Acoustic cavitation produced by microsecond pulses of ultrasound: A discussion of some selected results

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Because of its extensive utilization in clinical practice, and because the subjects examined are often fragile and sensitive to trauma, the safety of diagnostic ultrasound has always been of concern. Of the various mechanisms through which ultrasound could act in a manner deleterious to a patient, acoustic cavitation, should it occur, appears to possess significant potential for biological damage. This paper reviews several recent reports of progress by our two groups and demonstrates the conditions under which cavitation has been observed by microsecond pulses of ultrasound. Although these results give no indications that diagnostic ultrasound may pose a true risk to a patient, they do indicate that *in vivo* cavitation may occur under certain conditions.

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INTRODUCTION

The use of diagnostic ultrasound in medicine has expanded considerably over the past few years and has become a vital clinical tool in the diagnosis and assessment of a large variety of ailments and conditions. A measure of this increase in use is demonstrated by the fact that the enrollment of the American Institute of Ultrasound in Medicine has grown from a membership of 5000 in 1982 to its present number of near 9000. During this time there has been a steady evolution in the complexity and sophistication of the imaging and Doppler scanners that provide the principal instrumental tools for clinicians. These devices have tended, in general, to evolve to higher working frequencies to improve resolution, and consequently, because of the higher attenuation, to larger acoustic intensities and pressure amplitudes.

Since every ultrasonic instrument used in medical diagnosis poses a potential risk to the patient, the concern for the safety of these devices has always been great. Although there has been a close and continuous scrutiny of their safety, there appears to be little evidence, if any, that diagnostic ultrasound instruments pose even a measurable risk to the patient. Indeed, Ziskin[1] has commented that "There is nothing that I'm aware of that has a safer record than that of diagnostic ultrasound." Nevertheless, because of its extensive use and the delicate nature of the analyzed subjects (primarily pregnant women), continued research concerning the safety of these devices should be vigorously pursued.

A group of researchers at the National Center for Physical Acoustics and Yale University has carried out a sustained effort to understand the potential that diagnostic ultrasound devices have for inducing acoustic cavitation *in vivo*. We are certainly not unique in this study; for example, there are active groups at the University of Rochester and the University of Illinois, to mention a few. Since cavitation is such a violent phenomenon, its occurrence *in vivo* would be of major concern (provided, of course, that such cavitation is linked to significant biological damage). Progress has recently been made by the Yale/NCPA group and several papers have appeared in this Journal (and others) concerning these advances.[2–23]

It is beyond the intended scope of this paper to review all the recent work on this subject. Rather, we have opted to survey primarily our own results and attempted to synthesize from them some global features that only a general perspective can give. It will be seen in our discussions that it is still uncertain whether acoustic cavitation is a natural consequence of the use of diagnostic ultrasound and what role it might play in bioeffects, should it regularly occur. It is our hope that this discussion of our varied results be of use to others who seek also to find answers to these important questions.

There are two principal mechanisms whereby diagnostic ultrasound can interact with tissue: (a) a thermal mechanism resulting from absorption of the ultrasonic pressure wave and subsequent temperature elevation of the tissue; (b) the phenomenon of acoustic cavitation in which relatively small amounts of energy are concentrated to microscopic sizes, thus giving intense localized pressure and temperature elevations. Research into the thermal mechanism has made considerable progress over the last few years and most researchers in this area feel reasonably confident about their ability to assess the potential risks associated with this mechanism. The most recent World Federation of Ultrasound in Medicine and Biology Symposium on Safety and Standardization in Medical Ultrasound spent the overwhelming majority of its time describing and discussing the thermal mechanism in great detail.[24] Perhaps one reason the

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thermal mechanism is rather well understood is that, in general, it is a macroscopic phenomenon associated with a continuum, subject to the reasonably well-understood equations of thermal transport.

