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Studies of the cavitational effects of clinical ultrasound by sonoluminescence: 2. Thresholds for sonoluminescence from a therapeutic ultrasound beam and the effect of temperature and duty cycle

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Abstract. Sonoluminescence, produced when a therapeutic ultrasound generator operating at 1 MHz was used to insonate a tank of water, was detected using a photomultiplier tube and analysed using pulse height analysis. Spectra of the number of counts per second were obtained for the complete range of observed pulse heights, under exposure conditions similar to those used in clinical practice. Water containing different concentrations of dissolved gases and an agar solution were investigated during the course of the experiments.

Measurements were made to establish a threshold for sonoluminescence and the total sonoluminescent light output from tap water insonated with continuous wave ultrasound at 1 W cm^{-2} was estimated. The density of free radicals produced under these conditions was also estimated. The effects of temperature and duty cycle were investigated. Sonoluminescence increased with temperature over the range 22-45 °C and pulsed regimens produced more sonoluminescence than continuous wave ultrasound over a significant part of the pulse height spectrum.

1. Introduction

Sonoluminescence is the light emitted when a liquid is cavitated in a particular, violent manner (Harvey 1939) and the conditions that obtain during collapse cavitation may cause biological damage. The amount of sonoluminescence will depend on the nature of the liquid (Singal and Pancholy 1967), and its dissolved gases (Finch 1963), its temperature (Chendke and Fogler 1985), and hydrostatic pressure (Finch 1965), and the frequency (Griffing and Sette 1955), power and duty cycle of the ultrasound. A direct search for sonoluminescence *in vivo* is not normally possible and an assessment of the number and size of bubbles in body fluids and tissues is not easy (ter Haar and Daniels 1981). An alternative approach is to try to establish levels below which sonoluminescence is unlikely to occur. It should then be possible to state with greater confidence safe levels for work with ultrasound in patients. In this paper, some conditions under which sonoluminescence will occur in aqueous media are established and pulse height analysis is used to find the range of light outputs. An assessment is made of the amount of light produced in a given volume of liquid in a given time to provide an indication of the maximum amount of cavitation occurring under the conditions specified.

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Temperature effects have been investigated in the range 22-45 °C, and duty cycle experiments have compared continuous wave ultrasound and three pulsed regimens commonly employed by physiotherapists.

2. Materials and methods

A 1 MHz ultrasound generator (a Therasonic 1030, Electro-Medical Supplies) was used to generate intensities up to 3 W cm^{-2}. The available duty cycles were continuous wave, 1:2 (2 ms on and 4 ms off), 1:4 (2 ms on and 8 ms off) and 1:7 (2 ms on and 14 ms off). The power output of the generator was checked using a Biotec UWII Force Balance, and the manufacturer's figure of 440 mm^2 for the effective radiating area of the transducer was used to calculate spatial average temporal average (SATA) intensities. These figures agreed with the meter readings to within 10%. Using a needle hydrophone (Dapco NP10-3), the manufacturer's figures for the duty cycles were found to be accurate to within 5%, and are therefore adopted in this paper. The SATA intensities and the duty factors were used to calculate the spatial average temporal peak intensities for the pulsed regimens.

To study sonoluminescence the liquid to be investigated was placed in a glass tank on top of a photomultiplier (RCA 8575, photocathode diameter 50 mm) (figure 1) with the transducer facing downwards in the liquid. From hydrophone measurements of

