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● *Original Contribution*

METHOD FOR ESTIMATING THE ACOUSTIC PRESSURE IN TISSUES USING LOW-AMPLITUDE MEASUREMENTS IN WATER

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Abstract—The aim of this study was to evaluate a simple, reliable and reproducible method for accuracy in estimating the acoustic pressure delivered in tissue exposed to ultrasound. Such a method would be useful for therapeutic applications of ultrasound with microbubbles, for example, sonoporation. The method is based on (i) low-amplitude water measurements that are easily made and do not suffer from non-linear propagation effects, and (ii) the attenuation coefficient of the tissue of interest. The range of validity of the extrapolation method for different attenuation and pressure values was evaluated with a non-linear propagation theoretical model. Depending on the specific tissue attenuation, the method produces good estimates of pressures in excess of 10 MPa. *Ex vivo* machine-perfused pig liver tissue was used to validate the method for source pressures up to 3.5 MPa. The method can be used to estimate the delivered pressure *in vivo* in diagnostic and therapeutic applications of ultrasound. (E-mail: maverk@uw.edu) **© 2015 World Federation for Ultrasound in Medicine & Biology.**

Key Words: **Liver attenuation, Porcine liver, Non-linear distortion, Drug delivery, *In situ* pressure, Exposimetry, Derating.**

INTRODUCTION

Novel therapeutic methods such as sonoporation, sonothrombolysis and other recent gene and drug delivery techniques make use of the combined effects of ultrasound and microbubbles (Deckers and Moonen 2010; Kotopoulis et al. 2013; Martin and Dayton 2013; Molina et al. 2006; Rahim et al. 2006). Therapeutic ultrasound is also used in high-intensity applications that cause irreversible tissue changes, such as thermal ablation and mechanical tissue fragmentation (histotripsy) (Mahmoud et al. 2014; Vlaisavljevich et al. 2014). Accurate knowledge of the acoustic pressure in the region exposed to ultrasound (*in situ* acoustic pressure) is therefore essential for the aforementioned applications.

As ultrasound pressure employed for both diagnostic and therapeutic purposes varies greatly (up to three orders of magnitude) depending on the specific application, non-linear propagation effects are often encountered that cause errors in the linear pressure derating method. In addition to non-linear propagation, the attenuation of ultrasound in biological tissues plays an important role in calculation of the delivered pressure *in situ*. Measurements in water are strongly affected by non-linear propagation; thus various published methods propose accounting for non-linearity in the pressure derating process or measuring the acoustic field in dissipative media.

Schafer (1990) suggested the use of a wideband derating factor that would apply the deration of each frequency component of the measured ultrasound pulse. More recently, Bessonova et al. (2010) proposed a method for scaling the source amplitudes used to generate pulses in tissue and in water so that the propagated pulses yield the same acoustic pressure at the geometric focus of the source in both media. The derating method was proposed for therapeutic applications of high-intensity focused ultrasound and was validated with both simulations and experimental measurements, with good agreement between the derated method results and numerical simulations in tissues. However, this method produces very good results only in cases in which the pressure amplitude at the focus is much higher than the amplitudes along the rest of the propagation path (G = 20–50). Other methods propose the use of plastic disk attenuators in the acoustic path (Preston et al. 1991a, 1991b) and the substitution of water with attenuative fluid to create a tissue-mimicking

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environment in which to perform measurements (Szabo et al. 1999). Nevertheless, the use of attenuative fluids such as castor oil and water–glycerin mixtures to create a tissue-mimicking environment for measurements introduces errors and discrepancies such as variation in properties of the fluids between different laboratories and different attenuation frequency dependence different from that of tissue.