Acoustic cavitation, on the other hand, is by its very nature a discrete phenomenon that is both spatially and temporally localized. As an example of the contrast between these two mechanisms, consider the fact that with a focused ultrasound device, the volume of the region that would be heated is on the order of 1 cm^3; the time for significant temperature increases to occur is on the order of several minutes, say, 15. Thus the volume-time product is about 10^3 cm^3 s. The amount of energy involved in elevating the temperature of such a region by 1 K is about 1 J. For a cavitation event, however, the region occupied by a collapsing cavitation bubble is on the order of a micron and the time scales are on the order of microseconds, giving a volume-time product of about 10^{-18} cm^3 s. The amount of energy involved has been estimated to be on the order of 100 Mev,[2] which is deposited virtually instantaneously. This concentration of energy, although enormous on the microscopic scale, amounts to only 10^{-10} J based upon a macroscopic one. To carry this comparison one step further, consider next the ratio of the energy deposited to the volume-time product, giving units of W/cm^3, or "power density." For thermal effects, one obtains 10^{-3} W/cm^3; for cavitation effects, one obtains 10^8 W/cm^3. This 11 order-of-magnitude difference demonstrates rather dramatically the contrasts between these two effects. Thus "microcavitation" is difficult to detect; it is also difficult to ascertain its consequential bioeffects.

We now present a compilation of the results of our own recent research in acoustic cavitation and diagnostic ultrasound.

I. COMPILATION OF RESULTS

A. The existence of cavitation from microsecond pulses of ultrasound is consistent with theoretical predictions

In 1982, Flynn[25] and Apfel[26] independently predicted, on the basis of numerical and analytical calculations, that short pulses of megahertz-frequency ultrasound could induce acoustic cavitation in water. Because acoustic cavitation typically is associated with continuous-wave oscillations at kilohertz frequencies (e.g., in ultrasonic cleaners), it was generally assumed that a single-cycle acoustic pulse at megahertz frequencies would be unable to induce cavity growth. However, because the time scales required for a cavitation bubble to grow explosively in water are tenths of a microsecond or less, it was shown by Flynn and Apfel that neither the high frequency nor the short pulses placed any major theoretical restrictions on such cavitation inception. Figure 1, the results of which were obtained by Apfel and Holland,[17] shows the theoretical threshold pressure amplitudes required in order for cavitation to occur as a function of the assumed preexisting nuclei radius. These pressures are significantly less than those commonly achieved in clinical diagnostic instruments, which are commonly on the order of 1–3 MPa (10–30 bars), peak negative pressure.[27]

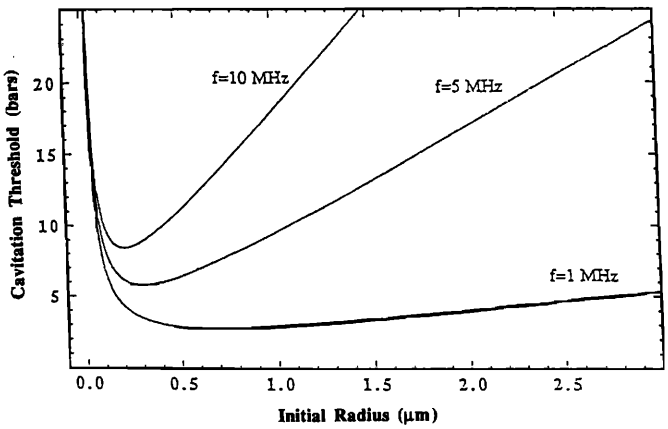

FIG. 1. Cavitation threshold pressure versus initial nuclei radii for three different insonifying frequencies. The nucleus was modeled as a free bubble in an infinite expanse of air-saturated water. Results taken from Ref. 17.

B. The existence of cavitation from microsecond pulses of ultrasound has been demonstrated

Starting in 1985, Crum and Fowlkes[3–5] presented evidence that a single cycle acoustic pulse at a carrier frequency of 1.0 MHz could produce chemiluminescence in water doped with luminol, a light-enhancing chemical. They observed dependences on pulse length and pulse repetition frequency (PRF) but were unable to observe luminescence from these pulses in pure water. Figure 2, curve (a) depicts the measured threshold for light emission as a function of pulse width for a constant duty cycle.[5] These data for the inception threshold, although subsequently shown to be high due to detector insensitivity, demonstrate that acoustic cavitation can be induced by microsecond-length pulses of ultrasound, and that the cavitation generated is sufficiently violent to produce detectable quantities of free radical species.[6,28] It can also be noted that the measured thresholds were significantly higher than those predicted by Flynn or Apfel, but still less than the acoustic pressure amplitudes generated by some clinical instruments.

