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Effect of pulse duration and pulse repetition frequency of cavitation histotripsy on erosion at the surface of soft material

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ABSTRACT

Cavitation histotripsy with the short pulse duration (PD) but high pulse repetition frequency (PRF) disintegrates the tissue at a fluid interface. However, longer PD and lower PRF are used in the other focused ultrasound applications, where the acoustic radiation force, streaming, and cavitation are different, and their effects on erosion are unknown. In this study, the erosion at the surface of phantom/*ex vivo* tissue and the characteristics of induced bubble cloud captured by high-speed photography, passive cavitation detection, and light transmission during histotripsy exposure at varied PDs and PRFs but the same duty cycle were compared. The peak negative pressure of 6.6 MPa at the PD of 20 ms and PRF of 1 Hz began to erode the phantom, which becomes more significant with the increase of peak negative pressure, PD, and interval time between bursts. The increase of the PRF from 1 Hz to 1000 Hz, while the decrease of the PD from 20 ms to 20 μs (duty cycle of 2%) at the same energy was delivered to the gel phantom immersed in the degassed water led to the decrease of erosion volume but a slight increase of the erosion area and smoother surface. Low PRF and long PD produce the significant tissue deformation, acoustic wave refocusing, confinement of bubbles in a conical region, and more bubble dissolution after the collapse for the high acoustic scattering and light transmission signals. In comparison, high PRF and low PD produce a wide distribution of bubbles with only little wave refocusing at the beginning of cavitation histotripsy and high inertial cavitation. Acoustic emission dose has a good correlation with the erosion volume. The erosion on the porcine kidney at the varied PRFs and PDs with the same energy output showed similar trends as those in the phantom but at a slow rate. In summary, the PRF and PD are important parameters for the cavitation histotripsy-induced erosion at the interface of fluid and soft material, and they should be optimized for the best outcome.

1. Introduction

Focused ultrasound (FUS) has become more and more popular in clinical therapy, such as high-intensity focused ultrasound (HIFU) in the treatment of cancer and tumor by the temperature elevation-induced coagulation since the middle of the 1990s because of its advantages of noninvasiveness, possible operation in the doctor's office or outpatient clinic with no requirement of a sterile operating room, few complications, less in-hospital cost and risk of metastasis [1]. At such high intensity at the focus (i.e., >1000 W/cm^2), mechanical effects of the acoustic wave are significant. Nonlinear acoustic wave propagation results in the formation of a shock front around the focus which creates dramatic mechanical stress in the tissue. The large tensile wave can cause sporadic inertial cavitation or even a cloud of bubbles in the focal region, whose violent collapse produces the tissue destruction. In addition, the production of high order harmonics due to the significant waveform distortion, especially the shock front, enhances the heat deposition and subsequently, the rapid temperature elevation. Such effects could be enhanced by the interaction with bubbles to create the new FUS applications [2]. For example, cavitation histotripsy which used a large number of short (i.e., a few microseconds) but high peak negative pressure at certain pulse repetition frequency (PRF) could physically disintegrate the tissue [3]. To avoid potential cavitation damage to intervening tissue (i.e., vessel and nerve), the peak negative pressure was further increased beyond the intrinsic cavitation threshold (i.e., >30 MPa) using very short pulses (<2 cycles), which was termed as microtripsy [4]. Whereas the boiling histotripsy utilizes the boiling bubble induced by the shock front of the pressure profile in milliseconds to liquefy the tissue [5,6]. Both cavitation and boiling histotripsy could be employed as a noninvasive treatment for

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many diseases, such as malignant tumors, benign prostatic hyperplasia, deep vein thrombosis, and hypoplastic left heart syndrome, with similar effects achieved by different acoustic pulsing schemes. The liquefied content can be passed out of the natural body orifices or easily reabsorbed by the surrounding tissue [7–9].

The targets of histotripsy could be categorized into two types: inside the soft tissue (i.e., liver and kidney) [10,11] and at the interface of soft tissue and fluid (i.e., prostate) [12]. In the tissue, the heat diffusion and convection (i.e., by the blood circulation) should be considered, especially for the boiling histotripsy if the interval time between ultrasound pulses is shorter than the thermal diffusion time. Otherwise, the thermal damage will also be produced. With the increase of pulse duration (PD) in boiling histotripsy, the type of emulsified tissue (void with no signs of thermal damage) will be changed to void filled with white paste and surround by the coagulated edge and then to a solid thermal lesion with an evaporated core [6]. In contrast, the application at the interface of soft tissue and fluid (i.e., urine and blood) is different. Because of the much lower acoustic absorption but more significant thermal diffusion of fluid, it's hard to produce the boiling bubbles in the fluid. Therefore, the bubbles at the interface of soft tissue and fluid are mostly induced by acoustic cavitation, and their sizes are smaller than those of the vapors in the tissue by boiling histotripsy. Using cavitation histotripsy, the bubble cloud can mechanically fractionate tissue in a controlled and predictable manner. In addition, the presence of bubbles and tissue disintegration can be visualized in real-time sonography as targeting feedback of the operation.

