Shear strain from irrotational tissue displacements near bubbles

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Particle displacements can be much greater near bubbles than they would be in a homogeneous liquid or tissue when exposed to an acoustic wave. In a plane wave, shear and bulk strains are of the same order of magnitude. In contrast, for a bubble oscillating close to its resonance frequency, the shear strain in the medium near the bubble is roughly four orders of magnitude greater than the bulk strain. This can lead to shear strains of a few percent even with acoustic excitation pressures far below the pressure thresholds required to cause inertial cavitation. High shear strains near oscillating bubbles could potentially be the cause of bioeffects. After acoustic exposures at audio frequencies, hemorrhages in tissues as diverse as lung, liver, and kidney have been observed at shear strains on the order of 1%. © 2011 Acoustical Society of America. [DOI: 10.1121/1.3626122]

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I. INTRODUCTION

Bubbles are involved in most of the nonthermal bioeffects that have been confirmed for ultrasound exposure, and a great deal of research has been devoted to the dynamics of bubbles. Somewhat less effort has been given to studies of the strain produced in the tissue by these bubbles. We may assume that strain or its time derivatives, as descriptors of the physical state of the tissue, are more direct predictors of biological effects than the forces that produce them.

In an effort to understand the mechanisms of ultrasound bioeffects, this paper presents a simplified model of the strains in the vicinity of an oscillating bubble. Small amplitude deformations are assumed and only irrotational, longitudinal oscillations are considered. In the realistic, general case for a bubble in tissue, it is necessary to consider both irrotational and rotational waves. However, even for purely spherical waves, where the rotational component of the displacement is zero, shear strains near the source are much larger than the dilatational strains. Of particular interest for oscillating bubbles is the fact that, in contrast with plane waves, the shear or deformational strains near small sources of spherically diverging waves ($kr \ll 1$, with k being the propagation constant for irrotational waves and r the radial position) may be orders of magnitude greater than the local bulk strain.

This paper presents estimates of strains in biological tissues near an oscillating bubble or within a model lung. The general equations for the strains due to spherically diverging waves are first summarized. Then predictions of strains near an oscillating bubble or lung when excited at resonance are

presented. Implications for ultrasound thresholds that produce biological tissue damage are then discussed.

II. MODEL

For the present discussion, the bubble is considered the source of spherical waves and the driving field is ignored. For irrotational waves [e.g., [Graff, 1975](#), Eq. (5.1.15)],

$$(\lambda + 2\mu)\nabla^2\Phi = \rho \frac{\partial^2\Phi}{\partial t^2}, \quad (1)$$

where λ and μ are the Lamé constants, ρ is the density of the medium containing the bubble, and $\vec{\xi} = \nabla\Phi$ is the particle displacement. For tissue, loss is important. Complex, elastic constants can be used to model viscoelastic behavior. In fact, over much of the frequency range of interest to biomedical ultrasound, the shear modulus of soft tissues is dominated by shear viscosity. That is not true for the bulk modulus or λ and the real part of propagation constant for irrotational waves is much greater than its imaginary part over most of the range of frequency and tissue properties of interest in this discussion.

In spherical coordinates

$$\frac{\partial^2\Phi}{\partial r^2} + \frac{2}{r} \frac{\partial\Phi}{\partial r} = \frac{1}{c_p^2} \frac{\partial^2\Phi}{\partial t^2}, \quad (2)$$

where $c_p^2 = (\lambda + 2\mu)/\rho$. For harmonic fields ($\Phi(r, t) = \Phi(r)e^{j\omega t}$),

$$\frac{\partial^2\Phi(r)}{\partial r^2} + \frac{2}{r} \frac{\partial\Phi(r)}{\partial r} + k^2\Phi(r) = 0, \quad (3)$$

where $k = \omega/c_p$. The solution to this equation for waves propagating radially outward is

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$$\Phi(r) = A \frac{e^{-jkr}}{kr}. \quad (4)$$

Therefore, the displacement vector is

$$\vec{\xi}(r) = \frac{d\Phi}{dr} \vec{e}_r = -A \frac{e^{-jkr}}{kr^2} (1 + jkr) \vec{e}_r \quad (5)$$

and the components of the strain are

$$\begin{aligned} \varepsilon_{rr} &= \frac{\partial \xi_r}{\partial r} = A \frac{e^{-jkr}}{kr^3} (2 + 2jkr - k^2 r^2), \\ \varepsilon_{\theta\theta} &= \frac{\xi_r}{r} = -A \frac{e^{-jkr}}{kr^3} (1 + jkr), \\ \varepsilon_{\phi\phi} &= \frac{\xi_r}{r} = -A \frac{e^{-jkr}}{kr^3} (1 + jkr). \end{aligned} \quad (6)$$