C. The measured inception threshold for cavitation produced by short acoustic pulses was found to be detector dependent

When Atchley and colleagues at Yale attempted to duplicate Crum and Fowlkes' results and found that optical detection of acoustic cavitation was a difficult process, they developed an acoustic detection scheme that was both effective and simple to implement.[7] The *passive acoustic detection system*, in which the sound generated by the source transducer was scattered by a cavitation event and then received by a second, tuned transducer, was found to be effective for acoustic pulses longer than a few cycles. Figure 2 compares cavitation threshold measurements obtained by Roy and Fowlkes[8] using the passive acoustic detector with those obtained previously by Fowlkes and Crum,[5] using their optical device. Note that the passive detection scheme gave consistently lower thresholds with no significant pulse-length dependence, provided the duty cycle is held constant. The probable reason for this lower threshold is that a long-lived

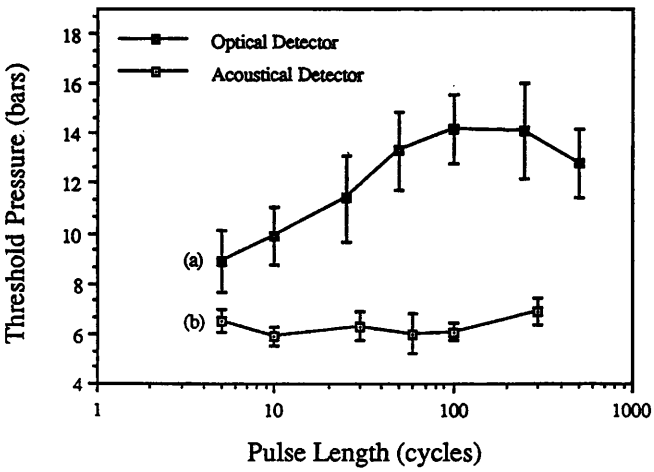

FIG. 2. A comparison of cavitation thresholds measured in water using two different detection schemes. Curve (a) was obtained using an optical detector that keyed on chemiluminescence; the detection criterion consisted of an elevated light reading that persisted for at least 100 ms.[5] Curve (b) was acquired using a passive cavitation detector, where the indicator was the onset of spurious scattering from transient microbubbles.[7] In both experiments the acoustic frequency was 1.0 MHz, the duty cycle was 10%, and the test liquid was air-saturated water filtered to 25 μm and doped with luminol.

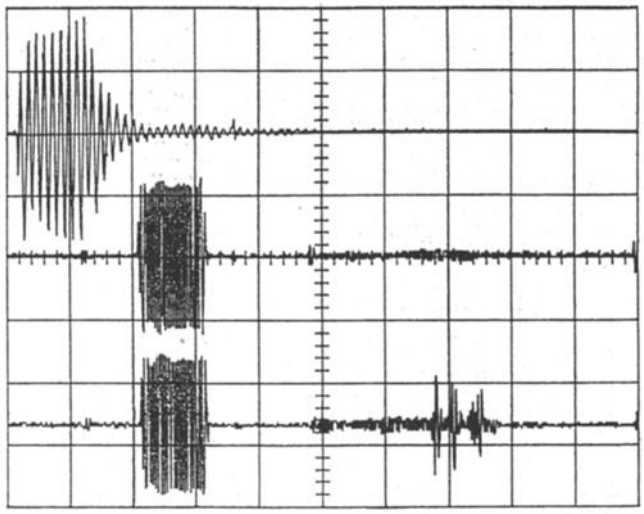

FIG. 3. Typical output from the active cavitation detector. The top trace is the electrical signal that is fed into the cavitation-producing transducer (10 cycles at 750 kHz). The middle trace is the delayed, 30-MHz signal which is delivered to the pulse-echo detection transducer as viewed at the output of the ACD *in the absence of cavitation*. (A delay is necessary since the transducers have differing focal lengths.) The bottom trace shows evidence of transient backscattering from transient cavitation microbubbles generated in the confocal region of the two transducers. For this test, the acoustic duty cycle was 1% and the test liquid was moderately degassed water seeded with 0.25-μm-diam polystyrene spheres. Results taken from Ref. 9.

