

Potential Adverse Ultrasound-related Biological Effects

A Critical Review

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ABSTRACT

Ultrasound energy exerts important cellular, genetic, thermal, and mechanical effects. Concern about the safety of ultrasound prompted several agencies to devise regulatory limits on the machine output intensities. The visual display of thermal and mechanical indices during ultrasound imaging provides an aid to limit the output of the machine. Despite many animal studies, no human investigations conducted to date have documented major physiologic consequences of ultrasound exposed during imaging. To date, ultrasound imaging appears to be safe for use in regional anesthesia and pain medicine interventions, and adherence to limiting the output of ultrasound machines as outlined by the Food and Drug Administration may avoid complications in the future. This article reviews ultrasound-related biologic effects, the role of the regulatory agencies in ensuring safety with the use of ultrasound, and the limitations and implications of ultrasound use in humans.

PIERRE Curie's discovery of the piezoelectric effect in 1880 launched the ultrasound technology revolution. This technology was first applied in ships for depth detection and in metallurgy for fracture identification, but medical applications were soon appreciated shortly thereafter.¹ Med-

ical ultrasound imaging has been used extensively for more than five decades, and the variety of uses for which this technology is used expanded rapidly. For example, the use of ultrasound for interventions during regional anesthesia and pain medicine allows the practitioner to reliably see the target, needle, and injectate with good resolution.² The primary advantages of ultrasound in these settings include real-time assessment, absence of radiation, decreased cost, and portability.² The use of ultrasound does not completely eliminate the possibility of nerve impalement or intravascular injections because inadequate needle visualization may still occur.^{3,4} Nevertheless, anesthesiologists and their patients have benefited from the use of ultrasound imaging because direct visualization of structures of interest is often possible.

Despite its widespread medical application, ultrasound causes important biologic effects that were recognized long before its use in diagnostic imaging became commonplace. The biologic effects of ultrasound have received little attention in the anesthesiology and pain medicine literature because ultrasound has a demonstrated safety profile in obstetrics. Considering that ultrasound is used on a routine basis in modern anesthesia practice, the authors sought to systematically review the biologic effects of ultrasound as they apply to anesthesiology. The history of ultrasound biologic effects research will be briefly examined, and evidence about the ultrasound biologic effects from experimental and human studies will be analyzed. Knowledge of the potential biologic effects of ultrasound imaging allows the practitioner to appropriately weigh the risks and benefits of its uses especially when targeting neural tissue.

Historical Background

The potential for ultrasound to produce biologic effects was first reported in 1917. Langevin demonstrated that fish in a small tank died when exposed to ultrasound.⁵ Subsequent studies confirmed that ultrasound also produces damage in other species.⁶ The thermal effects of ultrasound were used in the 1940s to cauterize tissue during surgery and to destroy cancerous cells *in situ*.^{7,8} Fry et al.⁹ examined the detrimental effects of focused ultrasound on neural tissue, including reversible and irreversible impairments in nerve conduction

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Table 1. Definitions of Common Ultrasound-related Terminology

Terms	Definitions
Acoustic power	The rate of transfer of energy along the beam is the acoustic power. A related term, acoustic output power, is the rate at which energy leaves the transducer. Acoustic power is the product of intensity and the area of the absorber. The acoustic power is measured <i>in vitro</i> with a radiation force balance.
Acoustic intensity	Acoustic intensity is defined as the power flowing per unit cross-sectional area of the pulse. The acoustic intensity is the ultrasound parameter associated with the possibility for thermal injury.
Acoustic impedance	Acoustic impedance is the resistance offered by tissues to the passage of sound waves. Measured in rayls (kilograms per square meter per second), acoustic impedance is a ratio of the acoustic pressure to the particle velocity. For a plane wave, it is a product of the average velocity and density of the tissue. The intensity of reflection increases with increasing impedance difference. When the impedances are identical, no echoes are generated.
Attenuation	The reduction in amplitude and intensity of the ultrasound wave as it passes through medium/tissues. Attenuation is frequency dependent and is due to reflection, scattering, absorption, refraction, and beam divergence. Attenuation is directly proportional to the frequency and the path length. Attenuation is described in decibels per centimeter of tissue traversed per megahertz and they range from 0.3–0.8 dB/cm/MHz for most tissues. Attenuation coefficient is the amount of attenuation that occurs every unit of travel of the sound wave and is approximately one-half the operating frequency.
Pulse repetition frequency	The number of ultrasound wave pulses occurring in 1 s.
Spatial-peak, temporal-peak intensity	Highest of the measured intensities. It is the peak intensity in space and time.
Spatial-peak temporal-average intensity	The largest intensity averaged over the pulse repetition period in the ultrasound field. This is the most commonly reported by the manufacturers and is the lowest intensity among all the calculated intensities. This intensity is most associated with thermal effects.
Spatial-average, temporal-average intensity	The peak intensity output of the device averaged over the pulse repetition period. This is the lowest measured intensity.
Spatial-peak, pulse-average intensity	The maximum intensity measured in space at the average of the pulse duration. This is related to cavitation development.
Radiation force	Radiation force is a temporal averaged effect of the acoustic wave on the medium and is directly proportional to the acoustic power and indirectly proportional to the speed of the wave in the medium. The radiation force by a plane wave on a reflecting surface is twice that on an absorbing surface.
Deration	Derating factor is applied for tissues to account for attenuation, as the initial measurements of ultrasound power and intensities of transducers are done in water. The derating factor is the attenuation coefficient of soft tissues which is assumed to be 0.3 dB/cm – 1/MHz – 1.
Pulse duration	The time taken by an ultrasound pulse and is expressed in ms.

