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Should the mechanical index be revised for ARFI imaging?

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Abstract

The mechanical index (MI) quantifies the likelihood that exposure to diagnostic ultrasound will produce an adverse biological effect by a nonthermal mechanism. The current formulation of the MI is based on inertial cavitation thresholds in two liquids, water and blood, as calculated by a formalism assuming very short pulse durations. Although tissue contains a high proportion of water, it is not a liquid but a viscoelastic solid. Further, acoustic radiation force impulse imaging employs high-intensity pulses up to several hundred acoustic periods long. The effect of these differences was studied in water, blood and five representative tissues.

Keywords

Acoustic Radiation Force Imaging; ARFI; bioeffects; inertial cavitation; mechanical index; MI

I. INTRODUCTION

In the United States (US), the acoustic output levels used in diagnostic ultrasound machines approved under the Food and Drug Administration's (FDA) track 3 process have been limited by federal statute since 1976. The original guidelines were determined based upon the highest output levels existing at that time, and for which no bioeffects had been reported; these limits were not based on scientific evidence related to specific bioeffects due to ultrasound [1]. In 1992, these guidelines were relaxed with the implementation of two new safety indices, the thermal index (TI) and the mechanical index (MI) [2]. These metrics were derived through an effort to relate output guidelines to potential bioeffects. However, the upper limits for acoustic output (Ispta, MI) were also tied to the pre-existing limits, rather than to scientific evidence of bioeffects [1]. Since 1992, acoustic output levels have increased within the context of the newer guidelines [3]. 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 [4], and acoustic radiation force-based elasticity imaging modes [5][6].

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 FDA, or if outputs should be determined via risk-benefit analysis based on the ALARA (as low as reasonably achievable) principle [7]. In 2008, the AIUM issued a consensus report on potential bioeffects of diagnostic ultrasound [1]. 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. This is especially true for ARFI imaging modes for which the depth of penetration is limited to 6 – 8 cm at the upper limit on the MI, 1.9. This study is part of an effort to assess the risk in vivo of the relatively long pulses necessary for ARFI imaging.

II. THE MECHANICAL INDEX

The MI is defined as the estimated peak rarefactional pressure in vivo, p_r , divided by the square root of the center frequency, f_c , of the acoustic beam. The expression is based on an analytical solution obtained by Apfel and Holland [8] for the radial motion of pre-existing air bubbles in water and blood exposed to a wave having a pulse length of a single acoustic period. Apfel and Holland determined the approximate acoustic pressure amplitude required to cause an optimally sized bubble (i.e., the bubble size having the lowest threshold) to undergo inertial cavitation, i.e., a large expansion followed by a rapid, violent collapse. Such a collapse can radiate damaging shock waves and cause the gas within the bubble to attain a very high temperature, 5000 K in the case of the MI, thereby producing large numbers of highly reactive free radicals.

In its current form, the MI uses only two of the many parameters that characterize an acoustic field: the peak rarefactional pressure and the center frequency. Further, the results upon which it is based are valid only for liquids. This work investigates the effects of pulse lengths much longer than the 14-period maximum reported earlier [9], and it also models several tissues using values for elasticity (or more precisely, the shear modulus) and viscosity determined experimentally rather than estimating these values as was done previously [10].

III. METHODS

A. Bubbles in Liquids

The acoustic response of bubbles in liquids was modeled using the Gilmore-Akulichev formulation for bubble dynamics; details of the general approach may be found in [9]:

$$\left(1 - \frac{\dot{R}}{c}\right) R\ddot{R} + \frac{3}{2} \left(1 - \frac{\dot{R}}{3c}\right) \dot{R}^2 = \left(1 + \frac{\dot{R}}{c}\right) H + \left(1 - \frac{\dot{R}}{c}\right) \frac{R}{c} \frac{dH}{dt}, \quad (1)$$

where R , is the bubble radius, c is the calculated speed of sound in the liquid, H is the enthalpy of the liquid, and t is time; the single and double overdots indicate first and second derivatives with respect to time. Liquids are modeled using a Tait equation of state.

