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● *Original Contribution*

INFLUENCE OF ACOUSTIC REFLECTION ON THE INERTIAL CAVITATION DOSE IN A FRANZ DIFFUSION CELL

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Abstract—The exposure of the skin to low-frequency (20–100 kHz) ultrasound is a well-established method for increasing its permeability to drugs. The mechanism underlying this permeability increase has been found to be inertial cavitation within the coupling fluid. This study investigated the influence of acoustic reflections on the inertial cavitation dose during low-frequency (20 kHz) exposure in an *in vitro* skin sonoporation setup. This investigation was conducted using a passive cavitation detector that monitored the broadband noise emission within a modified Franz diffusion cell. Two versions of this diffusion cell were employed. One version had acoustic conditions that were similar to those of a standard Franz diffusion cell surrounded by air, whereas the second was designed to greatly reduce the acoustic reflection by submerging the diffusion cell in a water bath. The temperature of the coupling fluid in both setups was controlled using a novel thermoelectric cooling system. At an ultrasound intensity of 13.6 W/cm^2, the median inertial cavitation dose when the acoustic reflections were suppressed, was found to be only about 15% lower than when reflections were not suppressed. **(E-mail: sid.becker@canterbury.ac.nz)** **© 2018 World Federation for Ultrasound in Medicine & Biology. All rights reserved.**

Key Words: **Inertial cavitation, Franz diffusion cell, Sonoporation, Passive cavitation detection.**

INTRODUCTION

Ultrasound-enhanced transdermal drug delivery involves exposure of the skin to an ultrasound field to increase the skin's permeability to topical drugs. The mechanism responsible for this permeability increase is believed to be inertial cavitation (Tang et al. 2002; Tezel et al. 2001, 2002) and is characterized by the violent collapse of gaseous cavities within the coupling fluid. This is believed to result in the disruption of the lipid bilayer structure of the stratum corneum (Azagury et al. 2014).

In vitro experimental studies that investigate the effects of ultrasound on skin permeability employ Franz diffusion cells (Merino et al. 2003; Mitragotri et al. 2000a, 2000b; Smith et al. 2003; Terahara et al. 2002; Tezel et al. 2001). These studies have considered the influence of parameters such as frequency (Tezel et al. 2002), exposure time (Terahara et al. 2002), duty cycle (Herwadkar et al. 2012), acoustic intensity (whether it be spatial peak temporal peak, spatial peak temporal average, etc.) (Tezel et al. 2001), distance from the transducer to the skin (Terahara et al. 2002) and chemical composition of the coupling fluid (Lavon et al. 2005). However, little attention has been paid to the potential influence of acoustic reflection in skin sonoporation studies. This was noted by Smith (2007), who stressed the importance of reporting the echoic conditions of the transdermal insonation apparatus.

Previous studies of the insonation of cells in cell culture plates have found that acoustic reflection from the walls of the cell culture plates may strongly influence the inertial cavitation activity. For example, Kinoshita and Hynynen (2007) illustrated that sonoporation could be doubled by facilitating the presence of a standing wave. Similarly, Jelenc et al. (2012) found that by suppressing the acoustic reflection using an acoustically absorbent lining, the maximum reflected pressure (at the cell suspension) was reduced by 81%. This motivates the question that is central to the present study: At ultrasound intensities relevant to skin sonoporation, do the acoustic reflections that occur within a Franz diffusion cell significantly influence the inertial cavitation dose?

Although, to the authors' knowledge, there are no published studies that explicitly investigate the influence of reflection in *in vitro* skin sonoporation setups, some researchers have employed experimental methods intended to suppress these reflections. For example, in their

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high-frequency *in vivo* study on transdermal transport through rat skin, Park et al. (2012) positioned a thermocouple outside of the direct beam of their transducer to avoid strong reflection. Mitragotri et al. (1995) inserted a 1-mm-thick Teflon sheet opposite the transducer in a high-frequency horizontal diffusion cell setup in an attempt to reduce multiple ultrasound reflections. In their high-intensity focussed ultrasound (HIFU), *in vitro* study on transdermal transport through pig skin, Helga et al. (2015) inserted a polyurethane absorber opposite the transducer to avoid reflections of the HIFU beam.