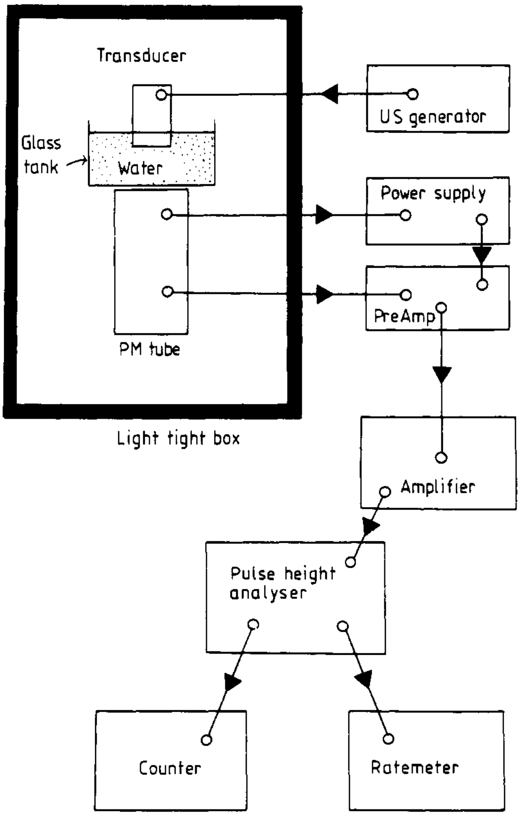

Figure 1. Schematic diagram of apparatus.

the acoustic reflection coefficients of a glass plate, the average reflection coefficient from the base of the glass tank was found to be in the range 45-62%. The transducer, tank and tube were enclosed in a wooden box which was covered with layers of blackout cloth.

Each collapsing bubble produced a short burst of light which appeared as a current pulse in the photomultiplier. A pulse height analyser with differential discriminator was used to count the pulses and to analyse the distribution of pulse heights in the light burst. For some of the temperature studies described in §3.4, this counting system was replaced by a Levell multitester type TM11 nanoammeter and an EMI 9781B side window photomultiplier with light guide was used. In some experiments the light intensity reaching the photomultiplier was reduced by inserting neutral density filters between the glass tank and the photomultiplier tube.

For the main set of experiments reported, freshly drawn tap water was used. This was allowed to settle and experiments were performed between 1 and 5 h later. In some cases tap water that had been left to stand for a few days, distilled or degassed water was used. The gas content of the water samples was measured using a Corning 178 pH/blood gas analyser. In one experiment, a solution of 1.875% agar, prepared by adding agar to boiling water, was used. After cooling, its viscosity was 170 cp.

The sonoluminescence produced was compared with a calibrated beta light, which gave a photon flux of 5×10^8 photons per second. The beta light has a faint yellow appearance so the wavelength of the light emitted is in the region of 580 nm. Sonoluminescence is essentially a black body radiation over the range 400-700 nm (Gunther *et al* 1959). Thus the 580 nm of the beta light is representative of the middle of the wavelength range of sonoluminescence and the overall detection efficiency of the system will be similar for the two sources of light. The effect of temperature was investigated using a thermoregulator and thermocouple (FH 15-V, Grant Instruments (Cambridge) Ltd). The water was heated to 37.9 °C and circulated around the water bath. To allow for clear viewing the thermoregulator was then switched off while readings were taken. When the temperature dropped to 36.5 °C, the thermoregulator was switched on. This range of temperatures centres on the normal body temperature of around 37 °C.

3. Results

3.1. Background spectrum

Since the ultrasonic vibrations could be transmitted to the photomultiplier tube in the experimental arrangement of figure 1, the background was tested in two ways: (1) with the ultrasound switched off; (2) with a continuous high power beam switched on, but with a piece of black card placed between the water tank and the photomultiplier tube to intercept any visible light generated. Both methods produced the same spectrum (figure 2(*a*)).

3.2. Threshold measurements

With freshly drawn tap water at room temperature in the tank, no difference was found between the pulse height spectrum generated at low intensities of ultrasound (<0.1 W cm^{-2}) and that produced under background conditions. At higher intensities (figure 2(*a*)) there was a marked increase in count rate for a given pulse height and

