CLOUD CAVITATION CONTROL FOR A THERAPEUTIC ULTRASOUND APPLICATION

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ABSTRACT

In the therapeutic ultrasound field, the cavitation frequently forms a bubble cloud that consists of many microbubbles. A method to control the violent collapse of cloud cavitation is being developed. It is comprised of two frequencies ultrasound. The first is a higher frequency ultrasound waveform that makes cloud cavitation at the surface of the object. The second is a lower frequency waveform that produces a violent collapse of the cloud cavitation. If the phenomena is well controlled in time and space, it can be utilized for the therapeutic benefit such as sonoporation, HIFU, and lithotripsy. From a numerical simulation, the controllability of the cloud cavitation is predicted [1,2]. A stable bubble cloud at the solid surface and the shock wave from the violent cloud cavitation collapse are observed by using high-speed camera photography. The shock wave pressure is estimated to be in the order of a few GPa at the solid surface. And the occurrence time of the phenomena is controlled within 65 ns and the area is controlled within 1 mm. Using the method, stones are chipped away such that scoop-like indentations are achieved with the efficiency that is comparable to the conventional Shock Wave Lithotripsy.

INTRODUCTION

In a HIFU application, high intensity ultrasound causes acoustic cavitation near the focal area. The violent collapse of cavitation bubble has a potential of causing tissue traumas [3], especially in the case in which the bubbles form a cloud. The maximum pressure in the cloud that reaches order of GPa is reported both in numerical [4] and experimental [5] studies.

On the other hand in the study of SWL (Shock Wave Lithotripsy), the complex effect of cavitation has been known in the early stage of its research history [6] and many researchers have investigated the role of the cavitation in SWL. The studies were conducted both as the factor of tissue damage [3], and of stone comminution accelerator [7]. In recently, cavitation control techniques by applying skillful shock wave combinations have been proposed and effective results have been achieved [8,9]. However, the main force that breaks the stone is still considered to be the incident plane shock wave that has a 10 ~ 40 mm focal region. Moreover cavitation collapse is utilized only to accelerate the stone comminution.

By utilizing two frequency focused ultrasound, extracorporeal lithotripsy method, Cavitation Control Lithotripsy (CCL) is being developed [10], that can erode and chip away the renal stone solely by the violent collapse of the cavitation that is induced by HIFU. If the cavitation phenomena are well controlled in time and space only at the stone surface, the extremely high-energy and high-pressure concentration can be utilized as a main factor of renal stone disintegration. In this paper, the concept of the method and the phenomena in the CCL protocol are explained and the results of the stone crushing are also discussed.

SCHEMATIC OF CLOUD CAVITATION CONTROL

Fig. 1 shows the schematic of Cavitation Control Lithotripsy (CCL). CCL method is comprised of two different of ultrasound frequencies. First, higher frequency ultrasound is focused at the stone surface (Fig. 1-1). It has a range about 1 ~ 5 MHz in its frequency for a shorter wavelength than the characteristic length of the renal stone. It creates a hemispherical bubble cloud consisting of very tiny bubbles only at the stone surface (Fig. 1-2). Immediately after the higher frequency is stopped, a short pulse of lower frequency ultrasound that has 100 kHz ~ 1 MHz in its frequency is focused at the hemispherical bubble cloud (Fig. 1-3). The lower one resonantly forces the cloud to oscillate (Fig. 1-4). Accompanied with the bubble cloud forced
Fig. 1: Schematic of cloud cavitation control

Fig. 2: Typical cavitation control waveform

Fig. 3: Experimental set-up

Fig. 4: Acoustic signal of one CCL cycle: Hydrophone is placed 1.6 mm away from the focal point.

oscillation, shock wave propagates inward from the hemispherical bubble cloud [1,4] (Fig. 12-5). At the center of the bubble cloud, the bubbles near the center collapse violently while they emit an extremely high-pressure wave that reaches order of GPa [4]. Therefore, only at the stone surface the stone is crushed resulting in scoop-like indentations, with a high-energy concentration and also with the minimum amount of cavitation.

Fig. 2 is the typical cavitation control ultrasound waveform. As indicated previously, high frequency ultrasound (bubble cloud creator) is immediately followed by low frequency ultrasound (cloud collapse inducer). The interval time should be enough long to dissolve all of the cavitation bubble into liquid. If this scheme can be finely controlled within cavitation area in space and the occurrence time of the bubble cloud collapse, a lithotripsy method utilizing only cavitation erosion can be developed that produces less tissue damage and more tiny fragments than conventional SWL.

