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ACOUSTIC CAVITATION AND MEDICAL ULTRASOUND

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INTRODUCTION

Ultrasound is used in a variety of ways in a medical environment and has come into widespread use in most hospitals and clinics. Among the ways that ultrasound is currently being utilized in medicine are: (1) as a diagnostic instrument, in which extremely short pulses of ultrasound in the megahertz frequency range is used in an echo-ranging format to obtain real-time images of internal organs and tissues, or in a Doppler format to obtain measurements of flow velocities within the vascular system, (2) as a therapeutic device, in which continuous wave (or relatively long pulses of) ultrasound is used in the megahertz frequency range to accelerate tissue repair and relieve pain, (3) as a surgical tool, in which vibrating horns or blades are used in the kilohertz frequency range as an 'ultrasonic scapel' to remove diseased or unwanted tissue, and (4) as a kidney or gall stone disrupter, in which extremely large amplitude pulses of ultrasound (in a variety of frequency ranges) is used to pulverize undesirable solid accretions within the body.

We have formed an informal, collaborative group to combine our talents to study each of these devices, primarily to assess their risk potential, but also to seek ways of improving their performance.

In this paper, we report on some studies of the first two of the above named devices. In particular, we describe some preliminary progress we have made in our assessment of the risks (and perhaps even benefits) associated with acoustic cavitation produced by these instruments. We shall first examine theoretical and experimental evidence that acoustic cavitation is probably being produced by short-pulse, diagnostic devices, and attempt to assess why this cavitation does not appear to result in any major health risk. Next, we examine the cavitation known to be produced both *in vitro* and *in vivo* by therapeutic ultrasound devices. With application to this area, we describe a theoretical mechanism for the production of macroscopic-size bubbles and show that this mechanism is consistent with the considerable experimental evidence available concerning observed bubble production. Lastly, we present some caveats associated with the use of these devices.

RESULTS

Short-pulse cavitation (diagnostic imaging and Doppler devices)
In 1982, Flynn [1] reported that his theoretical analysis led him to believe that violent, transient cavitation could be produced by microsecond-length pulses of ultrasound. Furthermore, the threshold acoustic pressure amplitudes necessary for cavitation inception were significantly less than those in current use by most diagnostic ultrasound devices.

Recently, Crum and Fowlkes [2] have reported an experimental confirmation of these predictions. Although the threshold pressure amplitudes required for the cavitation were larger than those predicted by Flynn, they were still less than those currently in use by these instruments. More recently, visible-size bubble production has been observed in agar gels, when irradiated with a short-pulse diagnostic device, that appears to be induced by acoustic cavitation [3]. We now briefly review the concept of acoustic cavitation of the 'transient' type, and its production by short, acoustic pulses.

Consider Fig. 1 which describes a theoretical calculation of the response of a bubble of 1.0 μm radius to an acoustic pulse of one cycle duration, with a frequency of 1.0 MHz and an acoustic pressure amplitude of 0.175 MPa. The bubble is assumed to be present in an infinite volume of water and not constrained in any manner. (The issue of where this bubble came from and why it is there is a subject of great complexity and will not be addressed here.) When the pressure becomes negative, the bubble grows very rapidly, fills with vapour and increases to over twice its size within 0.5 μs. However, as the instantaneous acoustic pressure turns positive, the bubble begins to collapse violently, its rapidly accelerating interface unable to be arrested by the water vapour in the interior of the bubble that rapidly condenses on its surface. Consequently, the bubble now collapses to a small fraction of its initial volume within a fraction of an acoustic cycle. The gas contained within the cavity can not escape by diffusion (because the collapse is too rapid, and the diffusion process is too slow) and subsequently is heated to a relatively high temperature. In this example, it is seen that the gas temperature within the bubble exceeds 1000 deg K (the ordinate is plotted in normalized values; 1.0 implies a temperature of 293 deg K)

