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Suppressing bubble shielding effect in shock wave lithotripsy by low intensity pulsed ultrasound

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ABSTRACT

Extracorporeal shock wave lithotripsy (ESWL) has been used as an effective modality to fragment kidney calculi. Because of the bubble shielding effect in the pre-focal region, the acoustic energy delivered to the focus is reduced. Low pulse repetition frequency (PRF) will be applied to dissolve these bubbles for better stone comminution efficiency. In this study, low intensity pulsed ultrasound (LIPUS) beam was aligned perpendicular to the axis of a shock wave (SW) lithotripter at its focus. The light transmission was used to evaluate the compressive wave and cavitation induced by SWs without or with a combination of LIPUS for continuous sonication. It is found that bubble shielding effect becomes dominated with the SW exposure and has a greater significant effect on cavitation than compressive wave. Using the combined wave scheme, the improvement began at the 5th pulse and gradually increased. Suppression effect on bubble shielding is independent on the trigger delay, but increases with the acoustic intensity and pulse duration of LIPUS. The peak negative and integral area of light transmission signal, which present the compressive wave and cavitation respectively, using our strategy at PRF of 1 Hz are comparable to those using SW alone at PRF of 0.1 Hz. In addition, high-speed photography confirmed the bubble activities in both free field and close to a stone surface. Bubble motion in response to the acoustic radiation force by LIPUS was found to be the major mechanism of suppressing bubble shielding effect. There is a 2.6-fold increase in stone fragmentation efficiency after 1000 SWs at PRF of 1 Hz in combination with LIPUS. In summary, combination of SWs and LIPUS is an effective way of suppressing bubble shielding effect and, subsequently, improving cavitation at the focus for a better outcome.

1. Introduction

Since the introduction of extracorporeal shock wave lithotripsy (ESWL) in the early 1980s, this noninvasive technology has revolutionized the urology worldwide for significantly reduced morbidity and mortality via open surgery for removal of upper urinary tract stone [1]. At present, about 80% of kidney stone diseases are treated by ESWL alone or in conjunction with the other modalities [2]. Recently, shock waves (SWs) could also provide additional benefits in rehabilitation and orthopedics for the treatment of musculoskeletal diseases, such as Achilles tendonitis, heel spurs, and nonunion stress fracture [3]. Despite its great success, both *in vitro* and *in vivo* investigations also illustrate some of its shortcomings [4]. For example, if the stone is in an anatomically difficult position (i.e., in the collecting system of lower pole of the kidney) or its size is larger than 20 mm, the performance of ESWL is not satisfactory. About 30% of patients need re-sessions [5]. In addition, renal injuries characterized by the rupture of vessels and capillaries are usually found at the proximal surface of the kidney after ESWL. Although debate exists for the association between hypertension and diabetes mellitus with ESWL [6,7], renal trauma caused by ESWL could lead to irreversible long-term complications and patients with pre-existing renal injury are at high risk [8,9]. Therefore, work is being carried out to understand the underlying mechanism of ESWL and to improve its performance, increasing the stone fragmentation and reducing the associated side-effects.

The dominating mechanism of ESWL is synergy of both mechanical stress induced directly by lithotripsy shock wave (LSW), including the superposition of longitudinal waves for stone spallation [10], circumferential stresses on the stone boundary for squeezing [11], and shear waves at the stone corners [12], and cavitation produced by the tensile component of LSW [13–15]. The stress wave causes the fracture of kidney calculi and usually dominates at the beginning of treatment. In contrast, cavitation and its associated formation of high-speed microjet produce fine

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fragments from the stone surface later, which is critical for spontaneously discharge although at a slower rate [16]. The pulse repetition frequency (PRF) for the delivery of SWs is usually 1 Hz, and the total number of SWs delivered in one session required by the Food and Drug Administration (FDA) is no more than 2000. In order to reduce the treatment time, fast PRF was tried [17,18]. However, less stone comminution and more renal injuries were found, which may be due to the shielding effect of bubble cloud in the pre-focal region (i.e., water in the coupling cushion) [19,20]. In the acoustic cavitation, non-condensible gas dissolves into the bubble and increases its equilibrium radius during the growth. In the collapse stage, a bubble may be broken into many "daughter" bubbles, which dissolve slowly into the surrounding medium in seconds. If the interval time of SW delivery is shorter than the bubble dissolution time (i.e., higher PRF), these remnant small bubbles will grow to large sizes and shield the propagation of the incident tensile component of LSW, but selectively transmit the leading compressive component, which is called the bubble shielding effect [21]. As a result, cavitation in the focal region surrounding the stone will be reduced significantly [22]. Meanwhile, strong back-scattering will also be produced by the pre-focal bubble cloud, which may be the reason of the presence of most SWL-induced renal injury on the proximal surface of the kidney. Although reducing PRF results in the improved stone comminution and less complication [23–25], the cost is the elongated treatment duration.