B. Bubbles in Tissues

The acoustic response of bubbles in tissues was modeled using a Keller-Miksis-like equation assuming a gas bubble in a linear Voigt viscoelastic solid [11]:

$$\left(1 - \frac{\dot{R}}{c}\right) R\ddot{R} + \frac{3}{2} \left(1 - \frac{\dot{R}}{3c}\right) \dot{R}^2 = \left(1 + \frac{\dot{R}}{c}\right) \frac{p_a - p_l}{\rho} + \frac{R}{\rho c} \frac{d}{dt} [p_a - p_l], \quad (2)$$

where ρ is the density of the surrounding tissue,

$$p_a - p_l = p_{g0} \left(\frac{R_0}{R} \right)^{3\kappa} - \frac{2\sigma}{R} - p_0 + P_A g(t) - \left[\frac{4G}{3R^3} (R^3 - R_0^3) + \frac{4\mu\dot{R}}{R} \right], \quad (3)$$

σ is the surface tension, p_0 is the hydrostatic pressure, P_A is acoustic pressure amplitude, $g(t)$ gives the shape of the driving pressure wave, G is modulus of rigidity (rigidity), μ is shear viscosity, and the subscript 0 indicates the initial value of a parameter.

C. Computational Approach

Thresholds for inertial cavitation are determined by performing numerical computations similar to the analytical work underlying the MI. In the work reported here, the acoustic frequency ranges from 0.5 to 10.0 MHz, and the pulse length is varied over the range 1 – 100 acoustic periods. The range of equilibrium bubble radii (R_0) studied is 0.1–10.0 μm . Two criteria for the threshold acoustic pressure (P_t) are used: $R_{max} = 2R_0$ and $T_{max} = 5000$ K (the criterion used for the MI).

In all cases, it is assumed that: (1) a spherical bubble is initially at rest (i.e., $dR/dt = 0$) in an infinite material, (2) there is no exchange of gas with the surrounding material, (3) the gas within the bubble pulsates adiabatically, and (4) the bubble radius is small compared to the wavelength. A fourth-order Runge–Kutta technique is used to solve the initial value problem. This formalism is quite similar to that forming the basis for the MI [8], although corrections for liquid compressibility are included, befitting the high pressure amplitudes studied in some cases.

The values for the physical parameters characterizing the materials surrounding the bubbles are given in Table I. The values for tissue were determined by experiments performed in the low- MHz frequency range by Madsen et al. [12] and Yang and Church [13].

The method used to determine the threshold for inertial cavitation, P_t , is essentially the same as that used by Apfel and Holland [8]. For a given combination of parameters, the minimal pressure amplitude required to satisfy the cavitation threshold criterion is determined for each equilibrium radius in the range studied, and the global value for P_t is then taken from the threshold for the bubble requiring the least acoustic pressure to satisfy the given threshold criterion; that bubble is described as being “optimally sized”. This procedure is repeated for each frequency, pulse length, and material studied.

IV. RESULTS AND DISCUSSION

A. Threshold as a Function of Bubble Radius

Representative results for cavitation threshold as a function of equilibrium bubble radius are given in Figs. 1(a) – (c) for the cases of air bubbles in blood, skeletal muscle and liver, respectively, for an acoustic frequency of 3.0 MHz. Results for the two threshold criteria, $R_{max} = 2R_0$ and $T_{max} = 5000$ K, are shown in each figure. Figure 1 illustrates several observations common to most or all of the data sets: (1) the effect of increasing pulse length is to reduce the threshold for most, although not all, bubbles near to, or larger than, the optimally sized bubble, (2) for a given pulse length, bubble radius, and liquid, the threshold pressure for $T_{max} = 5000$ K is always greater than that for $R_{max} = 2R_0$, (3) the threshold for either criterion increases with the material’s viscosity under equivalent exposure conditions, (4) for bubbles larger than the optimal size, there are usually several distinct local minima, the result of driven resonance responses, while (5) small bubbles usually exhibit few, and often no, resonance minima.

B. Threshold as a Function of Acoustic Frequency

The frequency response was determined for each pulse length by fitting the threshold data to a power law with and without an intercept: $P_t = A + Bf_c^n$ and $P_t = Bf_c^n$, respectively; the latter is that assumed for the MI [2]. Based on values of the correlation coefficient, the simple power law with $A = 0$ fits the data very well ($0.953 < r^2 < 1.000$), although the power law with an intercept fits somewhat better ($0.999 < r^2 < 1.000$).