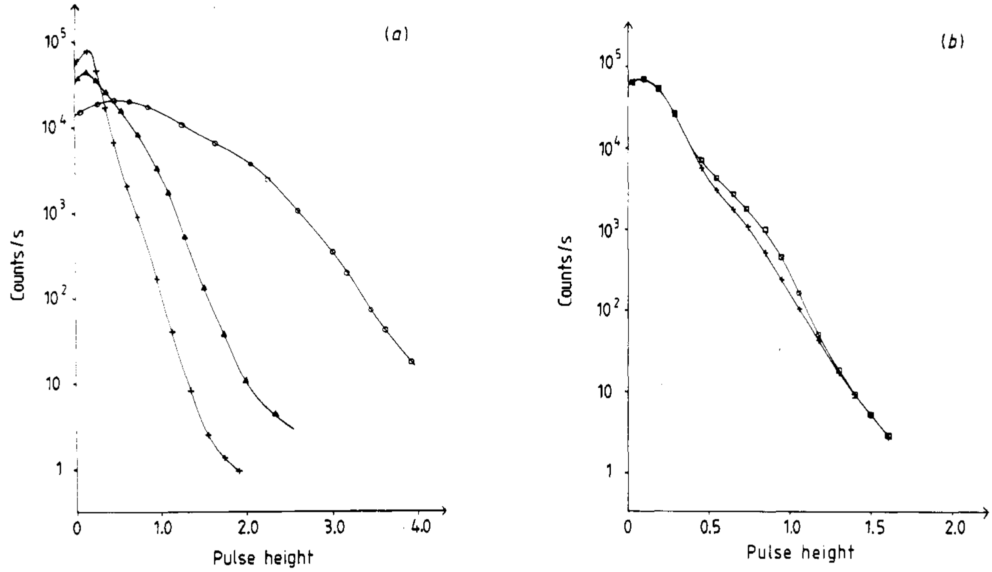

Figure 2. Sonoluminescence spectra from fresh tap water insonated with continuous wave, 1 MHz ultrasound, at various intensities: (*a*) (+) background; (▲) 0.5 W cm^{-2}; (○) 1.0 W cm^{-2}. (*b*) (+) background; (□) 0.25 W cm^{-2}. Every third point is shown on these graphs and figures 4, 5 and 8. This is sufficient to indicate the forms of the spectra, even on this log scale. Error bars are not shown as they are less than the size of the symbols; this also applies to figures 4-6 and 8. The crossing over of curves at very small pulse heights is the combined effect of pulse pile-up and saturation in the photomultiplier tube.

a shift in the mean pulse height to a higher value. The increases continued with intensity up to 3 W cm^{-2}, the highest intensity measured.

At 0.25 W cm^{-2} (see figure 2(*b*)), there was a slight, but not insignificant, increase in the recorded count rate over a range of pulse heights, so the threshold for cavitation-induced sonoluminescence, under the conditions described, lies between 0.1 and 0.25 W cm^{-2}. With our standing wave system, 0.25 W cm^{-2} corresponds to a pressure amplitude of 126-140 kPa at an antinode, and 33-48 kPa at a node. We have attempted to demonstrate that this is primarily a threshold and not simply a limit on the sensitivity of the detection system. Figure 2(*b*) can be used to find the percentage increase in light output over background at 0.25 W cm^{-2} for different pulse heights. The most sensitive pulse height for detection of sonoluminescence is 1.0. Figure 3 shows the percentage increase in sonoluminescence at this pulse height for the full range of powers investigated. Above the detection limit, light output rises extremely rapidly with increasing intensity.

When distilled or degassed water was used, the threshold for sonoluminescence was found to be higher, and for a given set of conditions the spectra were more similar to the background spectrum (figure 4). The results of measurements of partial pressures of O_2 and CO_2 for the various types of water are shown in table 1.

3.3 Assay of light output

Neutral density filters, increasing in value by 0.2, were inserted between the tank of freshly drawn tap water and the photomultiplier tube. At 1 W cm^{-2} a neutral density

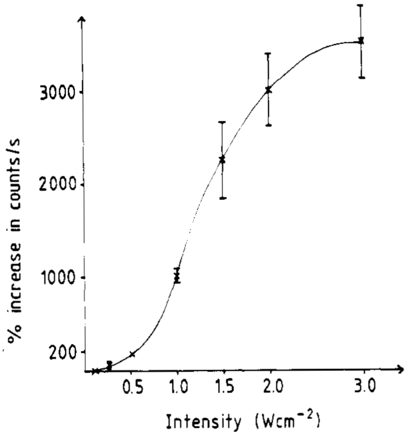

Figure 3. Percentage increase in count rate for different intensities of ultrasound at a pulse height of 1.0. The curve shows a sigmoid shape, which frequently characterises a threshold phenomenon. If the % increase is plotted on a logarithmic scale, it is clear that the threshold lies between 0.1 and 0.25 W cm^{-2}.