abnormalities. Transient (43.5 s) ultrasound exposure (35 W/cm²) caused transient conduction blockade in the ventral abdominal ganglia of crayfish. Brief exposure to an ultrasound beam of similar intensity produced complete paralysis with destruction of neurons in the lumbar enlargement of intact frogs.⁹ These data emphasized that ultrasound produces important thermal effects that are capable of interfering with nerve conduction similar to the actions of heat alone.¹⁰

These and other potential adverse biologic effects of ultrasound in experimental animals were formally recognized in 1983 by the American Institute of Ultrasound in Medicine and the National Electrical Manufacturers Association in the Safety Standard for Diagnostic Ultrasound Equip-

ment.¹¹ This report suggested that manufacturers of ultrasound equipment provide detailed information about parameters including power, spatial-peak temporal-average intensity (I_{SPTA}), and spatial-peak pulse-average intensity (I_{SPPA}), which were identified as important determinants of adverse biologic effects in animal experiments (table 1). The initial American Institute of Ultrasound in Medicine/National Electrical Manufacturers Association recommendations and the subsequent American Institute of Ultrasound in Medicine Acoustic Output Measurement and Labeling Standard for Diagnostic Ultrasound Equipment were developed with a recognition of these biologic effects and included ultrasound intensities (thought to be responsible for temperature increase) and waveform-related pressures (thought to

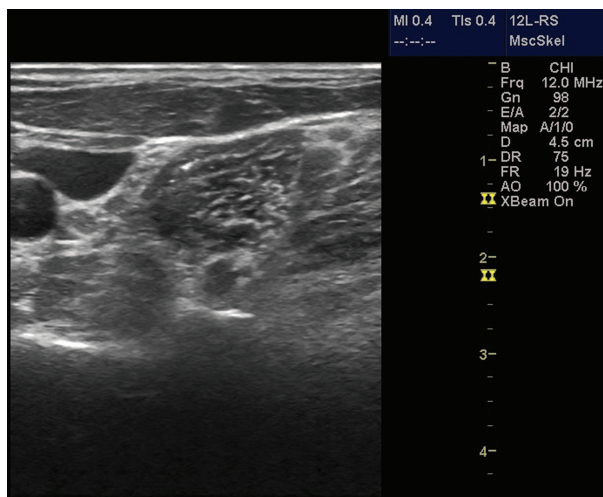


Fig. 1. Ultrasound image displaying the mechanical and thermal indices as MI and TIs, respectively. In this image the indices are displayed at the top right corner. The location may vary depending on the manufacturer.

be responsible for mechanical effects).¹² An expert National Institutes of Health panel convened in 1984 reviewed the relative risks of diagnostic ultrasound exposure from a clinical perspective. This panel concluded that ultrasound was most likely safe to perform during pregnancy but also recommended continued vigilance. The National Council for Radiation Protection established exposure criteria for the safe use of diagnostic ultrasound for the industry and research and education in the same year.¹³ In 1993, the Food and Drug Administration published regulations limiting ultrasound intensity for specific applications,¹⁴ but these recommendations were criticized because they established upper limits of ultrasound exposure.¹² Notably, the Food and Drug Administration regulations did not focus on safety and limited the development of higher intensity ultrasound devices with which potentially improved image resolution characteristics may have been obtained.¹⁵ The Standard for Real Time Display of Thermal and Mechanical Indices on Diagnostic Ultrasound Equipment, commonly referred to as the Output Display Standard, was developed in 1992¹⁶ (fig. 1). The incorporation of the output displays into ultrasound equipment shifted the responsibility for prudent use of diagnostic ultrasound from the manufacturer to the user, and in response, the Food and Drug Administration relaxed the previous restrictions on upper limits of ultrasound output.¹⁷