The dilatational (bulk) strain:

$$\begin{aligned} \frac{\Delta V}{V} &= \nabla \cdot \vec{\xi} = \varepsilon_{rr} + \varepsilon_{\theta\theta} + \varepsilon_{\phi\phi} \\ &= -A \frac{e^{-jkr}}{kr^3} k^2 r^2 = -A \frac{ke^{-jkr}}{r}, \end{aligned} \quad (7)$$

is contained in the last term of the first of Eq. (6). The other terms in Eq. (6) describe the shear/deformation inherent in the spherical wave.

For distances from the source much greater than a wavelength ($kr \gg 1$), the sound field takes on the characteristics of a classical plane wave. In this limit, the radial strain approaches the dilatational strain and the lateral strains become vanishingly small as $1/r^2$, that is,

$$\varepsilon_{rr} \rightarrow -A \frac{ke^{-jkr}}{r} = \frac{\Delta V}{V}, \quad \varepsilon_{\theta\theta} = \varepsilon_{\phi\phi} \rightarrow -jA \frac{e^{-jkr}}{r^2}. \quad (8)$$

At the opposite limit, near the source, i.e., when $kr \ll 1$,

$$\varepsilon_{rr} \rightarrow -\frac{2}{k^2 r^2} \frac{\Delta V}{V}, \quad \varepsilon_{\theta\theta} = \varepsilon_{\phi\phi} \rightarrow \frac{1}{k^2 r^2} \frac{\Delta V}{V} \quad (9)$$

and the strain tensor $\vec{S}$ approaches

$$\vec{S} \rightarrow -\frac{1}{k^2 r^2} \frac{\Delta V}{V} \begin{bmatrix} 2 & 0 & 0 \\ 0 & -1 & 0 \\ 0 & 0 & -1 \end{bmatrix}. \quad (10)$$

A useful approximation at $kr \ll 1$ is

$$\varepsilon_{rr} \sim -\frac{2\xi(r)}{r}, \quad \varepsilon_{\theta\theta} = \varepsilon_{\phi\phi} \sim \frac{\xi(r)}{r}. \quad (11)$$

Near the bubble, shear strains associated with compressional waves may be orders of magnitude greater than the bulk strain. There, the individual diagonal elements of the strain tensor are very much greater than its trace. To a rough approximation, if a bubble increases in radius by 1%, each tissue element near it is thinned by 2% and stretched laterally by a factor of 1%. These shear strains are simply a property of the irrotational wave radiated by the bubble.

III. BUBBLES AT RESONANCE

As resonant systems, bubbles have a high Q . It is reasonable, therefore, to focus attention on resonant bubbles as sources of strain in adjacent tissues. The linear analysis presented here only suggests the nature of the strains that tissues experience when nearby bubble amplitudes approach the inertial cavitation threshold.

For small amplitudes of oscillation, the Minnaert (1933) approximation for the relation between resonance frequency f_0 of a bubble and its equilibrium radius a ($f_0 a \sim 3 \text{ m s}^{-1}$), tells us that $ka \sim 0.01$ for a bubble oscillating at its resonance frequency. This tells us the order of magnitude of the parameter kr that is of interest in the above discussion of the strain in irrotational, spherical, acoustic fields and says that Eqs. (8)–(10) are reasonable approximations over most of the frequency range of interest for bioeffects of bubbles.

This criterion is useful even for bubbles in most soft tissues. The resonance frequency of a bubble in an elastic medium under linear conditions is given by (Emelianov *et al.*, 2005)

$$\omega_0^2 = \omega_g^2 + \omega_e^2, \quad (12)$$

where $\omega_g^2 = 3(\rho_g/\rho)(c_g^2/a^2) = 3(\kappa_g/\rho a^2)$ is the Minnaert frequency, the resonance frequency for a gas bubble in an incompressible fluid (κ_g being bulk stiffness of the gas), and $\omega_e^2 = 4(\mu/\rho a^2)$ is the resonance frequency of an empty cavity in an incompressible, elastic medium with shear stiffness μ . For the present purposes, incompressible means that for tissue $\kappa_t \sim \lambda_t \gg \mu_t$. At resonance, therefore,

$$k^2 a^2 = \frac{\omega_0^2}{c_t^2} a^2 = \frac{1}{\rho c_t^2} (3\kappa_g + 4\mu). \quad (13)$$

The shear modulus of most soft tissues is smaller than the $\sim 100 \text{ kPa}$ bulk modulus of air. At high frequencies, the contribution of tissue shear viscosity should not be ignored, but it is clear that the Minnaert equation gives us the order of magnitude for ka that is useful for a wide range of applications.

