 3) is the wave velocity in the liquid, and J_n and $H_n^{(1)}$ are the Bessel and Hankel functions of the first kind, respectively. The Lamé potential, Ψ , and components of the Lamé vector potential, $\mathbf{A}$, for the displacement vector, $\mathbf{u}$, in the tube, are:

$$\Psi = \frac{p_0 e^{-i\omega t}}{\rho_1 \omega^2} \sum_{n=0}^{\infty} \varepsilon_n i^n \left[b_n J_n(k_{2L} r) + c_n Y_n(k_{2L} r) \right] \cos n\theta, \quad (2)$$

$$\begin{aligned}
A_r &= 0, \quad A_\theta = 0, \\
A_z &= \frac{p_0 e^{-i\omega t}}{\rho_1 \omega^2} \sum_{n=0}^{\infty} \varepsilon_n i^n [d_n J_n(k_{2T} r) + e_n Y_n(k_{2T} r)] \sin n\theta,
\end{aligned} \tag{3}$$

where $\mathbf{u} = \nabla \Psi + \nabla \times \mathbf{A}$, b_n , c_n , d_n and e_n are constants, Y_n is the Bessel function of the second kind, $k_{2L} = \omega/c_L$, $k_{2T} = \omega/c_T$ are the wave numbers in the tube, and c_L and c_T are the longitudinal and shear wave velocities in the tube, respectively. The six sets of constants a_n , b_n , c_n , d_n , e_n and g_n are determined by assuming continuity of radial displacement, u_r , and stress, τ_{rr} , $\tau_{r\theta}$, at the liquid-tube interfaces:

$$\begin{aligned}
\text{At } r=a, \\
\tau_{rr}^{(2)} &= -p_1, u_r^{(1)} = u_r^{(2)}, \tau_{r\theta}^{(2)} = 0, \\
\text{At } r=b, \\
\tau_{rr}^{(2)} &= -p_3, u_r^{(2)} = u_r^{(3)}, \tau_{r\theta}^{(2)} = 0.
\end{aligned} \tag{4}$$

The absorption of the tube material was taken into account by the standard method of introducing complex wave numbers, i.e. $\bar{k}_{2L} = k_{2L} (1 + i\beta_L)$, $\bar{k}_{2T} = k_{2T} (1 + i\beta_T)$ as shown in (Vogt et al. 1975). Referring to the measured absorption coefficients $\alpha_L = 0.19$ dB (longitudinal) and $\alpha_T = 0.29$ dB (shear) in (Hartmann and Jarzynski 1972) for PMMA tubes, we obtained $\beta_L = 0.0035$ and $\beta_T = 0.0053$ (Schuetz and Neubauer 1977). The absorption of the silica tubes was neglected in the calculation.

A MATLAB program was developed to calculate the pressure field and its accuracy was verified by reproducing a previously-published scattered echo, Fig. 11 in (Gaunard and Brill 1984), and by comparing its output with results calculated by the commercial simulation software package COMSOL Multiphysics 3.3a (COMSOL AB, Palo Alto, CA, USA), as detailed in the supplement.

Results

The ultrasonic fields in PMMA and silica capillary tubes filled with and submerged in water were examined for incident waves with center frequencies of 10 MHz and 1 MHz, using the parameters listed in Table 1. The distribution of ultrasonic pressure amplitude inside and outside the micro-tubes (Fig. 1) strongly depends on the incident ultrasound frequency and tube geometry, and varies spatially across the tube. In order to calculate the spatial average of the acoustic intensity in the tube, we used a dimensionless parameter

$$\tilde{I}_{\text{SATA}} = \frac{\int_0^{\tau_v} dt \int_A |p_3|^2 dA}{\int_0^{\tau_v} dt \int_A |p_i|^2 dA} \quad \text{which is the spatial-average-time-average intensity normalized by that of the incident wave, where } \tau_v \text{ is the incident wave period and } A \text{ is the cross-sectional area of the tube.}$$