Plots of the cavitation threshold vs. frequency are shown in Fig. 2. The computational data are indicated by the symbols, and the curves are the best fits to $P_t = Bf_c^n$. The values for the fits shown in Fig. 2 are given in Table II. Notice that the values of the coefficients for the temperature criterion are approximately twice those for the radial criterion, indicating that it takes a more violent collapse to achieve the former endpoint. Similarly, values for the exponent n , are also larger for the temperature criterion, although the differences are not as great. Significantly, the exponent determined for each material is larger than the value assumed for the MI, suggesting that this index may unnecessarily restrict output levels at higher frequencies.

C. Threshold as a Function of Acoustic Pulse Length

Because the values of the dimensional thresholds are so different, it is convenient to normalize the threshold at each pulse length to the value at a pulse length of 1 period. The results for normalized threshold $P_{t,n}$, are shown in Fig. 3 for both criteria. The data are indicated by the symbols, and the curves are the best fits to $P_{t,n} = Bf_c^n$. The values of the parameters for the fits shown in Fig. 3 are given in Table III.

D. The Final Formulation

Because the two sets of data are both well fit by the same equation, it is convenient to combine the two sets of fits into a single result. The parameters for the final equation, $P_{t,tis} = Bf_c^n$, are given in Table IV. Notice that the exponent on frequency is greater than the 0.5 assumed for the MI, with the values for the more intense threshold criterion being approximately 0.75. This supports the possibility that the frequency response of the MI may be safely modified for certain selected imaging modes requiring greater outputs, e.g., ARFI imaging.

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Figure 1. Thresholds for inertial cavitation of air bubbles in (A) blood, (B) skeletal muscle and (C) liver at 3 MHz for both threshold criteria; the numbers in the legends indicate the pulse length.

Figure 2. Thresholds for inertial cavitation of optimally sized air bubbles in each material for threshold criteria of (A) $R_{max} = 2R_0$ and (B) $T_{max} = 5000 \text{ K}$. Curves are the best fits of $P_t = Bf_c^n$ to the numerical data (points).

Figure 3. Normalized thresholds for inertial cavitation in each material for threshold criteria of (A) $R_{max} = 2R_0$ and (B) $T_{max} = 5000$ K at a pulse length of 100 periods. Curves are the best fits of $P_t = Bf_c^n$ to the numerical data (points).

Table I

Material Properties.

Material	Density	Surface Tension	Viscosity	Rigidity
	(kg/m ³)	(mN/m)	(mPa-s)	(MPa)
Water	1000	68.0	1.0	0.000
Blood	1050	56.0	5.0	0.000
Heart	1080	56.0	16.0	0.124
Kidney	1100	56.0	5.0	0.180
Liver	1100	56.0	9.0	0.040
Muscle	1100	56.0	7.0	0.450
Skin	1070	56.0	130.0	4.000

Table II

Parameters for Best Fits of Threshold to Frequency.

Material	$R_{max} = 2R_0$		$T_{max} = 5000 \text{ K}$	
	B	n	B	n
	(MPa)	(non)	(MPa)	(non)
Water	0.170	0.451	0.325	0.617
Blood	0.199	0.576	0.440	0.798
Heart	0.427	0.601	1.003	0.875
Kidney	0.382	0.374	0.686	0.644
Liver	0.275	0.599	0.651	0.866
Muscle	0.682	0.285	1.107	0.537
Skin	5.686	0.394	10.916	0.700

Table III

Parameters for Best Fits of Normalized Threshold to Pulse Length.

Material	$R_{max} = 2R_0$		$T_{max} = 5000 \text{ K}$	
	B	n	B	n
	(MPa)	(non)	(MPa)	(non)
Water	0.271	0.231	0.811	0.070
Blood	0.572	0.281	0.95	0.027
Heart	0.821	0.112	1.000	0.000
Kidney	0.466	0.342	0.968	0.012
Liver	0.721	0.172	0.995	0.003
Muscle	0.505	0.314	0.975	0.013
Skin	0.941	0.033	1.000	0.000

Table IV

Average Parameters for Best Fits of Normalized Threshold to Pulse Length.

Material	$R_{max} = 2R_0$		$T_{max} = 5000 \text{ K}$	
	B	n	B	n
	(MPa)	(non)	(MPa)	(non)
All	0.941	0.681	2.142	0.737
All Tissue	1.090	0.680	2.455	0.746
Soft Tissue	0.237	0.731	0.762	0.755