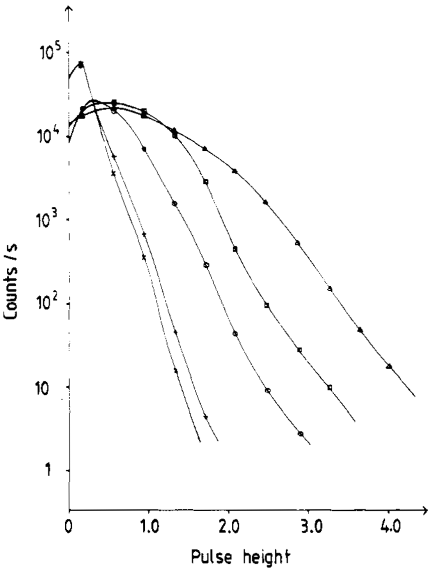

Figure 4. Spectra obtained by insonating (△) freshly drawn tap water; (□) old tap water; (○) degassed water; (+) distilled water, with 1 MHz, continuous wave ultrasound of intensity 1 W cm^{-2}. (×) is a background spectrum.

Table 1. Partial pressures of oxygen and carbon dioxide for various samples of water.

Sample	PO_2 (kPa)	PCO_2 (kPa)
Freshly drawn tap water	17.2	2.4
Old tap water (left to stand for a few days)	19.8	0.9
Distilled water	24.3	0.5
Degassed water	11.7	0.9

filter of value 2.0 was the minimum that produced a spectrum indistinguishable from background. Thus by attenuating 99 in every 100 photons, the limit of detection of this system has been reached. When filters were inserted between the beta light and the photomultiplier, a neutral density filter of value 5.0 was required, indicating that the sonoluminescence was 1000 times less intense than the photon flux from this source. Hence the photon flux from sonoluminescence will be of the order of 5×10^5 photons per second.

3.4. Effect of temperature

Figure 5 shows that increasing the temperature to 37 °C always produced more sonoluminescence for 1 MHz continuous wave ultrasound at 1 W cm^{-2}. The same effect was observed at 0.5 W cm^{-2}, and also with 1 : 4 pulsed ultrasound. The background count is greater at the higher temperature, an effect that is primarily due to warming of the photomultiplier, but inspection of the curves at a pulse height where the background is negligible at both temperatures shows that the increase in sonoluminescence is real.

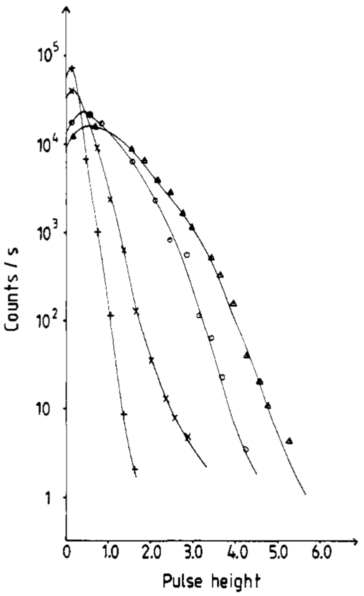

Figure 5. The effect of temperature on the sonoluminescence spectra. Samples were insonated with 1 MHz continuous wave ultrasound at 1 W cm^{-2}. (+) background at 22 °C; (×) background at 37 °C; (○) with ultrasound at 22 °C; (△) with ultrasound at 37 °C.

Figure 6 is an expanded version of the results at 37 °C when 1 : 4 pulsed ultrasound was used. This spectral curve contains several peaks, which correspond exactly to readings taken at 37.9 °C, subsequent readings being at successively lower temperatures until the next heating (see §2). This is further confirmation that light output is greater at higher temperatures and shows that the effect can be observed even when the change in temperature is small.