Ultrasound equipment manufactured before 1978 demonstrated a wide variation in ultrasonic power and intensity.¹⁸ In general, ultrasound intensity was greater in equipment manufactured after 1980 than before that year,¹⁹ and this increase in intensity was directly correlated with more pronounced temperature rise during use of the device.¹² A comparison of ultrasound output of equipment manufactured between 1995–1999 confirmed this previously identified increase in ultrasound intensities.²⁰ It appears highly likely that this trend of greater ultrasound intensity will con-

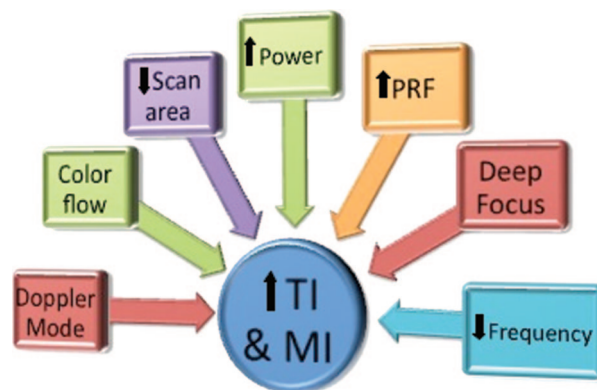


Fig. 2. Parameters affecting thermal and mechanical indices (TI and MI). PRF = pulse repetition frequency.

tinue, and the clinician may therefore be confronted with potential adverse effects when using newer generation ultrasound equipment. The Output Display Standard currently is the only information required by the Food and Drug Administration to alert the clinical user of the potential of an ultrasound device to produce tissue injury. The Output Display Standard purposefully overestimates such possible adverse biologic effects by assuming a reasonable “worst case” scenario. The Output Display Standard assumes linear propagation of ultrasound within a uniform, modestly attenuating tissue and describes “thermal and mechanical” indices. Acoustic power is the primary determinant of thermal and mechanical indices, but the ultrasound mode, color Doppler blood flow imaging, area of interest, transmission frequency, pulse repetition frequency, and focal zone also affect thermal and mechanical indices²¹ (fig. 2).

Thermal Effects

Heat produces a wide variety of tissue injury including necrosis and apoptosis, abnormal cell migration, altered gene expression, and membrane dysfunction. Thermal exposure has been shown to produce adverse changes in myelination and cell damage in neuronal tissue.²² Ultrasound increases temperature in the focal area of the beam and therefore has the potential to cause thermal changes in tissue.

Biologic Consequences of Thermal Effects

As much as 70% of the total temperature increase associated with ultrasound occurs within the first minute of exposure,²³ but temperature does continue to rise as exposure time is prolonged.^{24,25} A linear relationship between ultrasound intensities and temperature rise has been demonstrated.^{24,26} The relative protein content of each tissue is also an important determinant of ultrasound absorption, and hence, temperature rise. Absorption coefficients of tissues are directly related to protein content, thereby providing a surrogate marker for potential increase in tissue temperature. Absorption coefficients vary between 1 (skin, tendon, spinal cord) and 10 (bone) dB/cm MHz (table 2). The greatest temperature

Table 2. Attenuation Coefficient and Acoustic Impedance of Various Tissues

Tissue/Medium	Attenuation Coefficient (dB/cm/MHz)	Acoustic Impedance (Mrayl)
Water	0.0022	1.5
Blood	0.15	1.6
Soft tissue	0.75	1.6
Air	7.50	0.00001
Bone	15.0	8.0
Fat	0.63	1.4
Kidney	1.0	1.6
Lens of eye	0.05	1.7

increase resulting from ultrasound exposure occurs in bone because of its high absorption coefficient.²⁷ Indeed, a consistent tissue temperature rise in response to ultrasound exposure has been repeatedly demonstrated *in vitro*, *in vivo*, and *in utero*.^{24,26–28} Not surprisingly, temperature also increases in tissues adjacent to bone.^{23–25,28} The absorption coefficients of fetal bone are dependent on age-related changes in mineralization, density, and heat capacity, which correlate with a faster rate of temperature increase concomitant with fetal maturity.^{24,25,29} Whereas ultrasound intensity and exposure duration cause direct increases in tissue temperature, a wider beam width reduces the rate and extent of temperature rise by permitting the energy to be distributed over a larger perfusion territory.²⁸ The relative clinical significance of ultrasound-induced thermal effects may not be readily apparent unless the exposed tissue mediates a critical physiologic function or the volume of tissue is large. Ultrasound-induced temperature increases may be specifically pronounced in the absence of or during a decrease in perfusion.^{25,30} Thus, biologic tissues including the lens, cornea, tendon, and adipose tissue may be particularly susceptible to the thermal effects of ultrasound.