(order 100 ms) cavitation event is required to generate "detectable" optical emissions while scattered acoustic energy can be unambiguously detected from less persistent cavitation events. The reason for the longer time scale required for optical detection is that although a photomultiplier can detect the few photons that are released from a single cavitation event, the background noise overwhelms this small signal. It is only when this event has evolved to a cavitation complex of numerous events over a period of hundreds of acoustic cycles that the intensity of the optical signal comfortably exceeds the background.

D. The active cavitation detector (ACD) represents an extremely sensitive device for observing acoustic cavitation inception from short acoustic pulses

When using the passive detector, the pulse length of the cavitation-generating transducer must be long enough so that subsequent cycles of acoustic energy can be scattered from a cavitation event that develops from the initial cycles of the pulse. We have learned that a passive system cannot be used to detect cavitation from a pulse which is only one or two cycles long, such as an imaging pulse from a diagnostic scanner, apparently because it takes a few cycles for the cavitation bubble complex to grow to a sufficient size to scatter detectable acoustic energy. In response to this limitation Roy *et al.* developed the *active cavitation detector*,[9] which employs a tightly focussed, 30-MHz pulse-echo transducer positioned confocally with respect to the cavitation generating transducer. Any inhomogeneities that develop in the confocal region scatter some of the 30-MHz probe pulse energy which is subsequently detected by the pulse-echo receiver. Figure 3 shows representative oscillographs of the operation of this detector and provides some indications of temporal variations in the induced cavitation event. Because the probe frequency is much higher than that used to generate cavitation, it appears to be possible to detect not only the incidence of cavitation from a single pulse, but to estimate the relative size and temporal nature of the cavitation bubble that results.[10]

E. Acoustic cavitation can be induced in vitro by clinical diagnostic instruments

Using the active cavitation detector, Holland *et al.* performed an examination of the effect of a clinical diagnostic ultrasound instrument on artificial nuclei.[11] Shown in Fig. 4 is evidence, obtained in this study, that cavitation was induced by this scanner in a suspension of 0.25-μm-diam polystyrene spheres in moderately degassed water. Low-to-moderate amounts of cavitation were detected at 2.5 MHz in both *M*-mode and Doppler mode provided the peak negative pressure exceeded ≈ 1.1 MPa. No cavitation was detected at 5.0 MHz for peak negative pressures as high as 1.2 MPa (the limit of the instrument), regardless of the modality employed. These observations support the contention that some diagnostic scanners can indeed nucleate transient cavities *in vitro*. However, our knowledge base must be extended to *in vivo* studies before we can realistically assess the clinical significance of these and other results.

F. The passive and active cavitation detectors permit an examination of the characteristics of cavitation nuclei

Because the acoustic cavitation detectors constantly monitor the focal zone of a radiating transducer, (either pas-

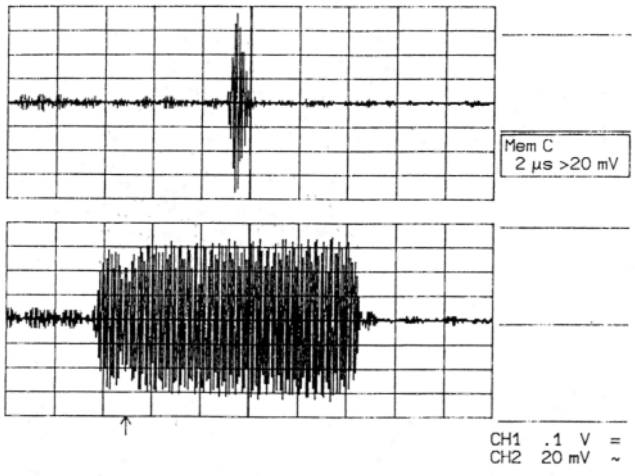

FIG. 4. Transient cavitation generated *in vitro* using a commercial diagnostic scanner (H–P 77020A), as indicated by an active cavitation detector. The test liquid was a suspension of 0.25-μm-diam polystyrene spheres in moderately degassed water. The scanner was operating in the *M*-mode (pulse length $\approx$1–2 cycles) at a frequency of 2.5 MHz and a peak negative pressure amplitude of approximately 12 bars. The ACD pulse length was 10 μs as indicated by the lower trace, which corresponds to backscatter from a nearly stationary object (i.e., an aggregate of polystyrene spheres). Conversely, the upper trace indicates the presence of a short-lived cavitation event. Note that the duration of the echo correlates well with the duration of the *M*-mode pulse. Results taken from Ref. 11.

