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Precise spatial control of cavitation erosion in a vessel phantom by using an ultrasonic standing wave

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ABSTRACT

In atherosclerotic inducement in animal models, the conventionally used balloon injury is invasive, produces excessive vessel injuries at unpredictable locations and is inconvenient in arterioles. Fortunately, cavitation erosion, which plays an important role in therapeutic ultrasound in blood vessels, has the potential to induce atherosclerosis noninvasively at predictable sites. In this study, precise spatial control of cavitation erosion for superficial lesions in a vessel phantom was realised by using an ultrasonic standing wave (USW) with the participation of cavitation nuclei and medium-intensity ultrasound pulses. The superficial vessel erosions were restricted between adjacent pressure nodes, which were 0.87 mm apart in the USW field of 1 MHz. The erosion positions could be shifted along the vessel by nodal modulation under a submillimetre-scale accuracy without moving the ultrasound transducers. Moreover, the cavitation erosion of the proximal or distal wall could be determined by the types of cavitation nuclei and their corresponding cavitation pulses, i.e., phase-change microbubbles with cavitation pulses of 5 MHz and SonoVue microbubbles with cavitation pulses of 1 MHz. Effects of acoustic parameters of the cavitation pulses on the cavitation erosions were investigated. The flow conditions in the experiments were considered and discussed. Compared to only using travelling waves, the proposed method in this paper improves the controllability of the cavitation erosion and reduces the erosion depth, providing a more suitable approach for vessel endothelial injury while avoiding haemorrhage.

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1. Introduction

Ultrasound can noninvasively penetrate soft tissues, focusing on a specific site in the human body. The high negative pressure in the focus area can lead to ultrasonic cavitation. Expansions and collapses of the cavitation bubbles produce shockwaves, microstreams, and microjets, leading to structural changes in the fluid-tissue interface [1]. Tissue erosion is one of the most important nonthermal physical phenomena during ultrasonic cavitation.

In blood vessels, cavitation erosion has been explored for therapeutic applications, including thrombolysis, etc. [2,3]. Besides therapeutic usages, cavitation erosion is also a promising method for atherosclerotic inducement in animal models [4]. Currently, mechanical arterial balloon injury combined with hypercholesterolemia is the most widely employed conventional method to induce atherosclerosis in animal models [5]. However, the balloon injury operation is invasive, excessive in arterial endothelial cell damage, and inconvenient in arterioles. In addition, the balloon injures the vessel in uncertain positions, resulting in atherosclerotic plaques developing at unpredictable sites. Cavitation erosion is able to cause endothelial cell damage as well as the balloon injury, providing another possible approach to induce atherosclerosis in animal models. Consequently, improvements in the spatial controllability and precision of cavitation erosion in blood vessels without haemorrhaging may have a significant impact both on the predictability of atherosclerotic locations and on the predictability of atherosclerotic sizes in animal models.

Short high-intensity ultrasound pulses can generate microbubbles at the focus of an ultrasound transducer in both cavitation histotripsy and boiling histotripsy [6,7]. Expansions and collapses of the microbubbles cause mechanical breakdown of a thrombus into acellular debris under high negative pressure [8]. To avoid excessive erosion damage to surrounding vessels and tissues, the number of cycles in one pulse has to be reduced to improve the precision of the cavitation erosion, even reduced to a half-cycle in "microtripsy" with lesion widths are less than a wave length of 3 mm. Extremely high negative pressure, between 26.4 MPa to

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30.0 MPa, is required to generate cavitation microbubbles as a result of the cycle reduction [9].

Conventional high-intensity focused ultrasound (HIFU) can erode the proximal vessel wall in a region of more than one centimetre in large blood vessels assisted by microbubble contrast agents. Microbubbles are utilised as cavitation nuclei, which reduce the cavitation pressure threshold and enhance the cavitation effects. The erosion phenomenon occurs under high power, ranging from 50 W to 90 W. According to Qiao et al., it is difficult to erode the distal wall because of the strong ultrasonic reflection from the crowded cavitation microbubbles [10].

Medium-intensity ultrasound pulses combined with microbubbles are able to induce long and thin tunnels in the distal walls of small blood vessels, increasing the endothelial permeability in drug delivery [11,12]. The peak negative pressure threshold of 1 MHz pulses tunnelled in the wall is 2.5 MPa under a pulse repetition frequency of 10 kHz and a pulse duration of 10 μs, and the thin tunnels extend over one millimetre in depth. The pressure threshold decreases while the pulse duty cycle increases [13].