Determinants of Thermal Effects

Ultrasound frequency, focusing, pulse duration, exposure time, and absorption coefficient are the primary determinants of temperature increase during ultrasound exposure (table 3). Such an increase in temperature occurs if the rate of ultrasound-induced heat production exceeds dissipation of heat through tissue perfusion. Assuming that no heat is lost,

Table 3. Causes for Tissue Temperature Changes by Ultrasound

Ultrasound Parameters	Tissue Characteristics
Frequency	Attenuation
Focusing	Absorption coefficient
Pulse repetition frequency	Acoustic impedance
Pulse duration	Thermal conductivity
Transducer self-heating	Tissue perfusion
Exposure time	Nonlinear propagation
Intensity	Density
Beam width	Protein content

the maximum temperature rise is directly related to the rate of heat production per unit volume and the duration of exposure. The rate of heat production in an ultrasound field of intensity, I , is equal to $2\alpha I$, where α is the absorption coefficient. If scattering of the ultrasound beam does not occur, this absorption coefficient is essentially equal to the attenuation coefficient in a given type of tissue. Temperature rise may be underestimated if the ultrasound beam encounters fluid along its path because nonlinear propagation may occur, but the contribution of nonlinear propagation to the thermal indices is usually negligible at decreased ultrasound intensities. Nonlinear propagation through water and biologic tissues are quite different. Linear propagation predominates in highly absorbing tissues such as bone. Ultrasound has a higher intensity when it is focused; conversely, intensity decreases when ultrasound energy is distributed over a larger area (unfocused). With higher ultrasound amplitudes, nonlinear propagation also becomes a factor because of the development of harmonic frequencies to the fundamental. Nonlinear propagation is especially important when ultrasound is used to interrogate large distances at longer focal lengths. Under these circumstances, intensity becomes the acoustic energy per cycle per unit area per pulse period, which is “equivalent to the pulse average intensity for a long pulse.”³¹ The ultrasound intensity and pressures are typically measured in water in a laboratory setting, and as a result may need to be adjusted when applied in a clinical context by correcting for attenuation in tissues or derating the underwater measurements and extrapolating the calculations for higher outputs.³¹

Minimizing the exposure time is probably the single most important factor for ensuring patient safety from thermal injury.²¹ In a homogenous perfused tissue where the contribution of perfusion is relatively small (*e.g.*, bone), instantaneous temperature rise (ΔT) may be estimated using the equation $\Delta T = W/4 d_6$, where W is the total acoustic power (mW) and d_6 is the beam diameter (mm). The magnitude of temperature increase is time dependent, and is more pronounced when the ultrasound beam is directed at tissue with high absorption (bone and cranium). Depending on the intensity, it takes a particular time period of exposure before the tissue temperature increases. This time to detectable “threshold” temperature rise, which is the time required for the tissue to reach a particular temperature after the tissue has been exposed to ultrasound waves, may permit the use of higher intensity ultrasound for shorter exposure times. Similarly, the “safe use time model” determines the safe exposure time for tissues and displays the duration of exposure to a particular tissue based on machine presets.^{32,33}

Measurement of Thermal Effects

The thermal index is defined as the ratio of the total system power to the power required to cause a 1°C increase in temperature (thermal index = W^0/W^{DEG} , where W^0 is the power of the machine and W^{DEG} is the power required to