BEHAVIOR OF BUBBLE CLOUD IN CCL METHOD

In this section, the observed bubble cloud phenomena in the CCL cycle are discussed. Fig. 3 shows the experimental set up. The concave PZT ceramics diaphragms that have the natural frequencies of 1.0 MHz and 500 kHz are used for the ultrasound transducer. They transmit higher amplitude of ultrasound at the frequencies of (2n+1) times of the fundamental frequencies than the other frequencies. Appropriate higher order harmonics coupled with fundamental frequency is used to realize CCL waveform (Fig. 2) by one PZT transducer. The maximum output voltage of CCL waveform is 1.6 kV in its peak-to-peak amplitude.

The aluminum ball or artificial stone, which is used as the crushing test material of the SWL machine, is fixed at the focus point. The cavitation phenomena at the focal point of the ultrasound are photographed by the ultra high-speed camera (IMACON200, DRS Hadland). It has the ability to take 16 frames with 5 ns in the exposure time and 5 ns in the minimum frame interval. IMOTEC needle hydrophone is placed near the focal region to detect the synchronized signal of the shock wave emitted by the cavitation collapse. The O2 concentration is controlled in 1 – 2 ppm during the high-speed photography.

PHENOMENA IN A CCL CYCLE

Fig. 4 is an overview of the acoustic signal of one CCL cycle that is taken 1.6 mm away from the focal point of focused ultrasound. The waveform is the same in Fig. 2. The maximum input voltage is 1.6 kV (peak-peak). First 46 µs high frequency ultrasound is irradiated. Around 20 µs cavitation bubbles begin to appear and grow. The acoustic signal also begins to be distorted at that point. Immediately after 46 µs irradiation of high frequency ultrasound, the frequency is switched to low frequency ultrasound. The bubble cloud is forced to oscillate by
low frequency ultrasound and one strong collapse signal at around 50 µs is observed. After low frequency ultrasound stopped, residual bubbles coalesce with each other becoming a few big bubbles dissolving into liquid phase while they collapse into each other and emit several small collapse signals. To eliminate the residual bubbles as the uncontrollable cavitation nuclei, a interval time enough long for them to dissolve into liquid phase is needed. In every case the PRF (Pulse repetition frequency) is fixed to 20 Hz, i.e. 50 ms interval time.

From the next section, the cavitation phenomena both in high and low frequency irradiation phases is shown in detail.

**High frequency phase: Stable cloud cavitation**

Fig. 5 shows the growth of cloud cavitation in the focal region of 1.64 MHz focused ultrasound. Taking into account the reproducibility of the phenomena, photographs of three different cases, which are shifted in the photographed time, are aligned. The time in the figure is the duration of 1.64 MHz focused ultrasound irradiation.

Cavitation bubbles are first generated and grow at the solid surface, because focused ultrasound creates a standing wave antinode at the solid surface and also the solid surface in itself promotes cavitation nucleation. After 16 µs irradiation of ultrasound, bubble clouds that can be recognized in the picture appear. Individual bubbles that consists cloud grow and collapse repeatedly along the ultrasound pressure fluctuation. When the bubbles collapse they fission and supply new cavitation nuclei [11]. The bubble clouds coalesce with each other around 40 µs, and form a hemispherical cloud cavitation on the solid surface. Afterward, the bubble cloud does not change in its size and shape. At 50 – 60 µs, it stays a stable bubble cloud. It is known that, inward bubbly flow, the wave that has the frequency beyond the natural frequency of the containing bubble does not propagate [12]. When the bubble cloud maintains stable shape, the ultrasound is almost all scattered at the surface of the bubble cloud, and does not proceed into the bubble cloud, and individual bubbles in the cloud are not affected by the ultrasound. Therefore, Fig. 5 shows that the bubble cloud maintains stable shape with conserving its void fraction and bubble cloud size after a certain irradiation period of ultrasound.

This result also indicates that continuous irradiation of focused ultrasound cannot transmit its energy efficiently to the solid surface. The bubble cloud that is induced by focused ultrasound shields the propagation of ultrasound to the solid surface, as shown in Fig. 5.

