Computers in Biology and Medicine 44 (2014) 37–43

Contents lists available at ScienceDirect

Computers in Biology and Medicine

journal homepage: www.elsevier.com/locate/cbm

Drug perfusion enhancement in tissue model by steady streaming induced by oscillating microbubbles

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ARTICLE INFO

Article history:
Received 1 July 2013
Accepted 19 October 2013

Keywords:
Drug delivery
Acoustic wave
Microbubble
Steady streaming
Computational fluid mechanics

ABSTRACT

Drug delivery into neurological tissue is challenging because of the low tissue permeability. Ultrasound incorporating microbubbles has been applied to enhance drug delivery into these tissues, but the effects of a streaming flow by microbubble oscillation on drug perfusion have not been elucidated. In order to clarify the physical effects of steady streaming on drug delivery, an experimental study on dye perfusion into a tissue model was performed using microbubbles excited by acoustic waves. The surface concentration and penetration length of the drug were increased by 12% and 13%, respectively, with streaming flow. The mass of dye perfused into a tissue phantom for 30 s was increased by about 20% in the phantom with oscillating bubbles. A computational model that considers fluid structure interaction for streaming flow fields induced by oscillating bubbles was developed, and mass transfer of the drug into the porous tissue model was analyzed. The computed flow fields agreed with the theoretical solutions, and the dye concentration distribution in the tissue agreed well with the experimental data. The computational results showed that steady streaming with a streaming velocity of a few millimeters per second promotes mass transfer into a tissue.

1. Introduction

The delivery of pharmaceutical agents to brain tissues is challenging owing to the difficulties in drug penetration through the tight endothelial junction of the blood–brain barrier (BBB) [1] and limited diffusivity of brain tissues [2]. To bypass the BBB, direct delivery of drugs to the brain parenchyma has been attempted. Biodegradable BCNU (bis-chloroethylnitrosourea) wafers have been implanted to deliver high concentrations of drugs directly to the surrounding tissues, but the penetration of drugs into nearby tissue is limited. Therefore, convection-enhanced delivery of drugs into specific regions of brain tissues via positive pressure infusion has been attempted for enhancing the efficiency of drug perfusion [3–6]; this method is especially useful for the delivery of large molecules to treat gliomas and Parkinson's and Alzhemer's diseases [7–9]. However, positive pressure infusion has limited efficiency because of inadequate drug distribution characterization, leakage of the infusate, deformation of solid tissues, and safety considerations [10,11].

Acoustical techniques have been used to increase the efficiency of drug delivery [12,13] because ultrasound can be transmitted into the target tissue noninvasively. The acoustic energy applied to a specific region in the brain can change the cell membrane and tissue permeability of the target region. Pressure and thermal stimuli from acoustic waves can be exploited for drug delivery applications. Local hyperthermia can be used to trigger local drug delivery as well as provide a synergetic effect with systemic chemotherapy. Ultrasound can be focused to produce a high-intensity focal volume, and interaction with tissue provides a strong mechanical stimulus [14,15]. High-intensity focused ultrasound (HIFU) has been used to selectively disrupt the BBB [16,17], but tissue damage due to the high energy of HIFU should be avoided. Incorporating microbubbles can significantly reduce the intensity of ultrasound energy while still maintaining the increased tissue permeability [18,19]. Ultrasound contrast agents (UCAs) are co-administered with the drug intravenously or intra-arterially, and focused ultrasound is noninvasively applied to the specific region. A regional increase in BBB disruption caused by cavitating bubbles increases drug permeability with reduced ultrasound intensity. Problems with ultrasound-enhanced drug delivery are related to the lack of controllability and difficulties with focusing ultrasound. Studies have attempted to correct steering and aberrations due to tissue structures in the ultrasound beam by adjusting the relative phases of elements in an array of transducers [20,21]. Ultrasound parameters have also been adjusted to disrupt the BBB without producing lesions and over-heating the skull [22].

The exact mechanism through which the BBB is disrupted remains unknown, but the effect may be attributed to cavitation activity. Microbubbles cavitated by acoustic excitation generate

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0010-4825/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.compbiomed.2013.10.020

convective fluid motion and stress on the target tissues, and this physical effect may cause changes to the tissue permeability. Ultrasound pressure waves can generate acoustic streaming in the absence of bubbles [23,24] and have the potential to promote drug diffusion. However, bulk streaming from propagating acoustic waves is far less mechanically powerful than microstreaming from cavitating bubbles and less effectively alters the membrane permeability and cell activity [25]. Inertial cavitation, which is characterized by violent bubble oscillation and breakup, may cause tissue damage, but stable cavitation with moderate radial oscillation can increase tissue perfusion with less damage. Stably cavitating bubbles generate a steady mean flow by nonlinear convective acceleration [26], and the streaming flow field may promote drug perfusion into tissue. Drug delivery enhancement by cavitating bubbles has been demonstrated in vitro [27], ex vivo [28], and in vivo [29,30], but the streaming flow field effects on drug perfusion have not been studied under a controlled environment.

In this study, we explored the physical effects of a steady stream generated by oscillating microbubbles on drug perfusion into tissue. Neurological tissue was modeled as porous media, and drug perfusion into neurological tissue was simulated by dye transport into the porous phantom. An experimental study on dye perfusion into a tissue model through streaming flow induced by oscillating bubbles was performed, and the effects of acoustic waves and steady streaming from oscillating bubbles on drug perfusion were compared. A computational model for predicting dye perfusion into tissue was developed, and its results were compared with those of the experiment.