At resonance, the diagonal components of the strain in the medium near a bubble are on the order of 10 000 times greater than their sum. That is to say that the shear strain in the medium just outside the bubble is 10 000 times greater than the bulk strain.

At amplitudes approaching the inertial cavitation threshold, strains are so large that they lose meaning in the sense of their small amplitude definitions. Large strains have been discussed in earlier reports using nonlinear models for bubble behavior. Gracewski *et al.* (2005), using the Raleigh–Plesset model predicted a strain in water of 0.1 at a distance of $4.5 \mu\text{m}$ from a $1.5 \mu\text{m}$ bubble oscillating in a 0.2 MPa, 1 MHz acoustic field. Church and Yang (2005) modified the Keller–Miksis equation for nonlinear bubble behavior to include the viscoelastic properties of the medium. They compute strains on the order of 0.3 in materials with shear stiffness of 1.5 MPa surrounding similar bubbles exposed to 1 MPa, 1 MHz acoustic fields.

While the models that were used to predict these large strains are greatly simplified, the implication is that shear strains near an oscillating gas body are orders of magnitude larger than strains due to the acoustic waves used to excite the gas body. Therefore, the use of microbubbles as contrast agents results in a qualitative increase in susceptibility of tissue to microhemorrhage. It is difficult at the scale of microbubbles to determine with precision the magnitudes of the tissue shear strains that lead to rupture of blood vessels. The experimental task is somewhat simpler on the scale of the mouse lung. Following are a few general observations concerning bioeffects thresholds for some specific tissues near oscillating gas cavities.

IV. BIOLOGICAL IMPLICATIONS

A. Lung near its resonance frequency

From the point of view of biological effects, what happens inside oscillating air bubbles is of little concern. That is not true for the lungs of divers.

The observed resonance frequencies of adult mouse lung have a mean of 330 Hz. In spite of the fact that lung is an order of magnitude stiffer than air and nearly three orders of magnitude more dense, the [Minnaert \(1933\)](#) relation gives a surprisingly good prediction for lung's resonance frequency.

The velocity of sound in inflated lung is about 1/30 that of water ([Dunn, 1986](#)). Thus, within lung at its resonance frequency, $k_{\text{lung}}a \sim 0.3$ and the wavelength of sound in the lung at its resonance frequency is approximately $20a$. In other words, at any instant, the pressure within the lung is approximately uniform.

The lung contains many individual gas pockets within a framework of solid tissue. The microscopic alveoli expand and contract with changing pressure and in the process produce a radial stretching of the framework tissue. Thus, on a macroscopic scale, the lung might be modeled as a sphere, in which the displacement of its tissue is directly proportional to the radial position

$$\zeta_r^l(r) = \epsilon_{rr}^l r. \quad (14)$$

The proportionality constant is the radial strain of the lung tissue, which is uniform throughout. Furthermore, the radial displacement must be continuous across the lung's bounding surface

$$\zeta_r^l(a) = \epsilon_{rr}^l a = \zeta_r(a). \quad (15)$$

Near resonance,

$$\epsilon_{rr}^l = \frac{\zeta_r(a)}{a} = -A \frac{e^{-jkr}}{ka^3} = \frac{1}{k^2 a^2} \frac{\Delta V}{V} \Big|_{r=a}. \quad (16)$$

From Eqs. (9) and (16)

$$\epsilon_{rr}(a) = -2\epsilon_{rr}^l(a)$$

and

$$\epsilon_{\theta\theta}(a) = \epsilon_{\phi\phi}(a) = \epsilon_{rr}^l(a).$$

The deformation inside the sphere is isotropic, so

$$\epsilon_{rr}^l = \epsilon_{\theta\theta}^l = \epsilon_{\phi\phi}^l = \frac{1}{k^2 a^2} \frac{\Delta V}{V} \Big|_{r=a}. \quad (17)$$

Inside the sphere, the lateral strains are equal to and in phase with the radial strain. In other words, for our idealized, homogeneous, spherical lung the internal strains at a macroscopic level are dilatational and uniform throughout and therefore, the shear strains are zero. The bulk dilatation of the lung

$$\frac{\Delta V^l}{V^l} = \frac{3}{k^2 a^2} \frac{\Delta V}{V} \Big|_{r=a} \quad (18)$$

is very much greater than the bulk dilatation of the surrounding solid tissue.