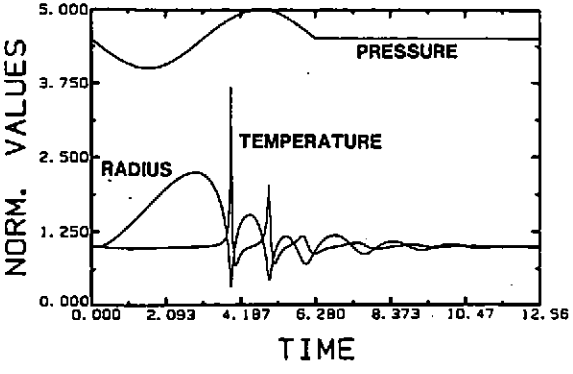

Fig. 1. Response of a microbubble of 1.0 μm radius to a single pulse of 1.0 MHz ultrasound. Here the initial radius was 1.0 μm, the frequency was 1.0 MHz and the acoustic pressure amplitude was 0.175 MPa. A time unit of 6.28 is equal to one acoustic period.

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The pressure waveforms generated by a typical diagnostic scanner are much more complicated than the sinusoidal one shown here, but still have large negative pressure amplitudes followed by large positive pressure amplitudes. For the example in Fig. 1, the acoustic pressure amplitude was 0.175 MPa; a typical medical scanner would have a value 10-20 times this much. Accordingly, on the basis of calculations similar to these, Flynn predicted that one should expect to see violent acoustic cavitation from microsecond-length acoustic pulses.

Crum and Fowlkes [2] were able to test this prediction because of the violent nature of the cavitation. As the gas contained in the bubble heats up, a threshold is reached wherein the water molecules also contained within the cavity dissociate into free protons and hydroxyl free radicals. These free radicals are extremely reactive and, during recombination, emit visible light [4]. This light emission is easily measured with a photomultiplier or similar instrument and served as Crum and Fowlkes' detection scheme.

Shown in Fig. 2 are the acoustic pressure amplitudes required to produce light emission as a function of the length of the acoustic pulse. For this case, an abscissa value of 3 implies that 1000 cycles were contained in the pulse, 2 means 100, 1 means 10 and 0 means that essentially one cycle was used (the acoustic frequency was 1.0 MHz.) This figure presents considerable evidence that diagnostic scanners can produce violent acoustic cavitation.

In an accompanying paper in these proceedings [3], Daniels and ter Haar report that a short-pulse diagnostic device has induced visible-size bubble production in an agar gel that has been insonified in a heated water bath. (The mechanism for the production of these visible-size bubbles will be examined below.)

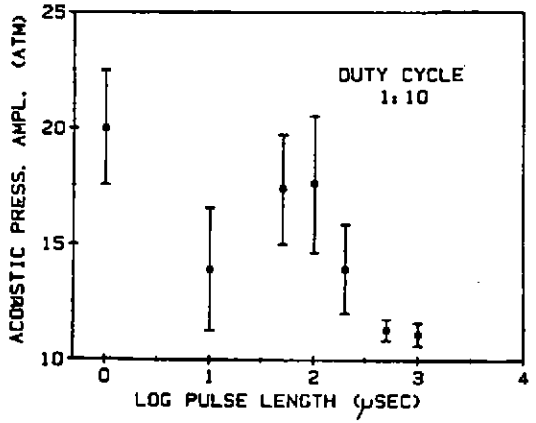

Fig. 2. Variation of the acoustic cavitation threshold with pulse length for short acoustic pulses in water. For these data, a focused 1.0 MHz transducer radiated into an echo-free tank filled with partially degassed water that contained a small amount of the light enhancing chemical luminol.

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Continuous wave cavitation (therapeutic instruments)
The use of ultrasound in physiotherapy has become so widespread that it can be considered a standard treatment. For example, it was reported in 1977 that there were over 4 million ultrasonic treatments in Canada alone [5]. It is applied either in a continuous wave mode, or in millisecond-length pulses with typical duty cycles of 1:1 and 1:4.

In 1981, ter Haar and Daniels [6] reported the detection of bubbles produced in vivo by a therapeutic ultrasound device. They have extended their studies to include the effects of increased ambient pressure [7] and have detected bubble formation in vivo even with pulsed beams [8]. Some recent results [3] detail a similar study of bubble growth in an agar gel that apparently duplicates conditions in vivo.