sively or actively) it is possible to insert "artificial" nuclei into this focal area and observe their ability (or inability) to nucleate cavitation. In particular, we have made studies of cavitation nucleated by polystyrene spheres and stabilized microbubbles as they are convected through the focal region of a radiating transducer.[9,12–14] Figure 5, which comes from Roy *et al.*,[12] shows an oscillogram of the scattering from cavitation events nucleated by stabilized microbubbles (Albunex®) as observed by the passive cavitation detector. The time scales have been compressed in order to better visualize the cavitation nucleation process. The top trace corresponds to the undisturbed passage of a group of stabilized microbubbles flowing through the focal region of the insonifying transducer operated at a pressure amplitude of 0.13 MPa.

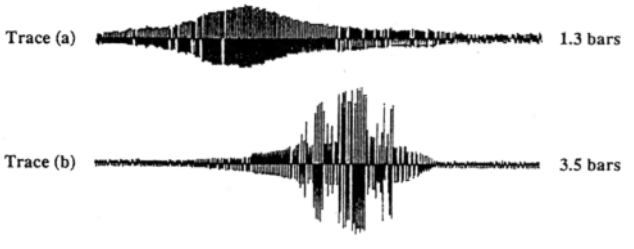

FIG. 5. Evolution of the scattered signal amplitude produced by a clump of stabilized microbubbles flowing through the focus of a 1-MHz transducer with a mean velocity of $\approx$3 cm/s. The acoustic pulse length and PRF were 10 cycles and 1 kHz respectively, and the test liquid was slightly degassed water seeded with Albunex.® Note that the elapsed time for the oscillogram is 200 ms, whereas the interval between adjacent acoustic pulses is only 1 ms. Thus each trace represents a highly compressed view of 200 scattered pulses, as detected by a passive cavitation detector. The gradual growth and decay evident in both traces corresponds to the traversal of "undisturbed" microbubbles. Spikes in the lower trace are indicative of transient bubble growth and collapse. Results taken from Ref. 12.

The lower trace illustrates what happens when the pressure amplitude is increased to 0.35 MPa. The spikes are indicative of scatterers that rapidly increase their cross section, a phenomenon that suggests transient cavitation, in which vapor bubbles grow to several times their initial size within a few acoustic cycles. An expanded view of these spikes indicates that the elevated scattering level persists for only a few milliseconds. When properly implemented, the active cavitation detector shows even greater promise than the passive detector for providing important details about the nucleation and bubble growth process,[10] although, in a Heisenbergian sense, Madanshetty has learned that our probe field may alter the characteristics of the nuclei themselves.[13]

G. Our ability to predict the absolute threshold pressure amplitude for cavitation inception and the dependence of this threshold on important variables (such as frequency) is considerably improved

Holland and Apfel[14] used the passive cavitation detector to measure the cavitation threshold for an artificial nucleus, a polystyrene sphere. Expanding on an analytical theory developed earlier by Apfel,[15] it was possible to predict correctly the frequency dependence of this measured threshold. Representative theoretical calculations and experimental measurements are given in Fig. 6. Because the actual physical mechanism whereby a cavitation bubble is nucleated from a polystyrene sphere is unknown, Holland and Apfel found it necessary to make a broad estimate of the initial nucleus size. However, when stabilized microbubbles were