For a 10 MHz ultrasound wave incident on the PMMA tubes examined here, there is a strong interaction between the water and the tube (Figure 1 a, b). For the larger PMMA tube ($D_i=195 \mu\text{m}$, $D_o=260 \mu\text{m}$), the maximum normalized amplitude of the spatial peak pressure within the micro-tube (throughout this paper, “normalized amplitude” refers to the pressure amplitude normalized by the incident pressure amplitude) is 3.09, while the minimum normalized pressure amplitude is 0.01 and $\tilde{I}_{\text{SATA}}$ in the tube is 1.26 (Fig. 1a and Table 2). For the same wave incident on a smaller PMMA tube ($D_i=12 \mu\text{m}$ and $D_o=50 \mu\text{m}$), the maximum and minimum normalized pressure amplitudes are 0.81 and 0.42, respectively and the $\tilde{I}_{\text{SATA}}$ is 0.41 (Fig. 1b and Table 2). For 1 MHz ultrasound incident on the same PMMA tubes, there is only weak interaction between water and the tube. For the larger tube, the maximum and minimum normalized pressure amplitudes are 0.88 and 0.78, respectively, and for the smaller tube the

maximum and minimum normalized pressure amplitudes are 0.75 and 0.74, respectively (Fig. 1c, d, Table 2). The corresponding $\bar{I}_{\text{SATA}}$ for PMMA tubing under 1 MHz insonation is 0.71 for the larger tube, and is 0.55 for smaller tube (Table 2)

The ultrasonic fields in silica tubes were also examined for incident waves with center frequencies of 10 MHz and 1 MHz (Fig. 2). During exposure to 10 MHz ultrasound, the maximum and minimum normalized pressure amplitudes in the larger silica tube are 1.85 and 0.00, respectively; thus the field variations are less than those in the PMMA tubing. The corresponding $\bar{I}_{\text{SATA}}$ in this tube is 0.72 (Fig. 2a, Table 2). For the other three cases examined (center frequency $f = 10$ MHz, $D_i = 12$ μm , $D_o = 50$ μm ; $f = 1$ MHz, $D_i = 195$ μm , $D_o = 260$ μm ; $f = 1$ MHz, $D_i = 12$ μm , $D_o = 50$ μm , Fig. 2b, c, and d), the $\bar{I}_{\text{SATA}}$ within the tubing is below 0.1 in each case (Fig. 2b, c, d and Table 2). Thus, the acoustic field within the tube is substantially reduced in intensity compared with the exterior field and as compared with PMMA tubing under comparable conditions.

The spectrum of the maximum normalized spatial peak pressure amplitude within PMMA and silica tubes with a ratio of inner to outer radius $b/a = 0.25$ and 0.75 , respectively, which are typical thin and thick tubing, is plotted in Fig. 3. The spatial pressure field within the tubing was evaluated at the resonant peaks for PMMA tubes, $k_1 a = 2.13$ and 7.81 (Fig. 4). When the system oscillates at resonance, the peak pressure within the tubing can be five times that of the incident wave due to standing wave patterns.

Discussion and Conclusion

Previously, the bulk acoustic impedance has been used as the primary criterion for selection of the tube material for *in vitro* studies of the acoustic response of microbubbles and nanodroplets in micro-tubes. This study considers 1 and 10 MHz insonation of tubes with inner diameters of 12 and 195 microns. We demonstrate that even for the same tube material, the interaction between the micro-tube and megaHertz-frequency ultrasound may vary drastically: the interaction of the ultrasound and the tube produces spatially-variant fields within the tube that can be much higher or lower in intensity than the incident field. Along with the acoustic impedance, attention should be paid to the applied ultrasound frequency, the tube diameter, and the relative wall thickness of the tube. PMMA tubing appears to be a reasonable choice for studies of oscillation within small vessels at 1 MHz, since its effect on the inner field is smaller than that of comparable silica tubing. For 1 MHz insonation, the ultrasonic field within PMMA tubing is homogeneous and the time-averaged field intensity is 55-71% smaller than that of the exterior field. In this scenario, the decrease in acoustic intensity within the tube results primarily from absorption by the tube material. At 10 MHz, the interaction between the acoustic field and the PMMA tube is substantial, producing a spatially-variant field and a greater effect on the time-averaged field: the time-averaged acoustic intensity can range between 41 and 126% of the exterior field, depending on the tube geometry. For silica tubing and the parameters considered here, the time-averaged inner field intensity can be as small as 1% of the exterior field intensity. In this case, the decrease in acoustic intensity within the tube is primarily due to tube barrier effects. In contrast with the negligible interaction between blood vessels and ultrasound, we find that the interaction of ultrasound and blood vessel phantoms is likely to be substantial. As demonstrated in this technical note, the interaction between micro-tubes and ultrasound increases with higher acoustic frequencies and larger tubes. With increasing interest in using high-frequency ultrasound in diagnostic and therapeutic applications, the interaction between ultrasound and tubing should be considered in the design and analysis of experiments. This study is based on the time-harmonic theory for analyzing the acoustic interaction between the liquid and the micro-tube, which is a good approximation for analyzing the effects of the long pulses used in ultrasound therapy. Waveform

decomposition could be used to extend this harmonic analysis in order to predict the effect of short imaging pulses.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1(a)

Figure 1.