We examine now the theoretical conditions necessary for the formation of bubbles in agar gels and show that the theoretical predictions are consistent with the experimental measurements. First, some experimental observations:

(i). If the gels are brought to (dissolved gas) equilibrium at a given temperature, they can be heated for several minutes in a water bath without developing bubbles, so long as the temperature does not exceed a critical value. If the gel is heated above this critical temperature, numerous bubbles develop in the gel within a few minutes. Here we assume no insonification.

(ii). If the gels are heated in a water bath to a temperature below the critical value, and then irradiated with ultrasound, bubbles can be produced with a relatively distinct acoustic threshold.

(iii). If the gels are insonified at the same temperature to which they have been brought to (dissolved gas) equilibrium, it is extremely difficult to produce bubbles.

(iv). Once the bubbles are produced, they continue to grow to relatively uniform sizes that are on the order of hundreds of microns.

(v). If an image intensifier is used to view the gel when insonified at an acoustic pressure amplitude sufficient to produce visible bubbles, optical emissions appear to be emanating from the bubbles at certain stages of their growth.

We believe that visible bubble production within the gel is a simple result of growth by diffusion of small microscopic gas pockets that have been stabilized against dissolution. We shall consider the growth of these bubbles by diffusion both with and without the presence of an applied acoustic field.

Let us consider the equation that describes the time rate of change of a bubble of equilibrium radius Ro, contained within a liquid of instantaneous dissolved gas concentration Ci and saturation concentration Co, with liquid surface tension S and external ambient pressure Po : eq. 18 in ref. [9]

(this equation is too complicated to be repeated here). For the bubble to remain fixed in size , dRo/dt=0, and the threshold condition applies, i.e.,

$$Ci/Co = 1 + 2S/RoPo. \quad (1)$$

This equation asserts that a free gas bubble will dissolve unless the liquid is supersaturated (Ci/Co > 1).

Suppose we first heat the gel without insonification. Since the gel is mostly water (and thus has good thermal conductivity), but relatively solid (and thus has a relatively slow diffusion rate), it is probably correct to assume that it will become supersaturated. Tables of dissolved gas volumes as a function of temperature are available, and we can estimate the level of supersaturation for a given temperature elevation. As an example from our experiments, a temperature rise of 16 deg C will result in a supersaturation level (Ci/Co) of 1.4. We have found that this temperature rise just elevates the gel to the critical temperature for nonacoustic bubble production, i.e., bubbles are produced in the absence of applied ultrasound. If we use eq. 1 and this level of supersaturation, we can determine the maximum size of the stabilized cavitation nuclei. Using S= 70 dyn/cm and Po = 1.0 bar, we can determine this radius to be 3.5 μm.

Consider Fig. 3 which demonstrates the application of diffusion theory to bubble growth in an agar gel. First, we examine the behaviour of bubbles slightly larger (3.6 μm) and slightly smaller (3.4 μm) than this critical radius. (The growth curves on this figure were generated by numerical integration of eq. 18, ref. [9].) It is seen from the figure that the 3.4 μm bubble rapidly dissolves within a few seconds. On the other hand, the larger bubble grows to nearly 100 μm within two minutes. Since we did not observe any nonacoustic bubble growth until we reached this level of supersaturation, we can conclude that the maximum size of the cavitation nuclei within the gel is about 3.5 μm.

We now introduce ultrasound and apply our analysis to the data obtained by Daniels and ter Haar [3] for bubble growth in agar gels. In Fig. 5 of ref. [3], the gels were brought to (dissolved gas) equilibrium at room temperature, immersed in a water bath at 37.5 deg C (and also at 43 deg C) and insonified for 5 minutes at various intensities. The frequency used was 0.75 MHz. The threshold for bubble production was found to lie between 0.12 and 0.21 MPa (here we use spatial peak pressure, 3 times the spatial average pressure, as the bubbles are much smaller than the cross section of the transducer). Assuming the room temperature was 25 deg C, we can estimate that for their measurements, the supersaturation level was approximately 1.2. It is seen from Fig. 3 that all bubbles larger than 1.75 μm will grow to visible (greater than 100 μm) size if an acoustic pressure amplitude of 0.12 MPa is used; bubbles smaller than 1.70 μm will dissolve within a few tenths of a second. Thus, if there are bubbles in the range 1.75 -3.5 μm (and it's quite reasonable to assume that there will be), then they will grow to visible size within the 5 minute insonification period.

