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● *Original Contribution*

A THEORETICAL STUDY OF INERTIAL CAVITATION FROM ACOUSTIC RADIATION FORCE IMPULSE IMAGING AND IMPLICATIONS FOR THE MECHANICAL INDEX[1]

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Abstract—The mechanical index (MI) attempts to quantify the likelihood that exposure to diagnostic ultrasound will produce an adverse biological effect by a non-thermal mechanism. The current formulation of the MI implicitly assumes that the acoustic field is generated using the short pulse durations appropriate to B-mode imaging. However, acoustic radiation force impulse (ARFI) imaging employs high-intensity pulses up to several hundred acoustic periods long. The effect of increased pulse durations on the thresholds for inertial cavitation was studied computationally in water, urine, blood, cardiac and skeletal muscle, brain, kidney, liver and skin. The results indicate that, although the effect of pulse duration on cavitation thresholds in the three liquids can be considerable, reducing them by, for example, 6%–24% at 1 MHz, the effect on tissue is minor. More importantly, the frequency dependence of the MI appears to be unnecessarily conservative; that is, the magnitude of the exponent on frequency could be increased to 0.75. Comparison of these theoretical results with experimental measurements suggests that some tissues do not contain the pre-existing, optimally sized bubbles assumed for the MI. This means that in these tissues, the MI is not necessarily a strong predictor of the probability of an adverse biological effect. (E-mail: cchurch@olemiss.edu) © **2015 World Federation for Ultrasound in Medicine & Biology.**

Key Words: **Acoustic radiation force imaging, ARFI, Bio-effects, Cavitation threshold, Inertial cavitation, Mechanical index, MI.**

INTRODUCTION

The concept of ensuring ultrasound safety by onscreen display of indices related to the probability of inducing biological effects by known physical mechanisms is now well accepted by the medical community. However, this was not always the case. When diagnostic ultrasound imaging was first introduced, little information was available on the acoustic fields produced by clinical machines, and in any case, few users were sufficiently trained to evaluate such information, even had it been obtainable. Then, on May 28, 1976, President Gerald Ford signed an act of the U.S. Congress, the Medical Device Amendments of 1976 (Pub L No. 94-295, 90 Stat 539, May 28, 1976) to the Federal Food, Drug and Cosmetic Act (Pub L No. 75-717, 52 Stat 1040, June 25, 1938), which required that new medical devices offered for sale in the United States be substantially equivalent in effectiveness to devices marketed for the same applications before that date (Nyborg 2003). Manufacturers provided various data to the U.S. Food and Drug Administration (U.S. FDA), including values for output power and intensities measured in water, as well as estimates of intensities expected in an average patient; safety was assessed by determining that these values were no greater than, or "substantially equivalent" to, those for "pre-Amendment devices," that is, diagnostic equipment in clinical use before May 28, 1976. By the late 1980s, it had become apparent to many users that the quality of diagnostic information could be improved by increasing acoustic outputs beyond the

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[1] A more limited version of this work, presented at the IEEE Ultrasound Symposium held in Dresden, Germany in October, 2012, contains additional plots of results for combinations of parameters and endpoints not shown explicitly here (Church et al. 2012).

levels approved under the existing regulations. This supplied the impetus for the joint development of the so-called "output display standard" (ODS) by the American Institute of Ultrasound in Medicine (AIUM) and the National Electrical Manufacturers Association (NEMA) for the display of safety information on diagnostic ultrasound equipment (AIUM/NEMA 1992). After the ODS had been reviewed and widely accepted by the user community as being superior to the then-current application-specific regulatory framework, the US FDA (1993, 1997) revamped its guidance for marketing of diagnostic ultrasound equipment in the United States. Note that much more extensive information on the development of the ODS is available (*e.g.*, Abbott 1999; Nyborg 2000, 2001).