The normalized amplitude of ultrasonic pressure in PMMA tubes ($|p_3|/|p_i|$). (a) 10 MHz incident ultrasound, $D_i = 195 \mu\text{m}$, $D_o = 260 \mu\text{m}$. (b) 10 MHz incident ultrasound, $D_i = 12 \mu\text{m}$, $D_o = 50 \mu\text{m}$. (c) 1 MHz incident ultrasound, $D_i = 195 \mu\text{m}$, $D_o = 260 \mu\text{m}$. (d) 1 MHz incident ultrasound, $D_i = 12 \mu\text{m}$, $D_o = 50 \mu\text{m}$.

Fig. 2(a)

Figure 2.

The normalized amplitude of ultrasonic pressure in silica tubes ($|p_3|/|p_i|$). (a) 10 MHz incident ultrasound, $D_i = 195 \mu\text{m}$, $D_o = 260 \mu\text{m}$. (b) 10 MHz incident ultrasound, $D_i = 12 \mu\text{m}$, $D_o = 50 \mu\text{m}$. (c) 1 MHz incident ultrasound, $D_i = 195 \mu\text{m}$, $D_o = 260 \mu\text{m}$. (d) 1 MHz incident ultrasound, $D_i = 12 \mu\text{m}$, $D_o = 50 \mu\text{m}$.

Fig. 3 (a)

Figure 3.

The maximum normalized amplitude of spatial peak pressure within PMMA and silica tubes as a function of wave number, **Error! Objects cannot be created from editing field codes..** (a) PMMA tube with a ratio of inner to outer radius (b/a) of 0.75. (b) PMMA tube with $b/a=0.25$. The values (**Error! Objects cannot be created from editing field codes.**) for PMMA with absorption at resonant peaks are listed. (c) Silica tube with $b/a=0.75$. (d) Silica tube with $b/a=0.25$.

Fig. 4(a)

Figure 4.

The normalized amplitude of ultrasonic pressure in PMMA tubes ($|p_3|/|p_i|$). (a) $b/a=0.25$,
Error! Objects cannot be created from editing field codes.; (a) $b/a=0.25$, **Error! Objects cannot be created from editing field codes..**

Table 1

Material parameters

Material	Density (kg/m ³)	Longitudinal wave velocity c_L (m/s)	Shear wave velocity c_T (m/s)	Normalized longitudinal absorption β_L	Normalized shear absorption β_T	Acoustic impedance (kg/m ² s)
Water	1000	1500	-	-	-	1.5×10^6
PMMA	1150	2700	1100	0.0035	0.0053	3.1×10^6
Silica	2200	5960	3760	0	0	1.3×10^7

Table 2

Parameters and results

f (MHz)	10	10	1	1
D_o (μm)	260	50	260	50
D_i (μm)	195	12	195	12
$k_1 a$	5.45	1.05	0.55	0.11
D_o/λ	1.73	0.33	0.17	0.03
$(D_o - D_i)/2\lambda$	0.22	0.13	0.02	0.01
$P_{s \text{ max}}$ (PMMA tube)	3.09	0.81	0.88	0.75
$P_{s \text{ min}}$ (PMMA tube)	0.01	0.42	0.78	0.74
$\tilde{I}_{\text{SATA}}$ (PMMA tube)	1.26	0.41	0.71	0.55
$P_{s \text{ max}}$ (silica tube)	1.85	0.18	0.48	0.12
$P_{s \text{ min}}$ (silica tube)	0.00	0.07	0.05	0.12
$\tilde{I}_{\text{SATA}}$ (silica tube)	0.72	0.01	0.07	0.01

Note: $P_{s \text{ max}}$, $P_{s \text{ min}}$ are the maximum and minimum normalized amplitudes of spatial peak pressure within the tube, respectively.