Even though the radial and lateral strains in the tissues outside the lung are relatively large, they are out of phase. Rather than being spatially uniform, strains external to the lung are proportional to the inverse cube of the distance from the sphere [Eq. (6)].

The conclusion that shear strains are absent within the lung is the result of the assumption that the medium is homogeneous. At a microscopic level, of course, the lung is far from homogeneous. In fact, the macroscopic elasticity of the lung comes from very small air pockets contained within alveolar tissue. On average, $\Delta V/V$ for the alveolus is of the same order of magnitude as $\Delta V/V$ for the whole lung. The model for the whole lung can thus be applied to the alveolus. The assumption that $kr \ll 1$ is still valid, of course. The air itself has only bulk strain but the bounding tissue has shear strain approximately equal to the strains at the surface of the whole lung. With this microscopic view, we find large shear strains more or less uniformly distributed throughout the tissues of the lung.

Of course, modeling the lung as a sphere is a gross simplification. Far more sophisticated methods are required to determine the actual distribution of strain. However, in view of the fact that, at resonance, the acoustic wavelength within the lung is an order of magnitude larger than the lung, it may be that the simple model described above contains an element of truth about the behavior of the physical lung.

Direct measurements of the radial motion of the lung ([McAleavey et al., 1999](#)) permit us to express the threshold for hemorrhage in mouse lung in terms of shear strain— ~ 0.01 at 330 Hz. Expressed in terms of acoustic pressure, the threshold is strongly frequency dependent near lung resonance ([Dalecki et al., 1999](#); [Dalecki, 2008](#)) This merely emphasizes the fact that acoustic pressure per se is a poor predictor of biological effects. That strong frequency dependence is largely removed when the threshold is expressed in terms of shear strain.

B. Liver hemorrhage

Liver is effectively in direct contact with the outer surface of the lung. Therefore, according the model just

described, the surface of the liver is subjected to shear strains of the same order of magnitude as the lung parenchyma. In spite of the qualitative differences in the microscopic structure of the two organs, the observed threshold for liver hemorrhage in mice is not statistically significantly higher than for lung (Dalecki *et al.*, 1999). At threshold, liver damage is superficial as would be anticipated by the rapid decline in shear strain with distance from a spherical source.

C. The mouse kidney paradox

The failure of acoustic pressure to serve as a predictor of hemorrhage is illustrated again by observations of the effects of shock waves on mouse kidney. Consider the following: (1) Exposure of mouse kidney to 200, 40 MPa, piezoelectric lithotripter shock waves caused only barely detectable superficial petechiae (Raeman *et al.*, 1994). (2) Exposure of mouse kidney to ten, spherically diverging, 3 MPa shocks from a spark-generated bubble produced significant hemorrhage throughout both cortex and medulla (Mayer *et al.*, 1990). In each example, peak positive pressures are cited. The first study had both positive and negative phases. In the second, the negative pressure was too small to be measured. The apparent discrepancy between the piezoelectric and spark generated shock waves cannot be explained by the frequency distributions of the pressure fields (Raeman *et al.*, 1994). Heating was not a significant factor in either of the studies but clearly not in the second study, which showed the greatest biological effect. Any of the acoustic pressures were great enough to produce cavitation in water. Indeed, cavitation may have been responsible for the minor surface damage observed after exposure to the 40 MPa fields of the piezoelectric lithotripter. However, failure of the piezoelectric lithotripter to produce internal damage in the kidney suggests that the normal organ contains negligibly few cavitation nuclei.

Instead of focusing on the acoustic fields, let us investigate what the exposures did to the tissue, i.e., the tissue strain produced. Exposure 1 involved waves that were effectively plane. Two hundred of these 40 MPa shockwaves caused no internal damage to the mouse kidney. In exposure 2, amplitude of the shockwave at the kidney was determined by distance of the spark source from the kidney. At threshold for hemorrhage, the spark was approximately 3 cm from the kidney. Temporal characteristics of the piezoelectric and spark-generated shocks were very similar. Considering the high frequencies involved in the shock waves, $kr \gg 1$ at the kidney even for the spark source. Thus, as discussed above, strains in the kidney tissue produced directly by either of the shockwaves were very small. It seems unlikely, therefore, that the damage seen in experiment 2 was caused directly by the shock wave.

