



● Original Contribution

DETERMINATION OF ACOUSTIC CAVITATION PROBABILITIES AND THRESHOLDS USING A SINGLE FOCUSING TRANSDUCER TO INDUCE AND DETECT ACOUSTIC CAVITATION EVENTS: I. METHOD AND TERMINOLOGY

JULIAN HALLER,^{*,1} VOLKER WILKENS,^{*} and ADAM SHAW[†]

^{*} Physikalisch-Technische Bundesanstalt, Braunschweig, Germany; and [†] National Physical Laboratory, Teddington, Middlesex, United Kingdom

(Received 5 December 2016; revised 30 July 2017; in final form 9 August 2017)

Abstract—A method to determine acoustic cavitation probabilities in tissue-mimicking materials (TMMs) is described that uses a high-intensity focused ultrasound (HIFU) transducer for both inducing and detecting the acoustic cavitation events. The method was evaluated by studying acoustic cavitation probabilities in agar-based TMMs with and without scatterers and for different sonication modes like continuous wave, single pulses (microseconds to milliseconds) and repeated burst signals. Acoustic cavitation thresholds (defined here as the peak rarefactional *in situ* pressure at which the acoustic cavitation probability reaches 50%) at a frequency of 1.06 MHz were observed between 1.1 MPa (for 1 s of continuous wave sonication) and 4.6 MPa (for 1 s of a repeated burst signal with 25-cycle burst length and 10-ms burst period) in a 3% (by weight) agar phantom without scatterers. The method and its evaluation are described, and general terminology useful for standardizing the description of insonation conditions and comparing results is provided. In the accompanying second part, the presented method is used to systematically study the acoustic cavitation thresholds in the same material for a range of sonication modes. (E-mail: volker.wilkens@ptb.de) © 2017 The Author(s). Published by Elsevier Inc. on behalf of World Federation for Ultrasound in Medicine & Biology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Key Words: Acoustic cavitation threshold, Agar phantom, High-intensity focused ultrasound.

INTRODUCTION

It is well known that acoustic cavitation can induce several biological effects, for example, cell lysis (destruction of the cell by rupture of the cell membrane) (Harvey 1930), sonoporation (transiently increased permeability of cell membranes) (Bao et al. 1997), (increased) heating (Holt and Roy 2001), and production of chemicals and free radicals that can affect the morphology of cells, membrane transport capabilities and/or DNA (Miller et al. 1996; O'Brien 2007). In Shaw et al. (2016), more than 50% of respondents to a survey about therapeutic ultrasound stated that cavitation effects (tissue or cell destruction) are relevant to their work. The likelihood of acoustic cavitation is expected to depend on many parameters of the exposure, including (but not limited to) the *in situ* peak rarefactional pressure $p_{r, is}$, on the temperature and, in the

case of burst mode sonication, on the burst duration, the time between bursts and the total number of bursts. For an inhomogeneous medium (or a nominally homogeneous medium that has been cut or has inclusions), it is also expected to depend on location within the medium: there is therefore no single “acoustic cavitation threshold” for a medium. In addition, different authors have used different insonation sequences and different measurement techniques, making it difficult or even impossible to compare results. It is therefore necessary to introduce clearly defined terms to describe the insonation. The question whether (and when and where) acoustic cavitation occurs during the application of an ultrasonic therapeutic treatment is of importance. One strategy to answer these questions would be to monitor acoustic cavitation during the treatment, for example, by means of passive acoustic detection methods (Atchley et al. 1988; Edmonds and Ross 1986; Gyöngy and Coussios 2010; Hoerig et al. 2014; Li et al. 2014). An alternative approach is to attempt to predict acoustic cavitation with appropriate treatment planning before starting the application. For this purpose, it is essential to know (1) the ultrasound field quantities at any

Address correspondence to: Volker Wilkens, Physikalisch-Technische Bundesanstalt, Bundesallee 100, 38116 Braunschweig, Germany. E-mail: volker.wilkens@ptb.de

¹ Present address: Sartorius Lab Instruments GmbH & Co. KG, 37070 Göttingen, Germany.