Fig. 6 shows the stable bubble clouds made by the different single frequency ultrasound at the focal point. After 100 - 200 µs irradiation of the single frequency ultrasound, stable bubble clouds are observed similarly. The bubble size seems to be dependent on the ultrasound frequency. Fig. 7 shows the measured characteristic length of the bubble cloud for different frequency. Then, there is a strong relationship between the size of the bubble cloud and ultrasound wavelength. At the focal point, because the standing wave field that is created by the incident and reflected ultrasound wave determines the pressure field, the size of stable bubble cloud is considered to be dependent on the wavelength of ultrasound. Fig.6 and 7 shows that the sizes of the area generated by the bubble cloud can be controlled with respect to the ultrasound frequency in the area restricted within 1 mm when ultrasound frequency is more than 1 MHz, i.e., in the focused ultrasound field, acoustic cavitation at the solid surface can be well controlled in space.

![Fig. 5: Growth of cloud cavitation: Ultrasound frequency is 1.64 MHz, interframe 2.0 µs, exposure 50 ns](image)

![Fig. 6: Stable cloud cavitation in various ultrasound frequencies](image)

![Fig. 7: Characteristic length of stable cloud cavitation](image)
**Low frequency phase: Bubble cloud collapse**

In the previous section, it is shown that focused ultrasound can create stable size cloud cavitation at the solid surface. If such stable cloud cavitation is forced to oscillate by the appropriate resonance frequency of the cloud, high-energy concentration at the center of the bubble cloud can be realized. In this section the stable bubble cloud is forced to oscillate by the low frequency ultrasound. And the high-pressure concentration and the reproducibility of the phenomena are examined by using hydrophone and high-speed photography.

Fig. 8 shows the photographs of the bubble cloud forced into oscillation. Immediately after 100 µs irradiation of 2.75 MHz ultrasound, 545 kHz pulse ultrasound is focused upon the cloud. The stable bubble cloud is forced to oscillate by 545 kHz ultrasound. The bubble cloud shrinks at the positive phase of 545 kHz ultrasound decreasing each bubble radii, and then at the 4th frame, the bubble cloud is forced to collapse. Shadowgraph photography of the shock waves emitted from the cavitation bubble collapses are shown in Fig. 9. Immediately after 46 µs irradiation of 3.82 MHz ultrasound, 545 kHz pulse ultrasound is focused upon the cloud. The hemispherical shock wave propagation from bubble cloud is observed. First frame of Fig. 9 corresponds to the phenomena that happened immediately behind the 4th frame of Fig. 8, for different frequency.

These cloud-collapsing phenomena are observed in the same frame for different cases. Then the reproducibility of the phenomena is indicated. Whereas, as shown in Fig. 10, only by 545 kHz ultrasound, i.e., low frequency only, cavitation bubbles are distributed in wider area and the shock waves occur also randomly in time. In this case individual bubbles are considered to collapse independent with each other.

![Fig. 8: A forced cloud cavitation collapse](image1)

![Fig. 9: Shock wave propagation from the cloud collapse](image2)

Fig. 11 shows the time history of the acoustic signals of hydrophone that is placed 1.6 mm away from the focal point. The acoustic signals are synchronized with the phenomena of Fig. 9 and Fig. 10. Solid line corresponds to the acoustic signal of Fig. 9. Broken line corresponds to that of Fig. 10. Peak amplitude of shock pressure that is considered to be the signal of bubble collapses overlap the acoustic signal time history against their occurrence time. They are taken from 15 different acoustic signals of the same condition of Fig. 9 and Fig. 10. They are plotted as the symbols of “○” and “▲”.

Low frequency (545 kHz) ultrasound creates wide area cavitation and they collapse as individual bubbles. Therefore, the shock pressures occur also wide in time. Maximum pressure is not so high, at most 2 MPa. But, when applying high frequency and low frequency combination waveform (CCL method), cloud cavitation collapse is strongly induced and shock pressure that reaches 3 MPa is observed once in the time history. Fig. 12 shows magnification of the cloud collapse occurrence time in Fig. 11. This shows the CCL method triggers the bubble cloud collapse with a very high reproducibility. The standard deviation of the occurrence time is 65 ns.