In addition to producing an acoustic shock wave, however, the spark source generated a bubble, which increased in radius to approximately 5 mm at 0.5 ms and collapsed at 1 ms (Campbell *et al.*, 1991). For a previously homogeneous, incompressible medium to accommodate a spherical cavity with radius r_0 , the medium at a distance r from the center of the cavity must be displaced approximately

$$\xi \sim \frac{1}{3} \frac{r_0^3}{r^2}. \quad (19)$$

At that position the radial shear strain is

$$\epsilon_{rr} = \frac{\partial \xi}{\partial r} \sim -\frac{2}{3} \frac{r_0^3}{r^3}. \quad (20)$$

Recall that at threshold for kidney hemorrhage in experiment 2, $r_0 = 0.5$ cm and $r = 3$ cm, giving a radial strain at the surface of the kidney of approximately 0.003. Analysis of this actual physical system is beyond this discussion. However, radial displacement is continuous across the water-tissue boundary and if we assume that the shear stiffness of the tissue does not significantly modify the local displacement, this number gives us an order-of-magnitude estimate of the shear strain experienced by the mouse kidney at threshold for hemorrhage. Thus, whereas the shock wave passes through the kidney in a few microseconds and produces little shear strain, the strain caused by expansion of the gas bubble is on the order of the threshold strains associated with liver and lung hemorrhage and lasts roughly 1 ms.

In the examples above, the effective frequencies for shear strain are on the order of hundreds of Hz. Shear strain per se clearly is not the critical parameter responsible for tissue damage because strains much greater than those discussed above occur at lower frequencies during normal activities. Elucidation of the detailed physical mechanisms of tissue damage will require further investigation including studies of the influence of the strain rate in biological effects.

D. Horn transducers and vibrating probes

In the general discussion and specific examples given above, the common factor is the strain associated with radial, longitudinal (irrotational) displacements produced by a source somewhat smaller than a wavelength. In contrast with the simple model of a radially oscillating bubble in an infinite medium, vibrating probes and certain horn transducers produce radial and transverse displacements when coupled directly to elastic media such as tissue. As in the above examples, these longitudinal displacements may lead to shear strains near the source. Analytical treatment of realistic applications is difficult. However, one of the best quantitative discussions of this general phenomenon is the paper on translational motion of a sphere in a viscoelastic medium by Hans Oestreicher (1951).

V. SUMMARY

Traditionally, the bioeffects of ultrasound have been classified either thermal or nonthermal. In the latter case, most potentially harmful effects have been associated with the presence of gas bodies. With the exception of lung and the intestine, naturally occurring gas bodies in mammalian tissues are rare. However, with the advent of microbubbles as contrast agents, greater concern for adverse effects is now warranted. In response, a great deal of research has been devoted to the dynamics of gas bodies in acoustic fields.

Safety guidelines have been expressed in terms of the parameters of frequency and pressure of acoustic exposure. The guidelines have been useful because they are expressed in quantities that are under control of the users of diagnostic ultrasound and because the very existence of guidelines alerts those professionals to the possibility of adverse bioeffects. Knowing the exposure conditions, however, tells us little about how the exposures produce damage. For that purpose, strain and its time derivatives promises to provide a useful parameter.

Tissue strain may be a step closer to a physical quantity that relates directly to biological effects. The little evidence that is available at the present time is consistent with the hypothesis that, at frequencies of a few hundred hertz, shear strains on the order of one percent cause hemorrhage in tissues as different as lung, liver and kidney. Although this review has been framed in terms of the strains near bubbles, it is reasonably clear that inertial cavitation that we associate with microbubble contrast agents is not involved in any of these examples. Rather it appears that the tissue damage is caused directly by the mechanical deformation of the tissue. Furthermore, shear strains of this magnitude are created near spherical sources such as bubbles even by irrotational particle displacements when those bubbles are exposed to acoustic fields far lower than the thresholds for acoustic cavitation. Undoubtedly, further testing of this hypothesis will reveal much greater complexity in the physical mechanisms.

Ultrasound's use as a therapeutic tool predates its diagnostic applications. In the early years, it was embraced by physical medicine for its superior ability to produce localized deep heating in tissues (Schwan and Carstensen, 1952). Like most therapies, it is possible to "overdose" with ultrasound and cause damage. From the bioeffects viewpoint, it is easier to study quantitatively obvious examples

of acute damage such as a hemorrhage than subtle, long-term bioeffects that may actually be therapeutic. However, if strain or strain rate plays a fundamental role in damage, these parameters warrant use as exposure quantities in therapy as well.

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