The presence of inertial cavitation has previously been reported to be observable by passive cavitation detection (PCD) (Farny et al. 2010; Hallow et al. 2006; Helga et al. 2015; Liu et al. 1998). In a PCD setup, a hydrophone is placed directly into the coupling fluid and confocally aligned with the ultrasound beam to measure the ultrasound pressure fluctuations that are radiated by the cavitation bubbles during ultrasound application. The voltage-versus-time data that this hydrophone records during ultrasound application are then filtered to isolate the broadband noise. The root mean square (RMS) value of the broadband noise is indicative of the magnitude of the inertial cavitation within the ultrasound field (Hallow et al. 2006). Cell sonoporation studies, such as those conducted by Chen et al. (2003) and Hallow et al. (2006), have found that it is the cavitation dose, as opposed to the magnitude of broadband noise emission, that best correlates with cavitation-induced enhancement of a bio-effect such as hemolysis or intracellular uptake. Because cavitation dose includes a temporal component, any changes in cavitation activity over the course of ultrasound exposure will alter the cavitation dose value.

Although PCDs have been employed frequently in studies involving the insonation of media other than skin (Coussios and Roy 2008; Farny et al. 2010; Liu et al. 1998; Tung et al. 2010), they have rarely been used in low-frequency *in vitro* skin insonation studies. This is probably due to the geometric constraints within the traditional Franz diffusion cell, which make it difficult to fit both a transducer and a hydrophone in the coupling fluid. In the study by Tang et al. (2002), a hydrophone was fixed to the outer surface of the bottom of the receiver chamber. This allowed for the PCD data to be recorded during skin insonation but did not directly capture the ultrasound field signal within the coupling fluid. Tezel and Mitragotri (2003) were able to directly monitor the ultrasound field in the coupling fluid but could not take measurements during skin insonation because the hydrophone was positioned where the skin sample would usually be positioned. An *in vitro* skin insonation apparatus that allows for a hydrophone to be positioned in the coupling fluid during skin insonation has not yet been reported. In part, the motivation for the current work was to develop an experimental apparatus that allows the PCD data to be gathered from the Franz diffusion cell during application of the ultrasound.

The application of ultrasound at intensities required for significant inertial cavitation has been reported to result in considerable heating of the coupling fluid from absorption (O'Brien 2007; Tezel et al. 2001). This heating is an important issue because extended exposure to temperatures as low as 40 °C has been found to increase skin permeability (Park et al. 2008), even though stratum corneum lipid fluidisation does not occur until around 65 °C (Golden et al. 1986, 1987). Two approaches to addressing this heating have been reported in the literature. Some studies replaced the coupling fluid within the donor cell during the application of the ultrasound field to limit the maximum temperature of the skin (Polat et al. 2012; Tang et al. 2002; Terahara et al. 2002). Alternatively, duty cycles have been used in which the total exposure was administered at regularly spaced intervals, allowing the coupling fluid to cool between applications (Lavon et al. 2005; Merino et al. 2003; Mitragotri et al. 2000a, 2000b; Paliwal et al. 2006; Terahara et al. 2002). The replacement of the coupling fluid and the use of duty cycles were both able to maintain the coupling fluid temperature below some specified maximum value. However, as cavitation activity is temperature dependent (Brabec and Mornstein 2007), a temperature control method that facilitates a constant coupling fluid temperature during the continuous application of high-intensity ultrasound would be more appropriate. Such a method is presented in the current study.

In this study, we introduce a modified Franz diffusion cell in which the transducer and the hydrophone were able to be simultaneously positioned in the coupling fluid. This allowed the cavitation dose to be calculated from data taken directly from the actual donor cell during insonation. The diffusion cell setup also employed a novel temperature control method to mitigate the coupling fluid temperature increases brought on by continuous ultrasound application. We used this setup to investigate whether the acoustic reflections that occur within a Franz diffusion cell significantly influence the inertial cavitation dose at an intensity relevant to skin sonoporation.

METHODS

Modified Franz diffusion cell

The modified Franz diffusion cell consisted of a donor chamber that was fixed to a receiver chamber with a specially designed acoustically transmissive clamp. The donor chamber had an inner diameter of 15 mm, an outer diameter of 19 mm and an aperture diameter of 9 mm. The total volume of the donor chamber was 6.7 mL. The receiver chamber also had a 9-mm aperture and a volume of 3.4 mL. The donor, receiver, and clamp geometries are illustrated in Figure 1.

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