It is concluded that cloud cavitation collapsing phenomena can be well controlled in time with a high pressure and energy concentration at the solid surface.
Fig. 12 Magnification of the pressure peak occurrence time of the cloud collapse: 40 cases (15 cases are also shown in Fig. 11 as circle symbols)

Fig. 13 Maximum pressure to the number of cycles of 545 kHz low frequency ultrasound.

**Low frequency effect for uncontrollable cavitation**

Fig. 13 shows the maximum shock wave pressure to the number of the low frequency. Red circles indicate maximum acoustic pressures of the CCL method and blue triangles indicate that of 545 kHz ultrasound. When the number of the cycle is one, maximum pressure of the CCL method is at most 1 MPa, which are the same with the case of low frequency only. At the second cycle of 545 kHz ultrasound, bubble cloud is forced to oscillate and the maximum pressure reaches 3 MPa.

To the contrary, in the case of CCL, the increase of the low frequency cycles does not affect the maximum pressure. Maximum shock pressure is saturated at 2 cycles of low frequency. This is strongly related to the cavitation phenomena that is induced by low frequency ultrasound in itself.

Fig. 14 is high-speed photography that is taken during the low frequency 1st – 5th cycle, which is forced upon the bubble cloud immediately after the high frequency ultrasound is stopped. The first frame, the 1st cycle of low frequency hits the stable bubble cloud. The bubble cloud does not react to the 1st cycle. Next, the 2nd cycle of ultrasound hits the cloud. Bubble cloud is forced to collapse, and then a strong shock wave is seen in the 5th – 7th frames. From the 7th frame, cavitation bubbles that are not attached to the solid surface begin to be generated with the increase the cycles of low frequency. They block the ultrasound propagation toward the bubble cloud with growing in size and collapse randomly as seen in the 12th – 15th frames. Such low frequency induced cavitation bubbles are distributed in wide area and are not attached to solid surface, so their collapsing phenomena is hard to control. To avoid their random collapse, the number of low frequency cycles should be 2. Because the strongest bubble cloud collapse occur at the 2nd cycle of the low frequency ultrasound as indicated in Fig. 13 and Fig. 14.

The residual bubbles that are seen in Fig. 20 coalesce with each other and turn into a few big bubbles and they collapse afterward. Fig. 15 is the residual bubble collapses. They also emit a shock wave, although their maximum pressures are at most 1 MPa at 1.6 mm away from the focal point (seen in Fig. 4: 100 – 120 µs).

It is important that every cavitation bubble in CCL method is restricted within 1 mm from the solid surface; even if low frequency induced bubbles are included. This means, CCL method can realize potentially less invasive renal stone treatment, compared with conventional SWL that has 10 - 40 mm cavitation area.
SHOCK WAVE VELOCITY OF CLOUD COLLAPSE

In this section the result of the shock wave velocity measurement is discussed. If the shock wave pressure of the bubble collapse is high enough that the water compressibility cannot be neglected, the shock wave propagates with higher velocity than the normal sound speed [13]. Fig. 17 and Fig. 18 show the measured shock velocity of the single bubble collapses (as shown in Fig. 13) and the bubble cloud collapses (as shown in Fig. 9), which are seen in the CCL method.

Assuming that the shock wave is spherical, the shock wave distance between the two consecutive photographs are divided by the interframe. In every case, the photographs that were taken with 100 ns interframe and 5 ns exposure time are used. The error of ±1 pix corresponds ±42 m/s error. And the total accuracy of shock velocity is about ±100 m/s in Fig 17, and ±400 m/s in Fig. 18. Though this value is a little large, the tendency is quite obvious as shown in Fig. 17 and Fig. 18.

In Fig. 17, single bubble case, shock velocity reaches 1700 m/s around 200 µm from the center of the collapse. And it decays exponentially to the sound speed of water. Fig. 15 shows the cloud collapse shock velocity. Near the cloud, the shock velocity is below the sound velocity of water. In a bubbly liquid, sound velocity falls below the single-phase sound velocity [14]. This phenomena may happen in this case. Then the shock wave increases its speed, and reaches 2000 m/s at 400 – 500 µm from the cloud center. After that, it decays to the normal sound velocity of water.