Erosion at the interface of soft tissue and fluid was found more efficient using certain parameters [3]. With the increase of PD from 3 cycles to 12 cycles, the tendency for the erosion becomes faster when decreasing the PRF from 19.6 kHz to 4.95 kHz. Although the axial erosion rate was slower, the threshold of erosion was found to be $I_{SPPA} \geq 4000$ W/cm^2 (the peak negative pressure, p^- = 8.3 MPa) at the driving frequency of 788 kHz, PD of 3 cycles, and PRF of 20 kHz for perforation on porcine atrial wall [13]. The treated tissue is fragmented to the subcellular level and surrounded by an almost imperceptibly narrow margin of cellular injury (a few microns between the completely fractionated and intact cells). In most of the cavitation histotripsy experiments, the duty cycle is within the range from 0.1% to 5%, the PRF > 100 Hz, PD < 50 μs, and p^- > 8 MPa. Furthermore, cavitation histotripsy at the driving frequency of 750 kHz, PD of 5 cycles, PRF of 1 kHz, p^- from 10 MPa to 24 MPa was applied to comminute urinary calculi and can produce only fine fragments as opposed to coarse ones by the conventional shockwave lithotripsy [14]. All natural and artificial stones exposed to ultrasound bursts at $p^- \geq 2.8$ MPa, frequency of 170 kHz, and PRF of 200 Hz were fragmented with a mean treatment duration of 36 s for the uric acid stones and 14.7 min for the cysteine stones [15].

The acoustic radiation force exerted on an absorbing target is due to the transfer of wave momentum by the beam [16], and its amplitude is proportional to the PD in the ultrasound exposure. In addition, the oscillatory force of bubble dynamics, shear stress related to the streaming of fluid around the bubbles, and the fluid velocity during streaming are dependent on the PD of ultrasound pulses. However, saturation on these mechanisms will occur for a longer pulse. It was found that sonication with very short pulses (PD of 10 μs, PRF of 1 kHz, and duty cycle of 1%) produce the blood-brain barrier (BBB) disruption at the threshold of 6.3 MPa [17]. However, the 10 ms-pulses at the PRF of 1 Hz (duty cycle of 1%) and p^- of 1 MPa produced about 13% signal intensity change as extravasation of MRI contrast agent [18]. Therefore, the PD is also an important ultrasound parameter in producing the beneficial and effective bioeffects of FUS. However, the long PD of cavitation histotripsy has not been investigated.

In this study, the effects of PD and PRF of cavitation histotripsy pulses on the erosion of gel phantom and soft tissue at the fluid interface were evaluated in order to optimize the operation parameters. The erosion area and volume produced by pulses at varied acoustic pressure, pulse duration, interval time with long PD but low PRF were investigated first. In addition, pulses with the same acoustic pressure and duty cycle (the same output power) but varied PRFs from 1 Hz to 1000 Hz and corresponding PD from 20 ms to 20 μs were tested. The acoustic emission signals were measured using passive cavitation detection (PCD) to calculate both inertial cavitation-induced broadband noise and acoustic scattering during the exposure, and bubble dynamics in the focal region were captured by both high-speed photography and light transmission approach. It is found that significantly different characteristics of bubble cavitation and subsequently, the erosion efficiency, are present at the various PRFs and PDs. Acoustic emission dose has a good correlation with the erosion volume and can be used as a monitoring and evaluation technique.

2. Materials and methods

2.1. Experiment setup

A HIFU transducer (H-102, outer diameter = 69.94 mm, inner diameter = 22.0 mm, F = 62.64 mm, f_0 = 1.1 MHz, Sonic Concepts, Woodinville, WA) was immersed in the degassed and deionized water (O_2 < 4 mg/L, T = 25 °C, measured by DO700, Extech Instrument, Waltham, MA) of a Lucite tank (L × W × H = 70 × 50 × 30 cm) and driven by sinusoidal bursts produced by a function generator (AF3021B, Tektronix, Beaverton, OR) together with a power amplifier (BT00250-AlphaA, Tomco Technologies, Adelaide, Australia). An acoustic absorber was placed on the opposite wall of the testing tank to prevent the ultrasound reflection. The transducer was attached to a three-axis positioning system (PT3/M, Thorlabs, Newton, NJ) to align its focus to the surface of the gel phantom (see Fig. 1). The alignment was made by obtaining the maximum echo signal using a pulser/receiver (5072PR, Olympus-IMS, Waltham, MA). A LabView program (National Instruments, Austin, TX) was written to control the ultrasound exposure.

2.2. Gel phantom

Alginate (Jeltrate, Dentsply International, York, PA) at the concentration of 5% was used as the gel phantoms because of its easy fabrication, low cost, biocompatibility, and close properties to those of soft biological tissue [19]. Alginate power was weighted by a digital analytical balance (ML54, Mettler Toledo, Columbus, OH) and then mixed with deionized and degassed water and 0.3 ml of gas relief drop (Pedia Care, Tarrytown, NY), which can reduce the surface tension, by a blender (Libre, Sharp, Osaka, Japan) for 1 min. The liquid mixture of gel constituents was poured into a mold for gelation at room temperature and then degassed for about 1–2 min in a desiccant chamber (420100000, Scienceware, Pequannock, NJ) with a vacuum pump (VTE8, Thomas, Sheboygan, WI) at a pressure of 150 mbars.

2.3. Erosion analysis

After the histotripsy exposure, the gel phantom was recorded photographically by a digital camera (PowerShot SX230 HS, Canon, Tokyo, Japan) and then the area of erosion on the surface was quantitatively determined in digital image processing software