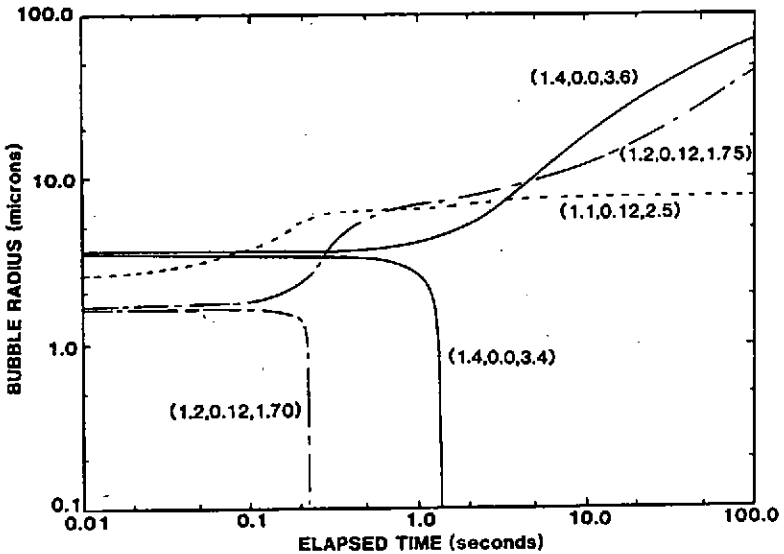

Fig.3. Growth of gas bubbles by diffusion in the presence of or absence of an applied acoustic pressure. The curves describe the growth of a free gas bubble with the conditions specified in the parentheses near the curve. These numbers refer to (concentration ratio, acoustic pressure amplitude in MPa, initial bubble radius in microns). The curves were obtained by numerical integration of eq. 18, ref [9], for a frequency of 0.75 MHz and a surface tension of 70 dyn/cm.

Note, however, that if the supersaturation level is only 1.1, then a bubble with initial size of 2.5 μm grows only to about 8 μm in radius and would not be visible. If there is no supersaturation at all, i.e., Ci/Co = 1.0, even an acoustic pressure amplitude of 0.21 MPa applied to a 3.5 μm bubble will not result in growth (note item (iii) above).

The above analysis applies to CW (or long pulse) irradiation for which many acoustic cycles cause a small microbubble to grow to visible size by rectified diffusion. For bubble production in agar gels by short pulses, as in Fig. (6), ref. [3], there are only a few cycles and ordinary rectified diffusion equations do not apply. From our preliminary analysis using a more sophisticated model, we have determined that the extremely large amplitude acoustic pulses associated with diagnostic instruments can result in a few percent change in radius. If the gel is already heated to a supersaturation level close to the critical value where growth can occur in the absence of ultrasound, then this slight push may enlarge a few microbubbles beyond the critical size and they will then continue to grow to visible size by ordinary 'static' diffusion.

Figure 3 thus indicates that bubble growth in an agar gel (which appears to duplicate bubble growth in mammalian tissue) can be reasonably described by the currently available equations of rectified diffusion. We now have a theoretical model that should enable us to argue inductively about the results of future experiments both in vitro and in vivo. Of course, many approximations were made in the above analysis (such as using constants applicable to water for the physical parameters of the gel), and a rigorous quantitative description should not be expected.

Next, consider Fig. 4, which shows the result of examining the field of a therapeutic ultrasound generator with an image intensifier when a plane reflector is placed perpendicular to the axis of the transducer. The figure shows that light emissions occurred from bubbles that were trapped near the pressure antinodes of the standing wave. For this case, the host medium was saturated tap water at 37.5 deg C. The light emission was observed for acoustic pressure amplitudes as low as 0.2 MPa (1.3 w/cm-cm) and even for a pulse-mode of operation with a 1:4 duty cycle.