The relation between shock wave pressure and shock wave velocity are given by Cole [15] as equation (1). Where $p$ is shock wave pressure, $B = 275$ MPa and $n = 7.44$ are the constants in Tait equation, $v$ is the shock wave velocity and $c (=1472$ m/s at 290 K) is sound velocity of water.

$$p = B \left( \frac{n-1}{n+1} \left( \frac{v}{c} - 1 \right) + 1 \right)^{\alpha (v/c-1)} - B$$  \hspace{1cm} (1)

By estimating shock pressure by this equation, 1700 m/s corresponds to about 180 MPa, and 2000 m/s corresponds to about 470 MPa. This indicates that the shock pressure reaches the order of GPa at the center of the bubble cloud.

Consequently the CCL method is summarized as follows. By utilizing two different ultrasound frequencies, (1) cavitation area can be restricted within 1mm in space,(2) cloud collapsing phenomena is controlled within 65 ns in time, and (3) at the center of the cloud, i.e., at the solid surface, very high pressure that reaches GPa may appear when the bubble cloud collapses.

IN VITRO STONE CRUSHING TEST

In this section, the crushing tests of model stone, which are used as the test material of SWL machine, are discussed. The PRF of the ultrasound pulse and the amplifier voltage are fixed at 20 Hz and 1.6 kV (peak-to-peak). The irradiation time of the each waveform is 3 minutes. That is 3600 pulses of focused ultrasound are forced upon the model stones.

To investigate the advantages of the CCL method, 4 types of waveform were applied to the cylindrical model stones (diameter 10mm, height 10mm). Fig. 19 shows the results. The waveforms are (a) high frequency, (b) high frequency and 2 cycles low frequency combination (seen in Fig. 2), (c) high frequency and 5 cycles low frequency combination (d) 2 cycles of low frequency, and (d) 5 cycles of low frequency. In these cases high frequency is 3.82 MHz and 46 µs, and low frequency is 545 kHz.

Fig. 19 shows the picture and the surface plot of the indentation shape of model stones. The waveforms, high frequency only, (a), erode the stones a little, 1 mm depth. In the case low frequency only waveforms, (d) and (e), erodes the stone more. In the case of 2 cycles, (d), the depth of the erosion is about 2.5 mm. In the case 5 cycles, (d), 4.3 mm. In the (c) and (d), high and low frequency combination waveform, the depth of the scoop indentation reaches 6 mm. In the case of the (c),
very acute hole is created by cloud cavitation collapse, and there seems to be no damage at the surface of the stone.

On the other hand, in case (d), CCL waveform with 5 cycles low frequency, a lot of erosion scratches around the main hole is seen. Increase of the number of the cycle of low frequency causes a lot of cavitation bubbles in its wide focal area as discussed in Fig. 14. Such kind of the uncontrollable collapses of cavitation bubble may result in the tissue damage. The same scratch is also seen in case (e). That is, the waveform, two cycles low frequency follow high frequency, is the best waveform with minimal tissue damage and also with maximum indentation depth. The indentation shape of each case quite matches the discussion in the previous section.

These results show by controlling acoustic cavitation phenomena, high-pressure and high-energy concentration is realized within a fine spatial and timing resolution. The estimated total break up time by CCL is comparable to the conventional SWL methods. Also the resulting fragments are sufficiently small to pass through the urethra.

CONCLUDING REMARKS

An extracorporeal lithotripsy method, Cavitation Control Lithotripsy (CCL) is being developed utilizing two frequencies focused ultrasound. By controlling cloud cavitation phenomena, high-energy and high-pressure concentration only at the stone surface is obtained. Cavitation phenomena are well controlled both in time and space. That is,

1. During the high frequency phase, cavitation bubbles form the stable cloud cavitation at the solid surface. And the size is much dependent on the ultrasound frequency. Therefore, the area of the cavitation can be controlled by altering the ultrasound frequency. The area is less than 1 mm, when the frequency is larger than 1 MHz.
2. Low frequency ultrasound pulse can force the stable cloud to collapse. The occurrence time of the bubble cloud collapse can be controlled within 65 ns. The shock pressure induced by the cloud collapse is far more than that of a single bubble’s independent collapse. It is suggested that the pressure in the order of GPa may appear at the center of the cloud.
3. A model stone is efficiently chipped away. The stone comminution mechanism is attributed solely to the cavitation erosion. Compared with conventional ESWL, the cavitation spatial range is narrower and input energy is also smaller.

The CCL method has the potential to provide a less invasive and more controllable lithotripsy system.

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