Currently, the *in situ* pressure delivered from diagnostic ultrasound scanners and, thus, the mechanical index (MI) are estimated using measurements in water that are derated for the traveled distance according to a known tissue attenuation value at the center frequency of the propagated pulse. However, for estimation of the *in situ* pressure, the World Federation of Ultrasound in Medicine and Biology (WFUMB) recommend also the use of low-amplitude hydrophone measurements, linearly scaled based on the source pressure and the attenuation of tissue (WFUMB 1992). Such a method avoids experimental errors associated with hydrophone measurements of sound fields at high output levels and simplifies the theoretical and computational aspects of the derating problem (Christopher and Carstensen 1996).

Previously published works have dealt with linear derating method issues. Bacon (1989) established a non-linear propagation model to predict acoustic levels in tissue. In that work, linear extrapolation of low-amplitude measurements in water was used to calculate the input data for the simulations and to validate the non-linear propagation model. The author compared non-linear theory results and linear extrapolation pressure values with measurements after propagation through a tissue-mimicking gel phantom. He concluded that linear extrapolation from measurements made in water is inadequate in predicting *in situ* exposure to ultrasound as it might contain errors up to 80%. However, Bacon evaluated the method only under the assumption of the specific properties of the tissue-mimicking gel phantom rather than using real tissue. Christopher and Carstensen (1996) used a non-linear propagation model that takes into account the effects of diffraction, attenuation, non-linearity and planar (fluid) boundary transmission of axially symmetric acoustic beams to evaluate the nature of the effects that occur under realistic exposure conditions encountered in diagnostic procedures. Simulations based on water, liver and fat tissue properties were compared with linear theory to point out the necessity for considering non-linear propagation when estimating the *in situ* pressure. The review by Duck (2002) provides a detailed description of finite-amplitude wave effects associated with non-linear propagation, distortion and harmonic component generation, which are associated with ultrasound beams used in therapeutic applications.

If the measurements are performed in a non-dissipative medium such as water, the attenuation values used in the derating process are very important. Liver attenuation, which was used in our work, has been extensively studied in animal liver samples (Bamber et al. 1977; Goss et al. 1978), postmortem specimens of human liver (Chivers and Hill 1975; Goss et al. 1978) and *in vivo* measurements (Maklad et al. 1984; Parker et al. 1988). The liver attenuation reported in these studies varied between 0.3 dB/cm/MHz (3.45 Np/m) and 1.2 dB/cm/MHz (14 Np/m) for healthy livers (human and animals) and even more widely for diseased livers (cirrhotic livers and liver with malignancies). As there are great deviations in the published values, the accurate knowledge of tissue attenuation in individuals could obviously improve the estimation of pressure *in situ*. However there are difficulties in collecting measurements from each patient. To this end, measurements of attenuation in a well-functioning machine-perfused liver environment could improve the estimation of *in situ* pressure.

In this work, a method for estimating the acoustic pressure delivered in tissue based on extrapolation of low-amplitude water measurements with linear theory was evaluated with respect to accuracy. The aim of this study was to establish and test a simple, reliable and reproducible tool with known limitations and errors that can be used to quickly predict the pressure delivered in an area exposed to ultrasound. The acoustic field was measured in water only under low-amplitude conditions; thus, linear scaling of the source amplitudes was adequate for estimation of higher source pressures. The method was validated by comparing the extrapolated values with actual measurements of the acoustic pressure after propagation through samples taken from *ex vivo* machine-perfused porcine livers. Knowledge of the attenuation coefficient of the tissue was necessary for use of the extrapolation method. Thus, to assess the exact acoustic properties of the experimental samples used to validate the linear extrapolation method, porcine liver attenuation was measured in the range 2–8 MHz. The range of validity of the extrapolation method for different pressures and attenuation values was also investigated with a non-linear propagation theoretical model.

METHODS

Theory

Linear propagation of ultrasound in an absorptive medium. Linear propagation of ultrasound in an absorptive medium is described with the equation

$$p(x,y,z) = \frac{p_{02}}{p_{01}} p_1(x,y,z) e^{-\alpha z} \tag{1}$$