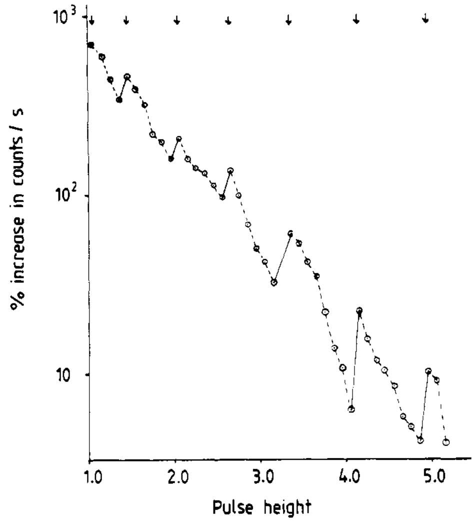

Figure 6. Expanded version of part of the sonoluminescence spectrum from pulsed ultrasound (duty cycle 1:4) at 1 W cm^{-2} at 37 °C. All the points are shown. The vertical arrows indicate readings taken at 37.9 °C, with subsequent readings (to the right) being taken at lower temperatures until the next arrowed point where the water was reheated to 37.9 °C. Background has been subtracted from all readings.

The variation of sonoluminescence with temperature for pulse heights below 0.5 is not amenable to testing with the above methodology because of saturation of the photomultiplier. The temperature variation was therefore also tested simultaneously over the entire range of pulse heights, by replacing the photomultiplier and counting system with the EMI 9781B photomultiplier and nanoammeter. Sonoluminescence produced in the water bath was carried to the photomultiplier tube by a light guide, so temperature variations in the bath did not affect the photomultiplier.

The results show an increase of sonoluminescence with temperature in the range 22-45 °C (figure 7), for ultrasound intensities of 1 and 3 W cm^{-2}. In all cases a constant dark current of 0.11 nA has been subtracted.

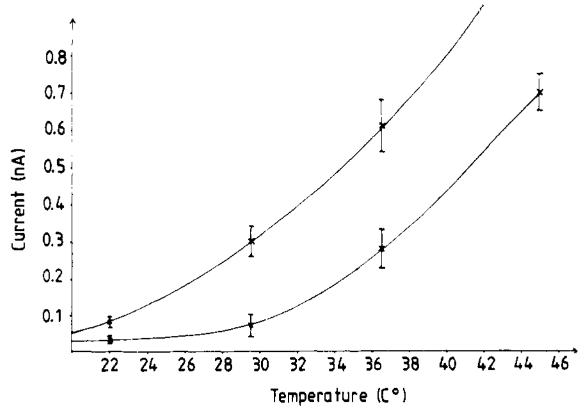

Figure 7. Total photomultiplier current as a function of temperature: lower curve, 1 W cm^{-2}; upper curve, 3 W cm^{-2}.

3.5. Effect of duty cycle

The effect of changing the duty cycle was investigated, keeping the frequency fixed at 1 MHz and the spatial average temporal peak intensity fixed at 1 W cm^{-2}. The continuous wave beam would be expected to give the highest count rate for all pulse heights, with the 1 : 2 duty cycle next, followed by the 1 : 4, then the 1 : 7, and the count rate should be in the ratio 1 : 1/3 : 1/5 : 1/8. This is indeed observed for the smaller pulse heights, but as the discriminator level is set higher, the continuous wave spectrum falls off faster than the others (figure 8(*a*)). At very large pulses, the 1 : 7 duty cycle produces most light, followed by 1 : 4, 1 : 2, and continuous wave ultrasound.