After implementation of the Medical Device Amendments, diagnostic ultrasound machines were classified as being either "track 1" for those having very low output levels or "track 3" for those with higher outputs ("track 2" was an interim procedure and is no longer used). The original track 3-guidelines were determined based on the highest output levels in use as of May 28, 1976, and for which no bio-effects had been reported. The upper bounds on the outputs permitted under track 3 were application-specific in that they differed depending on the medical specialty (cardiology, obstetrics, *etc.*) for which they were intended to be used. These limits were not based on scientific evidence related to specific bio-effects of ultrasound (Fowlkes et al. 2008). In 1993, the guidelines for track-3 devices were modified with the implementation of two new safety indices, the thermal index (TI) and the mechanical index (MI) (AIUM/NEMA 1992; US FDA 1993, 1997). The equivalent international standards, "Particular Requirements for the Basic Safety and Essential Performance of Ultrasonic Medical Diagnostic and Monitoring Equipment" (IEC 2007), and its subsidiary "Test Methods for the Determination of Thermal and Mechanical Indices Related to Medical Diagnostic Ultrasonic Fields" (IEC 2010), were developed by the IEC.

The MI and TI were derived through an effort to relate output guidelines to potential bio-effects. However, the upper limits for acoustic output (I_{spta}, MI) were also tied to the pre-existing limits, rather than to scientific evidence of bio-effects (Fowlkes et al. 2008). Since 1993, acoustic output levels have increased within the context of the newer guidelines (Martin 2010). Concurrently, new imaging technologies have been developed that employ unique beam sequences that often approach the upper bounds of current limits, including harmonic imaging modes (Kollman 2007) and acoustic radiation force-based elasticity imaging modes (Mendelson et al. 2009; Palmeri et al. 2011).

When the MI and TI were first implemented, consideration was given to the question of whether upper limits on acoustic output should be retained by the U.S. FDA, or if outputs should be determined via risk–benefit analysis based on the "as low as reasonably achievable" (ALARA) principle (O'Brien et al. 2002). In 2008, the AIUM issued a consensus report on potential bio-effects of diagnostic ultrasound (Fowlkes et al. 2008). In this report, it was recommended that the FDA be encouraged to develop an open, scientifically valid process for assessing the benefits and risks of removing or modifying upward the current regulatory limits. It is widely recognized that many imaging modes may benefit from transient increases in both thermal and non-thermal parameters, particularly in cases where tissue overlying the beam focus is highly attenuating. For example, in tissue harmonic imaging (THI), the production of harmonics is proportional to the square of the pressure at the fundamental frequency of the transmit wave (Christopher 1997), and increased MIs would lead to increases in the depth of penetration. The desirability of increased output is especially true for acoustic radiation force impulse (ARFI) imaging modes for which the depth of penetration may be limited to only 6–8 cm at the upper limit on the MI, 1.9 (Cosgrove et al. 2013; Park et al. 2013). This situation has provoked renewed interest in raising the acoustic outputs for diagnostic ultrasound machines.

Although it has been the subject of study for many years, the precise relationship between the acoustic output parameters used to formulate the safety indices (*e.g.*, acoustic pressure, frequency, pulse duration and repetition frequency, intensity) and biological effects is still not completely understood. The AIUM periodically reviews the status of this research and publishes its conclusions (Abramowicz et al. 2008; Church et al. 2008; Miller et al. 2008; O'Brien et al. 2008; Stratmeyer et al. 2008). More recent reviews are also available (ter Haar 2012). This study was undertaken as part of an ongoing effort to assess the ability of the MI to quantify the probability of harm to the patient from exposure to the relatively long pulses necessary for ARFI imaging, a modality that was only just beginning to be explored when the ODS was developed. In the work described in this article, the effect of pulse duration on inertial cavitation thresholds is determined computationally using the same methods and assumptions as in the original work of Apfel and Holland (1991), insofar as this is possible. However, there are two significant differences between the methods used previously and those employed in this study. Fist, as noted above, the pulse duration is increased from a single acoustic period to $\geq$100 periods. Second, the list of materials surrounding the bubble is now expanded to include three,