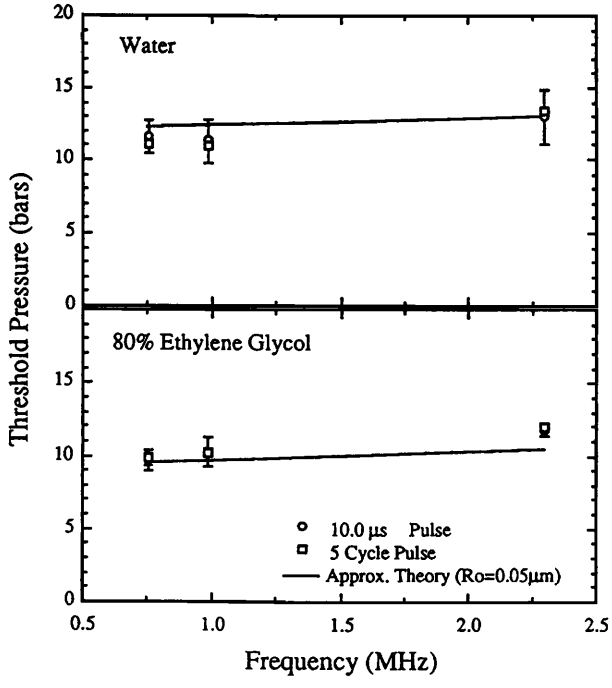

FIG. 6. Frequency dependence of calculated and measured transient cavitation threshold pressures obtained in water and in an ethylene glycol and water mixture, as indicated by a passive cavitation detector. The pulse repetition frequency was 1 kHz (duty cycle $<$1%) and both of the test liquids were thoroughly degassed and seeded with 0.25-μm-diam polystyrene spheres. For the theoretical calculations, the initial nuclei radius was taken to be 0.05 μm. Results taken from Ref. 14.

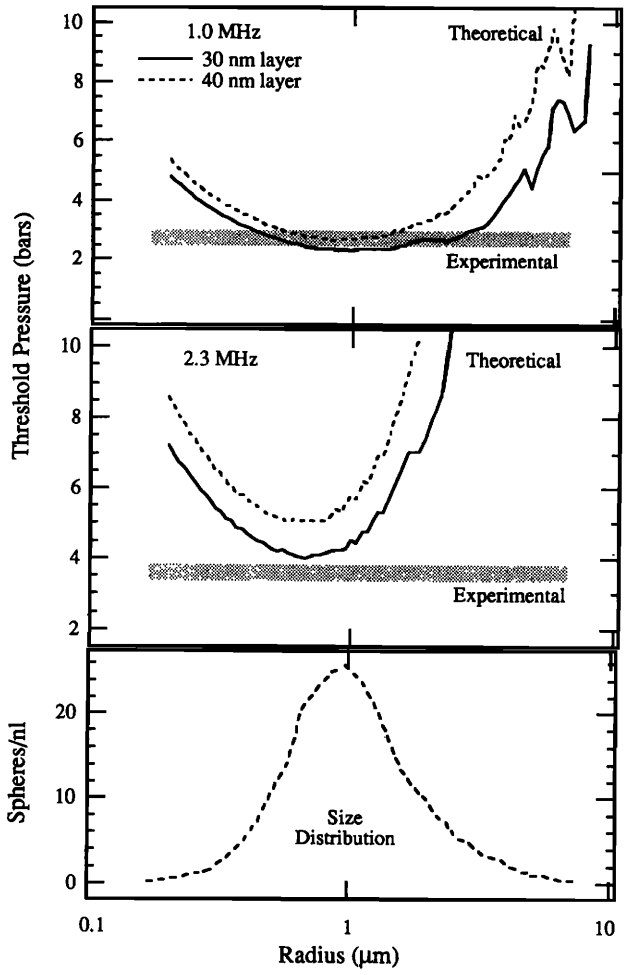

FIG. 7. Calculated and measured transient cavitation thresholds obtained in slightly degassed water seeded with stabilized microbubbles, as indicated by a passive cavitation detector. The acoustic pulse length was 10 cycles and the PRF was 1 kHz (duty cycle $\leqslant 1\%$). The nuclei size distribution, which was provided by the manufacturer, was measured using a Coulter counter. Theoretical threshold calculations were based on a numerical model for the dynamics of a bubble that is encapsulated by a viscous "skin" between 30 and 40 nm thick. Results taken from Ref. 12.

used as the nucleating particles (for these, the size distributions are relatively well known) and estimates made of the mechanical characteristics of the albumin shell that stabilizes this particular nucleus, a relatively close estimate of the absolute threshold can be obtained. Figure 7 shows the comparison of the measured thresholds for cavitation nucleation from a population of stabilized microbubbles with calculations based on a numerical model for bubble dynamics in a viscoelastic medium developed by Church. Since the threshold for cavitation nucleation occurs at the onset of cavitation production, one would expect the measured thresholds to coincide with the minimum in the theoretical curve. This notion is well supported by the experimental data shown. Details of the theory and experiment are provided in Roy *et al.*[12]

H. With the information learned from these recent studies, a cavitation index can be developed for use in specifying output characteristics for diagnostic ultrasound devices