To summarise, though "microtripsy" can produce cavitation erosion precisely, the dependence on special ultrasound transducers and special high-power amplifiers restricts the scenarios in which it can be used. The conventional HIFU combined with microbubble contrast agents is able to erode the proximal vessel walls on a large scale. However, the cavitation erosion that results from HIFU is not precise enough to avoid an excessive lesion, and the irreversible adverse thermal effect also exists as a consequence of the high power. The medium-intensity cavitation pulses assisted by microbubble contrast agents produce long and thin tunnels in the distal walls in small vessels, but these long tunnels cause bleeding and may not be enough to induce atherosclerosis in animal models [14]. Additionally, for atherosclerotic inducement by cavitation erosion, although arterial ruptures and haemorrhages must be avoided, all of these methods produce lesions that mainly extend in the direction of sound propagation, producing injuries too deep in the blood vessel walls. Moreover, microbubble contrast agents are adopted to decrease the pressure threshold of cavitation and enhance erosion. However, microbubble contrast agents distribute in all of the blood vessels because of blood circulation. As a result, excessive erosion during cavitation becomes a potential hazard. Fortunately, ultrasonic standing wave (USW), which has been widely used for concentration, separation, and transportation of microparticles or cells in microfluidics, has been proven to be potentially used to trap microbubble contrast agents at a desired site in a blood vessel, controlling the spatial distribution of the cavitation nuclei [15–18].

The objective of this paper is to provide a method to realise precise spatial control of superficial erosion in a vessel phantom by using an USW with the participation of cavitation nuclei and medium-intensity cavitation pulses. In this method, the cavitation erosion that was generated at the antinode of the USW with submillimetre-scale accuracy could be designated to be in the proximal vessel wall or in the distal vessel wall. The erosion position could be shifted along the vessel by modulating the USW instead of moving the transducers. The shallow erosion holes extended mainly in the vessel axial direction instead of in the direction of sound propagation, hence the term "superficial erosion". Different erosion geometries were produced under different ultrasonic conditions in the experiments. Effects of the flow conditions on the erosion in the vessel were investigated. The conventional transducers used in this study were easily manufactured. In addition, the medium-intensity cavitation pulses could avoid irreversible adverse thermal effects on blood vessel walls.

In the following sections, the method is introduced in detail. Section 2, methods and materials, presents how the experiments were prepared and conducted in three parts: experimental setup, materials, and control methods. To further describe the advantages of this method, the characteristics of controlled superficial erosion, the position shift of the erosion, the effects of acoustic parameters and the effects of flow velocity on the erosion are introduced and discussed in Section 3.

2. Methods and materials

The experimental setup consists of the USW setup, cavitation setup and high-speed photomicrography setup. The USW setup was used for the erosion control, the cavitation setup was adopted to generate the cavitation erosion, and the high-speed photomicrography setup was the system for observing the experiments. Section 2.2 details the materials, including the blood vessel phantom, cavitation nuclei, and ultrasonic parameter choices depending on the cavitation nuclei. Section 2.3 shows the erosion control methods. The USW regulated the distribution of cavitation nuclei. Hence, the superficial erosion was controlled.

2.1. Experimental setup

2.1.1. USW setup

The schematic of the system setup is depicted in Fig. 1. Two channels of a double-channel arbitrary wave generator (AWG 420, Tectronix, Beaverton, OR, USA) were utilised to generate continuous sinusoidal waves, which were amplified by power amplifiers (AG1016, T&G Power Conversion Inc., Rochester, NY, USA). Two unfocused ultrasonic transducers (1 MHz, aperture diameter 30 mm, TAPMM25W, Wuxi Lanhui, Wuxi, JS, CN) driven by the power amplifiers were mounted on a water tank with an angle of 120°. Degassed water contained in the water tank, 32 cm (long) × 24.5 cm (high) × 10 cm (wide), was maintained at 37 °C Transmitting powers of the power amplifiers were set at 1 W. An USW of 300 kPa was generated by the interference of two ultrasonic beams. The transducers were located on the same side of the vessel to avoid potential hindrances, such as acoustic shielding by bones and the space limitations for placing transducers.

2.1.2. Cavitation setup

Two focused ultrasonic transducers were used separately as the cavitation transducer, driven by a tone burst pulser-receiver system (RPR-4000, Ritec Inc., Warwick, RI, USA) and synchronised with the emission of the USW. The centre frequency of one transducer (aperture diameter 28.575 mm, I8-0518-P, Olympus NDT Inc., Waltham, MA, USA) is 5 MHz, and the other one (aperture diameter 38.100 mm, V392, Olympus NDT Inc., Waltham, MA, USA) has a centre frequency of 1 MHz. The frequencies of the cavitation transducers were chosen depending on the cavitation nuclei, which were discussed in Section 2.2.2. The pulse durations were no longer than 8 μs, which was in the imaging range, while the peak negative pressures were lower than 1.8 MPa. The spatial peak time average sound intensity of the cavitation pulses ranged from 3.8×10^{-4} W/cm^2 to 8.6×10^{-2} W/cm^2. The axes of the transducers in the USW setup, the axis of the vertical cavitation transducer (5 MHz or 1 MHz), and the axis of the horizontal vessel in the phantom were located in the same plane. The two transducers in the USW setup were placed symmetrically with respect to the vertical cavitation transducer. The focus of the cavitation transducer and the pressure antinode of the USW field overlapped at the vessel in the phantom.

2.1.3. High-speed photomicrography setup

The controllable cavitation erosion of the vessel wall was observed through a long working distance microscope (Questar QM 100, Company Seven Inc., USA) with a magnification ranging

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