If the bubble shielding effect can be reduced (fewer number or less density of cavitation nuclei along the LSW pathway) between successive SWs, higher PRF can be applied without negatively affecting stone comminution. It is noted that bubble proliferation is a critical issue after delivery of several SWs. Cavitation nuclei can be suppressed by vacuum water degassing [26]. A jet of degassed water with an exit velocity of 62 cm/s could remove cavitation nuclei from the coupling cushion between successive SWs [27]. Consequently, the lifetime of pre-focal bubble nuclei was reduced from 7 s to 0.3 s detected in B-mode ultrasound image, and the stone fragmentation efficiency increased from 22 ± 6% to 33 ± 5% after 250 shocks at PRF of 1 Hz. If a weak preceding shock wave is delivered at an sufficiently long interval delay before the subsequent major one that the cavitation cluster generated by the first SW has already collapsed, a significantly pronounced bubble activity with high void fraction could be produced by the second SW [28]. Low frequency pulses (350 kHz) with pulse duration in the order of milliseconds were delivered between LSWs to effectively enhance the bubble coalescence with amplitude larger than 250 kPa [29,30]. Bubble removal pulses reduced the bubble excitation along the SW axis and drastically enhanced the stone comminution at the higher rates (120 and 60 SW/min).

Several approaches have been utilized to capture the bubble dynamics. Light transmission is an easy and reliable method to measure bubble activities in the illumination area [31], but it cannot be used *in vivo*. Meanwhile, optical detection of tiny bubble nuclei is not as sensitive as acoustic approach because of the much more similarities in the optic index between water and air (1.33 vs. 1.0) than that of acoustic impedance (1.5 MRay vs. 416 Ray). Therefore, light transmission or photography cannot discern the remnant bubbles between SW intervals. Active cavitation detection (ACD), such as using B-mode ultrasound image, illustrated the lifetime of detectable bubble nuclei in the lithotripter field after 20 SWs delivered at PRF of 3 Hz is ~7 s [27]. SW-induced echogenic areas enlarged with the increase of delivered pulses, discharge voltage and PRF both *in vitro* and *in vivo* [32], which is believed to be in the pre-focal region. Passive cavitation detection (PCD) has a characteristic double-burst structure and shows the presence of bubble cavitation by ESWL in animal experiment [33] and in clinics [34]. Correlation was found between the appearance of echogenic regions and the cavitation signals in PCD [35]. Using an ultrasound array, microbubble emission could be passively measured and dynamically focused at multiple depths. Agreement was found between the real-time passive imaging of cavitational acoustic emission and single or contiguous and disjoint cavitation regions [36,37].

Low intensity pulsed ultrasound (LIPUS) is a medical technology, using ultrasound pulses at 1–2 MHz with a pulse duration much longer (>10 ms) than that of diagnostic one at the intensity of no more than 2 W/cm^2. It is becoming popular in the rehabilitation and has been approved by FDA for use in orthopedics, such as promoting bone-fracture healing, treating orthodontically induced root resorption, regrow missing teeth, enhancing mandibular growth in children with hemifacial microsomia, promoting healing in various soft tissues such as cartilage, inter vertebral disk, and improving muscle healing after laceration injury [38].

In this study, a novel therapy strategy was proposed and tested by combining SWs and LIPUS, which were aligned confocally and delivered different acoustic pulses in turn. Light transmission signal through the focal region was used to evaluate the compressive wave and cavitation, two major mechanisms of stone comminution in ESWL, in the free field during the SWL treatment. The bubble shielding effect produced in the pre-focal region was found to have much more influence on cavitation than the compressive wave, but can be suppressed using the new strategy, which is dependent on the trigger delay between SWs and LIPUS, the duration and acoustic intensity of LIPUS and the energy flux of SWs. High-speed images illustrated bubble activities using SWs alone or combination of SWs and LIPUS both in the free field and close to a stone surface. Motion of remnant bubble nuclei during LIPUS sonication illustrated the mechanism of suppression bubble shielding effect. As a result, there is a 2.6-fold increase in the stone fragmentation efficiency using the novel strategy *in vitro* while LIPUS alone had negligible influence. It suggests that this approach can effectively suppress the bubble shielding effect in ESWL and, subsequently, improve the performance.

2. Materials and method

2.1. Acoustic sources

SWs were generated by a focused piezoelectric transducer (FB10 G4, PiezoSon 100 plus, Richard Wolf GmbH, Knittlingen, Germany) with an aperture of 100 mm and a focal length of 40 mm, the energy flux in the range of 0.03–1.05 mJ/mm^2, the measured focal peak pressure in the range of 11–126.3 MPa, and 6 dB beam size of 1.1–3.2 mm in radius and 6.1–14.8 mm in length [39]. LIPUS was generated by a flat and circular transducer (Model X, Rich-Mar, Chattanooga, TN, USA) with an emission area of 10 cm^2. These two transducers were immersed into a testing tank ($L \times W \times H = 36 \times 22 \times 25$ cm) filled with degassed and deionized water (O_2 < 4 mg/L, T = 25 °C, measured by DO700, Extech Instrument, Waltham, MA, USA) and aligned perpendicular to each other (see Fig. 1). A LabView (National Instruments, Austin, TX, USA) program on a personal computer (PC) was written to control the delivery of SW and LIPUS by setting the transistor–transistor logic (TTL) level of the trigger circuit of these two devices through a data acquisition (DAQ) board (USB-6008, National Instruments). Variations of SW and LIPUS parameters used in this study are listed in Table 1. Trigger delay is determined as the delay time of triggering SW and LIPUS at the same PRF and is kept consistent throughout the whole sonication. At least 60% of the maximum output of SW (~0.63 mJ/mm^2) is required to produce detectable cavitation in our experiment.

2.2. Cavitation detection

A broadband 10 MHz polyvinylidene fluoride (PVDF) focused membrane transducer (PA381, Precision Acoustics, Dorchester,