The extended analytical theory of Holland and Apfel[16] demonstrates the existence of an optimally sized nucleus at a given frequency for which the threshold has a minimum (see Fig. 1). By applying this analytic model to a population of nuclei to predict the onset of cavitation in host fluids, Apfel and Holland developed an index that can gauge the likelihood of substantial microbubble growth in the presence of short-pulsed diagnostic ultrasound.[17] This "mechanical energy index" is given by $I = P^*/(f^*)^{1/2}$, where the normalized pressure is $P^* \equiv P/(10\,\text{bars})$, P is the peak negative, or rarefaction pressure, and the normalized frequency is $f^* \equiv f/(1\,\text{MHz})$. This index indicates the relative behavior of the threshold for the onset of cavitation versus frequency in a water- or bloodlike host fluid with optimally sized nuclei present at each frequency.

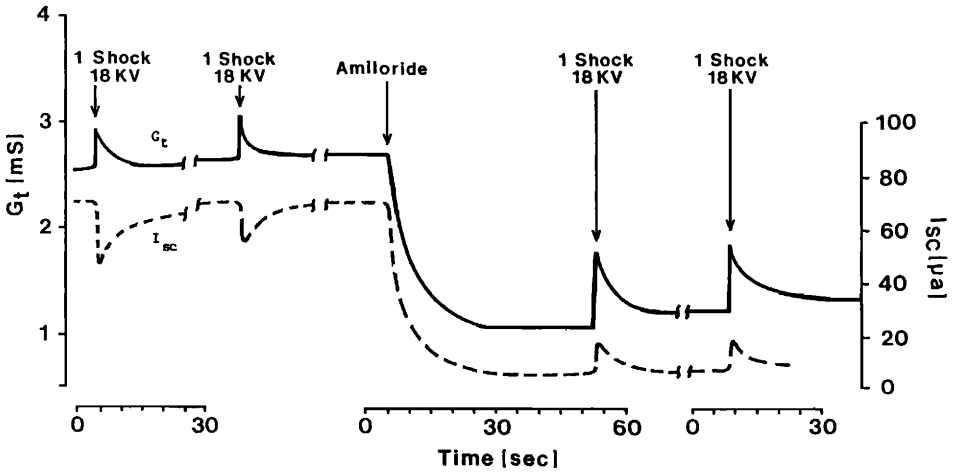

FIG. 8. This figure depicts an actual tracing of one of the experiments in which the abdominal region of frog skin was exposed to shock waves. The solid trace represents the total ionic conductance across the skin and the dotted trace represents the short circuit current through the skin. This current is a measure of net sodium absorption. At the first arrow one shock from the research lithotripter was applied. As shown, this caused a transient increase in ionic conductance and a decrease in the short circuit current. After recovery, this sequence was repeated and a similar effect was produced. At the third arrow amiloride was added. The addition of amiloride caused a decrease in the sodium absorption and total ionic conductance. Subsequent application of shock waves (forth and fifth arrows) caused a very large increase in both the sodium current and the total ionic conductance. Such an effect is usually a result of electrochemical and structural changes in the tissue.

I. High-amplitude shock wave pulses give us some indication of possible biological effects from acoustic cavitation

Among the reputed side effects of extracorporeal shock wave lithotripsy[29–33] are increased sodium excretion and proteinuria. These effects are likely associated with structural and functional changes that lead to an increase in ionic and molecular permeability across the renal tubule. Recently, we have designed and conducted experiments that give real-time responses of biological membranes to high intensity acoustic pulses. There are, of course, several other studies in this area; however, the scope of this paper permits a description only of our own results. The abdominal region of frog skin, which has a reasonable similarity to that of the distal, convoluted, renal tubule, was used as a model membrane. Exposure of this tissue to a single shock produced by a research lithotripter caused a reversible increase in the total ionic conductance and a decrease in the short circuit current.[18] These results are similar to those observed by Dinno *et al.*,[19] with a 1-MHz therapeutic ultrasound device in which it was concluded that acoustic cavitation was the principal contributory factor. We present in Fig. 8 some recent results of our shock wave studies which again implicate acoustic cavitation as the principal source of the ion transport changes. It is also noted in Fig. 8 that in the presence of amiloride, a diuretic that blocks the movement of sodium, the short circuit current was stimulated by the acoustic shock wave. This effect points toward important functional changes of an electrochemical nature.