When degassed water was insonated, the curves still crossed over but at lower light levels (figure 8(*b*)). If an agar gel was used instead of freshly drawn tap water, no crossing over of the four curves was seen, and the continuous wave ultrasound always

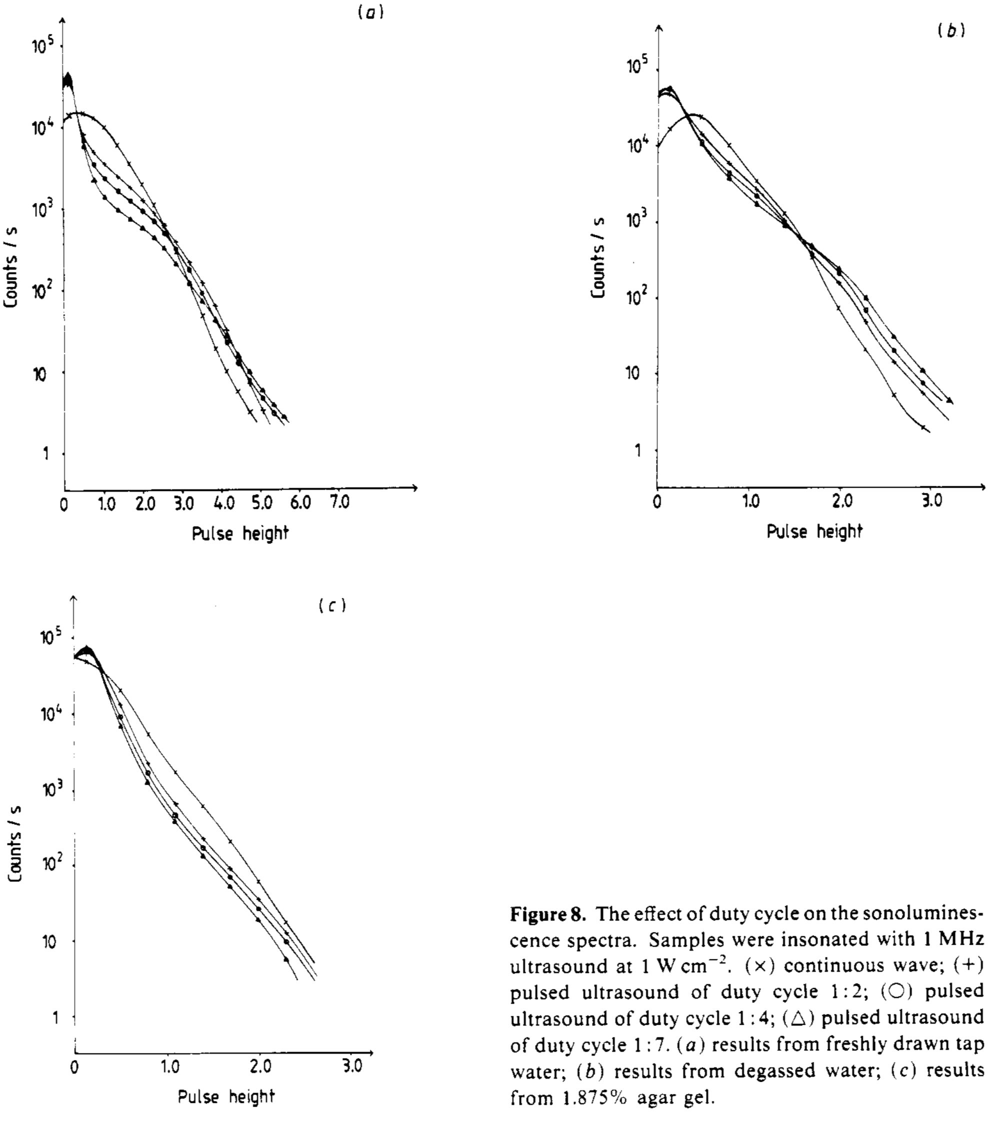

Figure 8. The effect of duty cycle on the sonoluminescence spectra. Samples were insonated with 1 MHz ultrasound at 1 W cm^{-2}. (×) continuous wave; (+) pulsed ultrasound of duty cycle 1 : 2; (○) pulsed ultrasound of duty cycle 1 : 4; (△) pulsed ultrasound of duty cycle 1 : 7. (*a*) results from freshly drawn tap water; (*b*) results from degassed water; (*c*) results from 1.875% agar gel.

produced most light (figure 8(*c*)). When using agar the insonated medium contained less gas, because preparation of the gel involved boiling, but it was also more viscous. Note that because of the log scale in figure 8, the differences in light output are quite large and were consistently reproducible.