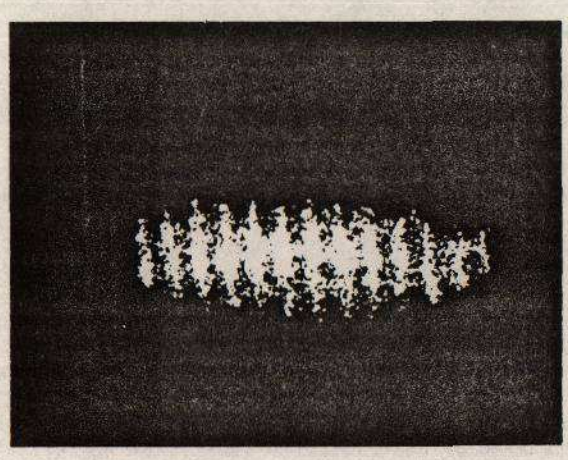

Fig. 4. Light emissions observed from the field of a therapeutic ultrasound device when the radiating transducer was directed toward an acoustic reflector. The photograph shows bands of light emissions associated with small gas bubbles that are trapped near the pressure antinodes and driven into such violent oscillations that the gas in the bubble's interior luminesces. These observations were made with an image intensification technique that permits spatial as well as temporal resolution of the light emissions [4].

Finally, as indicated in item (v) above, if the image intensifier is used to examine an insonified gel in which bubbles are being produced, light emission is present when bubbles are produced and absent when they are not. (Although we think it is unlikely, there is a possibility that light produced in the bulk of the liquid is being channeled into the image intensifier tube by the bubbles within the gel acting as small reflectors or scatterers.) If light emission does result from oscillating bubbles in a gel, however, then it can probably also be produced by oscillating bubbles *in vivo*. Since light emission indicates free radical production, it appears that there is another mechanism that could lead to acoustic bioeffects from cavitation other than the commonly cited one of acoustic streaming. It is possible, however, that these free radicals would not sufficiently penetrate from the interior of the bubble to any depth within the liquid to be a threat to tissues; nevertheless, this particular type of damage mechanism needs further study.

DISCUSSION AND CONCLUSIONS

It is becoming more and more apparent that diagnostic and therapeutic devices used in medicine may induce acoustic cavitation *in vivo*. This conclusion should not be treated with alarm, however, for the following reasons:

short-pulse ultrasound

(1). Violent acoustic cavitation resulting from short pulses must arise from a narrow size range of stabilized gas pockets or cavitation nuclei present within the liquid.

(2). Although cavitation nuclei are known to exist in mammalian tissue [10], and even within the amniotic sac [11], the number of these nuclei are much smaller than those present in water, where the cavitation experiments were made.

(3). The duty cycle used in diagnostic scanners is typically on the order of 1:1000, as compared to 1:10 for the results in Fig. 2. There are few cavitation events per unit time for a duty cycle of 1:10; for the 1:1000 duty cycle, one should expect on the order of one hundred times fewer.

(4). The principal damage mechanisms associated with transient cavitation of this type appear to be restricted to small, nearly cell-size volumes.

(5). Even though there have been extensive epidemiological studies of the use of diagnostic ultrasound, no conclusive evidence exists for any undesirable effects associated with its use.

long-pulse or CW ultrasound

(1). Although those instruments that generate many acoustic cycles appear to be able to induce bubble formation of relatively large size, effects such as violent acoustic streaming and free radical production will only occur at high acoustic intensities that are above those generally used in therapy, although still available with most machines.

(2). At high intensities, absorption of the ultrasound results in significant temperature rises that induce thermal effects. These effects would probably mask the discrete and localized cavitation events and also induce a warning--in the form of pain--that would cause the operator to reduce the intensity.

(3). At low intensities, the applied ultrasound would induce only mild acoustic streaming, which would most likely result in increased molecular diffusion. This increased diffusion may be the mechanism for the many desirable effects associated with therapeutic ultrasound [5].

Finally, a few caveats need be cited concerning the use of medical ultrasound and the incidence of acoustic cavitation.

(1). The introduction of free radicals, if only a small number at occasional times, into tissue during its formative stage should be avoided unless the benefit far exceeds the risk.

(2). Therapeutic ultrasound intensities should be kept as low as possible and used primarily in a pulsed mode.

ACKNOWLEDGEMENT

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