II. DISCUSSION

As indicated by the series of significant advances reported in the previous section, excellent progress has been made toward a fuller understanding of the phenomenon of cavitation inception by microsecond length pulses of ultrasound. Yet, there are still many unanswered questions that must be resolved before the potential risk associated with clinical ultrasound units can be accurately assessed. Some applicable comments follow.

A. *In vivo* cavitation will be extremely difficult to observe

With the development of the active cavitation detector it is now possible to observe even the most minute and transitory evidences of cavitation. Furthermore, since this system uses a form of energy propagation that is nearly transparent to biological tissue, it is now becoming possible to look for (and even expect to see) cavitation produced by a short acoustic pulse within certain types of tissue. Of course, as always happens in these situations, the extreme sensitivity of this device will make its application to *in vivo* studies most challenging: the intrinsic inhomogeneities present in biological tissue may cause the background to be overwhelming. Nevertheless, signal processing algorithms designed to enhance signal-to-noise by exploiting the scattering attributes which are unique to transient cavitation microbubbles are currently under development and show great promise. It is noted that evidence of gas bubble production *in vivo* has been obtained previously by ter Haar and Daniels;[34] however, their studies involved insonification with therapeutic ultrasound, either in a cw mode, or with a relatively long (of order milliseconds) pulse.

B. *In vivo* cavitation, if it does occur, may have few biological consequences

Although the energy deposition associated with a single cavitation event is enormous on a microscopic scale (tens of MeV's) such an event would most likely affect only one or a few cells and thus have little consequence. However, if such an event were to take place during the first 8 weeks of embryonic development,[20] when early histogenesis was occurring, the results may have larger impact. Embryonic cells are ionically coupled via gap junctions and these pathways provide for cell to cell communication through electrochemical signals. If cavitation occurs, with resultant free radical production, then changes in membrane potentials and currents along the dividing cells may lead to teratogenic changes. Thus although the number of damaged cells may be small, the sensitivity of the damaged area may be large. It is important also to note, however, that since there are probably few available cavitation nuclei, and conditions have to be optimal to activate them, the total number of *in vivo* events would most likely be small. Risk assessment, therefore, should focus on the possible sites for cavitation inception, and the consequences of small scale cellular damage at these sites.

C. Extra corporeal shockwave lithotripsy (ESWL) can provide us valuable information on what to expect from *in vivo* acoustic cavitation

Although a comparison between diagnostic ultrasound units and lithotripters may seem a bit tenuous, lithotripters also generate single cycle pulses of acoustic energy. They differ principally (and significantly) in the amplitude of the pulse and its temporal extent. It has been learned from ESWL studies that an acoustic shock wave can activate cavitation nuclei, *in vivo*, which, in addition to the desired stone communication, probably results in undesirable biological effects.[29–33] With lithotripters, the negative acoustic cycle is of sufficient length so that gas that is dissolved in the liquid is rapidly pumped into the expanding cavitation bubble.[21] The consequence of this diffusion is that preexisting nuclei are multiplied by the acoustic shock wave rather than destroyed. The analogy to diagnostic ultrasound instruments is this: If the pulse length is sufficiently long for a given PRF, or if the PRF is sufficiently high for a specified pulse length, any nuclei that are activated by a single pulse may survive to the succeeding pulse. If this occurs, rectified diffusion becomes important and the size and/or number of nuclei could be increased. Manifestations of such pulse length/PRF effects have been observed on several occasions in various *in vitro* and *in vivo* studies.[5,7–9,30] Furthermore, the evidence that a single lithotripter pulse can produce cavitation bubbles that result in high-velocity liquid jets of enormous local damage potential,[22,23] indicates that since diagnostic ultrasound devices also produce cavitation bubbles, these violent liquid jets are probably also generated by diagnostic instruments.

We are confident that future studies (our own or those of others) will soon give some guidelines as to what diagnostic ultrasound instrument output parameters should be monitored so as to reduce any potential risks of these widely used and extremely valuable instruments.

III. SUMMARY

Evidence is steadily being accumulated on the conditions under which microsecond length acoustic pulses similar to those used in diagnostic ultrasound units generate acoustic cavitation. Since this cavitation has been observed under simulated clinical conditions (although still only *in vitro*) this research should be of continuing interest.

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