time and at any point in the field and (2) under which conditions (in terms of field quantities and sonication sequence) acoustic cavitation occurs in the particular medium. Although the possibility of addressing the first issue has significantly improved within recent years through improved methods for characterizing high intensity ultrasound sources (Haller et al. 2012; Kreider et al. 2013; Wilkens et al. 2016) and improved methods for non-linear simulation of ultrasound fields (Bessonova and Wilkens 2013; Gélat et al. 2011; Yuldashev and Khokhlova 2011), there is still a lack of knowledge on the second issue. Commonly, the terms *acoustic cavitation onset* and *acoustic cavitation threshold* are used to describe the condition (usually in terms of peak rarefactional pressure) at which acoustic cavitation starts to occur. However, there is neither a clear definition of these terms yet, nor standardized methods to determine them. Furthermore, there are several fundamental open questions about the nature of “acoustic cavitation thresholds” for which systematic experimental studies would be beneficial. Acoustic cavitation thresholds are often given as a frequency-dependent peak rarefactional pressure, for example, as the mechanical index (MI) (defined as the *in situ* peak rarefactional pressure divided by the square root of the center frequency of the beam) based on the work of Apfel and Holland (1991) that was created as a safety parameter for diagnostic ultrasound where acoustic cavitation should be avoided. However, this parameter is quite simplifying and is not specific for different media and sonication conditions. There remain several open issues that are not covered by such parameters, including a possible influence of the peak compressional pressure on acoustic cavitation probability (Maxwell et al. 2011) or how the acoustic cavitation threshold in tissue and tissue-like media depends on the temporal sonication parameters (burst length, burst period, sonication duration) and how the sonication history at a particular position within a medium changes the (local) acoustic cavitation threshold. Only for the former has a modification of the mechanical index been suggested (Church 2005).

Within this first of two articles, standard terminology is proposed in the Appendix that will help describe the

insonation conditions (in particular, the temporal sequencing of tone bursts), and a simple method that uses a focusing transducer for both inducing and detecting acoustic cavitation in a tissue-mimicking material (TMM) is presented and evaluated. The results obtained with this method are not discussed in detail within this article, but only in Part II (Haller and Wilkens 2017b), as Part I primarily intends to present and evaluate the method. The influence of scattering of the incident ultrasound on acoustic cavitation bubbles on the driving voltage has been used to monitor acoustic cavitation previously (McLaughlan et al. 2010; Thomas et al. 2006), but to the authors’ knowledge not for a quantitative determination of acoustic cavitation probabilities, which has been done in this work with statistical analysis methods.

In the accompanying Part II, the method presented here is used to systematically study the acoustic cavitation probabilities in agar-based TMMs for different sonication parameters. All results from Part I are additionally given in the Appendix in Part II.

METHODS

Principle

The general principle used within this work is based on monitoring and analyzing the voltage signal at the input of the impedance matching network of the high-intensity focused ultrasound (HIFU) transducer (Fig. 1). The underlying principle is that the transducer acts as a receiver as well as a transmitter, and any ultrasound returning from the medium will generate a voltage that can be measured. By use of a focusing transducer, the maximum receiving sensitivity is to reflections arising from the focal region, which is also where the acoustic pressure is maximum and, therefore, where acoustic cavitation is likely to occur first. Although some scattered signal from the medium is expected even in the absence of acoustic cavitation, this signal should increase greatly once gas regions begin to form. This effect has been used previously by other authors to monitor acoustic cavitation (McLaughlan et al. 2010; Thomas et al. 2006), but will be studied in more

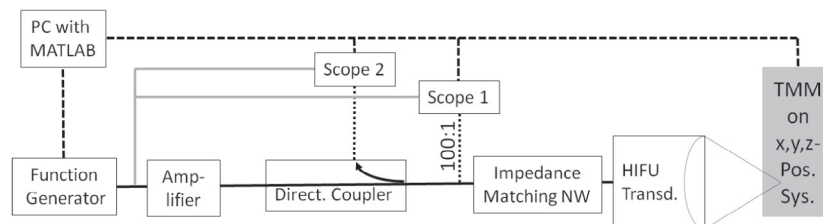


Fig. 1. Schematic setup of the devices. Full black lines indicate the radiofrequency signal path; dotted black lines the measuring lines; dashed black lines the data lines; and gray lines the trigger lines. PC = personal computer, Direct. Coupler = directional coupler, NW = network, HIFU Transd. = high-intensity focused ultrasound transducer, TMM = tissue-mimicking material, Pos. Sys. = positioning system, 100:1 = 100-fold attenuating voltage probe.

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