2. Methods

2.1. Experimental study

Ultrasound contrast agents (UCAs), which are less than 5 μm in size, were applied to enhance the efficacy of the ultrasound-assisted drug delivery. Because detailed quantitative measurement of tissue perfusion caused by a micron-size bubbles is difficult, a scaled-up experiment was performed using bubbles with 500 μm diameters. Although the difference in scale was significant, the streaming flow velocity was maintained at a similar order of magnitude as that of an oscillating UCA through control of the radial oscillation amplitude of the bubble and excitation frequency. The radial velocity of a 5-μm UCA oscillating at 1 MHz is similar to that of a 500-μm bubble oscillating at 10 kHz. Smaller UCAs, which have diameters of about 1–3 μm, are commercially available; the radial and streaming velocities of these bubbles at resonance frequency would be a similar order of magnitude on a scaled-up experimental model.

An air bubble of 500 μm diameter was generated using a microsyringe and placed 0.5 mm away from the tissue phantom. For acoustic excitation, sine wave voltage was generated by a function generator (33210 A, Agilent Co., CA) and amplified up to a few hundred volts by a voltage amplifier (PZD700, Trek Co., NY). The amplified voltage signal was transmitted to a cylinder-type piezoactuator (disk type PRYY-1133, PI Ceramics, Germany) attached to the bottom of the chamber. The bubble was excited by the acoustic wave generated by the piezoactuator, which was excited by a 12-kHz continuous sinusoidal voltage signal with an amplitude of 300 V, and bubble oscillation was observed with a charge-coupled device (CCD, EO-1312C, Edmund Optics, NJ) integrated with a zoom lens (VZM™ 450i, Edmund Optics, NJ). The experimental setup is shown in Fig. 1. The acoustic pressure at the agar sample surface was measured with a calibrated hydrophone (0.2 mm polyvinyl difluoride (PVDF) needle hydrophone, Precision

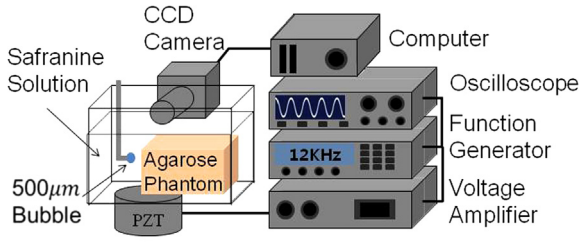

Fig. 1. Schematic diagram of experimental setup.

Acoustics, Ltd. Dorchester, UK). The peak-to-peak amplitude of the measured pressure wave was about 8 kPa.

An aqueous solution of safranin (Samchun Chemical, Korea) was used to mimic a low molecular weight anti-cancer drug with moderate water solubility such as temozolomide [31] and sapphyrin compounds [32]. Although safranin may not represent the physicochemical properties of clinically used anti-cancer drugs, water-soluble dyes are widely used in tissue diffusion experiments [33]. Agar phantoms were used to model neurological tissue because they show similar perfusion characteristics [34,35]. A tissue phantom was prepared by mixing agarose powder (Samchun Chemical, Korea) and distilled water at a concentration of 0.6 wt%. The mixture was boiled for 10 min and cooled down to room temperature. The samples were prepared by cutting the agar phantom into hexahedral blocks (15 mm × 15 mm × 12 mm), and drug perfusion into the tissue was optically measured by examining the histology of the agar phantom [34,35]. The phantom was immersed in the safranin solution (0.03 wt%, 50 ml) and fixed at the bottom of the chamber (40 mm × 40 mm × 30 mm). It was exposed to a streaming flow induced by the oscillating bubble for 30 s. A 0.7-mm-thick slice of the phantom was taken at the location closest to the bubble center, and its cross-section was imaged by a digital camera. The captured image was imported into ImageJ (NIH, MD), and the color intensity was measured along the perfusion distance of the sliced sample.

In order to quantify the color intensity of the sliced agarose sample, the correlation between the safranin concentration and image color intensity was obtained. The image intensity is affected by not only the dye concentration but also other factors such as the three-dimensional geometry, nonlinear capture characteristics, and light source uniformity [36]. Safranin dye of a known concentration was enclosed in the 0.7-mm-thick transparent hexahedron box with the same size as the sliced agarose sample in order to exclude the volume effect of the sample for intensity measurement. It was placed on a collimated light source, and the color image was captured by a camera (AM 313, Dino-Lite, ANMO Co., Taiwan). The color intensity was decomposed and mapped to red (R), blue (B) and green (G) color intensities. The color intensities (R-G-B) were calculated by subtracting the background-corrected green and blue intensities from the red intensity; they showed a linear correlation with the dye concentration at low concentrations (less than 0.03 wt%). The color intensity (R-G-B) distribution from the phantom surface along the penetration depth was determined by converting image pixels into distance. Experiments were performed for more than 11 phantom slices, and at least four color intensity profiles were extracted for each sliced sample. Statistical analysis was performed with SPSS 17.0 (SPSS, Chicago, IL), and the statistical differences with the population average were determined by the paired *t*-test.

2.2. Computational analysis

Dye perfusion into the tissue model by streaming flow fields from an oscillating bubble presents multiphysics problems such as bubble dynamics, fluid dynamics, and mass transfer. Instead of