4. Discussion

4.1. Threshold measurements

When tap water was insonated with 1 MHz continuous wave ultrasound, light output was a function of ultrasound power output (figure 2(*a*)). If the ultrasonic power was gradually reduced, the minimum intensity at which sonoluminescence was just discernible was about 0.25 $\mathrm{W\,cm^{-2}}$ (figure 2(*b*)). No sonoluminescence was ever detected at intensities below 0.1 $\mathrm{W\,cm^{-2}}$. The steep rise in sonoluminescent output with intensity in the most sensitive part of the detector range suggests that this is a threshold for our system for practical purposes.

4.2. Gas content

Freshly drawn tap water always gave more sonoluminescence than either degassed tap water or distilled water (figure 4). There are few measurements reported in the literature on the gaseous condition of liquids during sonoluminescence experiments. The data in table 1 and figure 4 indicate that in our work the partial pressures of both oxygen and carbon dioxide may affect light output. Comparison of the first three sets of figures suggests that dissolved CO_2 is an important source of gas required for bubble growth prior to unstable collapse. Although distilled water showed a higher PO_2 than degassed water, it should be noted that the process of distillation is likely to remove a number of potential nucleation sites as well as dissolved gas.

4.3. Light output measurements

At 1 $\mathrm{W\,cm^{-2}}$ and 1 MHz, the photon flux from sonoluminescence was of the order of 5×10^5 photons per second. The region of water under investigation had a volume of about 20-25 $\mathrm{cm^3}$, so the photon flux was 2×10^4 photons $\mathrm{cm^{-3}\,s^{-1}}$. Assuming that each free radical pair produced one photon when it recombined, this is also an estimate of the number of free radicals produced per $\mathrm{cm^3}$. It is of interest to note that background radiation produces free radicals as a result of ionisation at a rate of approximately 10^4 ion pairs $\mathrm{cm^{-3}\,s^{-1}}$. Using different insonation conditions, Carmichael *et al* (1986) have reported free radical concentrations from sonoluminescence comparable to those produced by 10 μGy of ^{60}Co gamma radiation. We have shown (Leighton *et al* 1988) that sonoluminescence and hence presumably the free radicals can be highly localised at the pressure antinodes.

4.4. Temperature

Results in figures 5, 6 and 7 show conclusively, using two independent systems, that sonoluminescence increased with temperature in the range 22-45 °C for our experimental system. Such a conclusion is consistent with an early observation of Blake (1949), who showed that cavitation thresholds decreased with temperature. We are aware that there are a number of reports in the literature suggesting that over most, if not all, of the temperature range studied here, sonoluminescence falls with temperature (Sehgal *et al* 1980, Chendke and Fogler 1985, Jarman 1959, Iernetti 1972). However, all these workers used frequencies lower than MHz, most used liquids other than water and some found an increase in sonoluminescence with temperature over part of the temperature range they studied. Furthermore, other factors likely to affect the amount of sonoluminescence were not always well controlled. The results in figures 6 and 7, which were repeated on several occasions, appear to show conclusively that sonoluminescence increases with temperature.

4.5. Duty cycle

For large pulse heights, continuous wave ultrasound produces least light in water, whilst the 1:7 duty cycle produces most, even though the ultrasound is on for the shortest time. This effect is not seen in agar, where continuous wave ultrasound produces the most light for all pulse heights.

Pulsed enhancement of the effects of stable cavitation has been reported by Hill *et al* (1969), and Ciaravino *et al* (1981) reported pulsed enhancement of unstable cavitation. These workers were using different experimental conditions and different regimens, and their explanations, and those of Flynn and Church (1984) cannot entirely explain our results. The transient excitation theory proposed by Leighton *et al* (1988) will cause pulsed enhancement of sonoluminescence. However, this cannot explain all the features of figures 8(*a*), (*b*) and (*c*), particularly the crossing over phenomenon. The explanation we favour is based on the clustering of small bubbles at the pressure antinodes as a result of Bjerknes forces (Walton and Reynolds 1984). This creates local degassing and acoustic impedance mismatch, thereby inhibiting cavitation. The bubbles migrate away from the pressure antinodes during the off-time and some regassing of the medium occurs. They return when the sound is switched on again. Theoretical calculations (Leighton to be published) show that this explanation is consistent with the time scale of bubble migration required to explain the results of figure 8. The crossing over effect did not occur in agar where bubble migration would be greatly reduced. In future work the effect of pulsing will be studied in agar solutions of different concentration. The anomalous behaviour of pulsed ultrasound might not occur in body tissues, but the behaviour of blood, which is of intermediate viscosity, cannot be predicted without further experiments.

Experiments are also in progress, using the conditions known to cause sonoluminescence in water, to study the viability of mammalian cells when insonated in aqueous media and in agar, and to search for direct evidence of sonoluminescence in biological tissues.

Acknowledgments

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Résumé

Etude par sonoluminescence des effets de cavitation des ultrasons utilisés en clinique: 2. Seuils de sonoluminescence pour un faisceau d'ultrasons à usage thérapeutique et effet de la température et des conditions d'utilisation.

Les auteurs ont détecté, à l'aide d'un photomultiplicateur et d'un analyseur de hauteurs d'impulsions, la sonoluminescence produite lors de l'irradiation d'un récipient d'eau avec un générateur d'ultrasons à usage thérapeutique fonctionnant à 1 MHz. Les spectres des nombres d'impulsions par seconde ont été obtenus pour toute la gamme des hauteurs d'impulsions observées, dans des conditions d'exposition comparables à celles utilisées en pratique clinique. Pendant les expérimentations, les auteurs ont effectué des essais avec de l'eau contenant diverses concentrations de gaz dissous et une solution d'agar. Les auteurs ont affectué des mesures pour établir le seuil de sonoluminescence et la production totale de lumière sonoluminescente pour de l'eau du robinet irradiée avec des ultrasons en onde entretenue à 1 W cm^{-2}. Ils ont aussi évalué la densité de radicaux libres produits dans ces conditions. Ils ont recherché les effets de la température et du temps d'utilisation. Il est apparu que la sonoluminescence s'accroît avec la température dans la gamme 22-45 °C et que les régimes pulses produisent plus de sonoluminescence que les ultrasons en onde entretenue dans une portion significative du spectre en hauteurs d'impulsions.

Zusammenfassung

Untersuchungen der Kavitationseffekte von klinischem Ultraschall durch Sonolumineszenz: 2. Schwellenwerte für die Sonolumineszenz bei einem therapeutischen Ultraschallstrahl und der Einfluß von Temperatur und Impulsleistungsverhältnis.

Die Sonolumineszenz, die entsteht, wenn ein therapeutischer Ultraschallgenerator bei 1 MHz betrieben wird, wurde zur Beschallung eines Wassertanks verwendet. Der Nachweis erfolgte mit einem Photomultipier und die Analyse mit Hilfe eines Impulshöhenanalysators. Die Verteilung der Anzahl der Impulse pro Sekunde wurde erhalten für den gesamten Bereich der beobachteten Impulshöhen, wobei die Bedingungen ähnlich denen in der klinischen Praxis waren. Wasser mit verschiedenen Konzentrationen an gelösten Gasen und eine Agarlösung wurden untersucht im Laufe der Experimente. Messungen wurden durchgeführt, um einen Schwellenwert für die Sonolumineszenz festzustellen. Die gesamte Lumineszenz-Lichtausbeute von Leitungswasser, beschallt mit kontinulierlichen Ultraschallwellen bei 1 W cm^{-2} wurde bestimmt. Der Einfluß von Temperatur und Impulsleistungsverhältnis wurde untersucht. Die Sonolumineszenz steigt mit der Temperatur über einen Bereich von 22-45 °C und gepulste Wellenformen erzeugen mehr Sonolumineszenz als Ultraschall mit kontinuierlichen Wellen über einen großen Teil des Impulshöhenspektrums.

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