increase the tissue temperature by 1°C). Thermal indices are conservatively determined to ensure patient safety. Under most clinical conditions, the thermal index closely approximates or overestimates the maximum temperature increase for ultrasound exposure. Three different thermal indices (depending on the structures encountered in the path of the ultrasound beam, soft tissue or TIs, bone or TIb, and cranium or TIc) are used to estimate temperature increases associated with an ultrasound beam. In fact, thermal indices in soft tissue or bone provide fairly accurate *in vivo* estimates of ultrasound-related temperature rise in the tissue types.¹² Thermal indices assume a homogenous ultrasound path and a constant attenuation coefficient ($0.3 \text{ dB/cm}^{-1}/\text{MHz}^{-1}$). Contemporary ultrasound equipment has the theoretic capability to cause a tissue temperature increase greater than 4°C at the focal point.³⁴ “Worst case” temperature elevations of 8.7°C have been estimated using data provided by device manufacturers and calculating the temperature rise using the National Council for Radiation Protection formula, assuming a third-trimester abdominal ultrasound exposure in the Doppler mode for a duration of 120 s.³⁵ A bone thermal index of 10 (corresponding to a temperature rise of 10°C) was reported by one manufacturer.¹² When the maximum possible intensity of diagnostic ultrasound corrected for attenuation in tissue was computed with acoustic output data provided by the manufacturers, thermal indices that were greater than Food and Drug Administration-approved limits were obtained (table 4). For example, the maximum soft-tissue thermal indices of 2.2 and 2.3 were calculated using pulse wave or color Doppler ultrasound applications, respectively. Similarly, a maximum bone thermal index of 2.8 was estimated during B-mode and pulsed wave Doppler ultra-

sound.³⁶ These data suggested that diagnostic ultrasound equipment may be associated with a potential maximal temperature rise of 2.2–2.8°C. Local tissue heating resulting directly from the transducer itself may also occur,³⁷ and may cause a temperature increase exceeding 20°C.³⁸ This form of temperature increase with the potential for local thermal injury may not be noted if a thermocouple is used to measure the temperature rise at the ultrasound beam focal point because the metallic thermocouple may conduct at least some of the heat away from the area.³⁹

Mechanical Effects of Ultrasound

Ultrasound energy creates mechanical forces independent of thermal effects, thereby causing biologic effects that are not related to temperature rise alone (termed nonthermal). The mechanical effects result in shear forces, pressure changes, and release of various reactive molecules.

Biologic Consequences of Mechanical Effects

Gas-containing structures (*e.g.*, lungs, intestines) are most susceptible to the effects of acoustic cavitation. Mechanical effects of ultrasound also occur in tissues near bone. Petechial hemorrhages developed on the mucosal surface of the intestines after ultrasound exposure at or above typical diagnostic frequencies.^{40,41} Ultrasound exposure has increased small intestinal cell apoptosis through a cavitation mechanism.⁴² A combination of thermal and nonthermal effects are purported to be responsible for hemorrhage adjacent to bone.^{43,44} The degree of hemorrhage increased linearly with acoustic intensity, pulse repetition frequency, and transducer frequency in neonatal rats.⁴⁴

Determinants of Mechanical Effects

The interaction of ultrasound with gas bubbles or contrast agents causes rapid and potentially large changes in bubble size. This process, termed cavitation, may increase temperature and pressure within the bubble and thereby cause mechanical stress on surrounding tissues, precipitate fluid microjet formation, and generate free radicals.⁴⁵ Ultrasound wavelength has an important role in bubble formation and growth: short wavelength ultrasound (observed at higher frequencies) does not provide sufficient time for significant bubble growth; therefore, cavitation is less likely under these circumstances compared with long wavelengths. Acoustic cavitation is usually defined as inertial or noninertial. The inertia of inrushing surrounding fluid after the rapid contraction or collapse of a gas bubble causes inertial cavitation, which may be symmetrical or asymmetrical. Symmetric inertial cavitation may cause mechanical injury by producing local temperatures approaching 1,000°C, thereby causing profound internal thermal damage or facilitating the formation of highly reactive chemical intermediates. In contrast, asymmetric inertial cavitation generates high-velocity jets of liquid that affect solid tissues and cause direct mechanical damage. Noninertial cavitation results from repetitive bub-

Table 4. Factors Increasing Ultrasound Output

Parameter	Method of Increasing Output
Output power setting	Increased output power leads to an increase in peak pressure and energy
Deep transmission focus	Increases negative pressures and heating, secondary to increase in power
Color flow mapping and spectral Doppler imaging	High I_{SPTA} and power with a narrow and deep box
Spectral Doppler mode	Increase in Doppler frequency scale and pulse repetition frequency lead to increase in power and I_{SPTA}
M mode and spectral Doppler imaging	Larger negative pressures and I_{SPTA} are produced when the focus is close
Write zoom box	When narrow and deep, leads to a high pulse repetition frequency and negative pressure

I_{SPTA} = spatial peak, temporal average intensity.

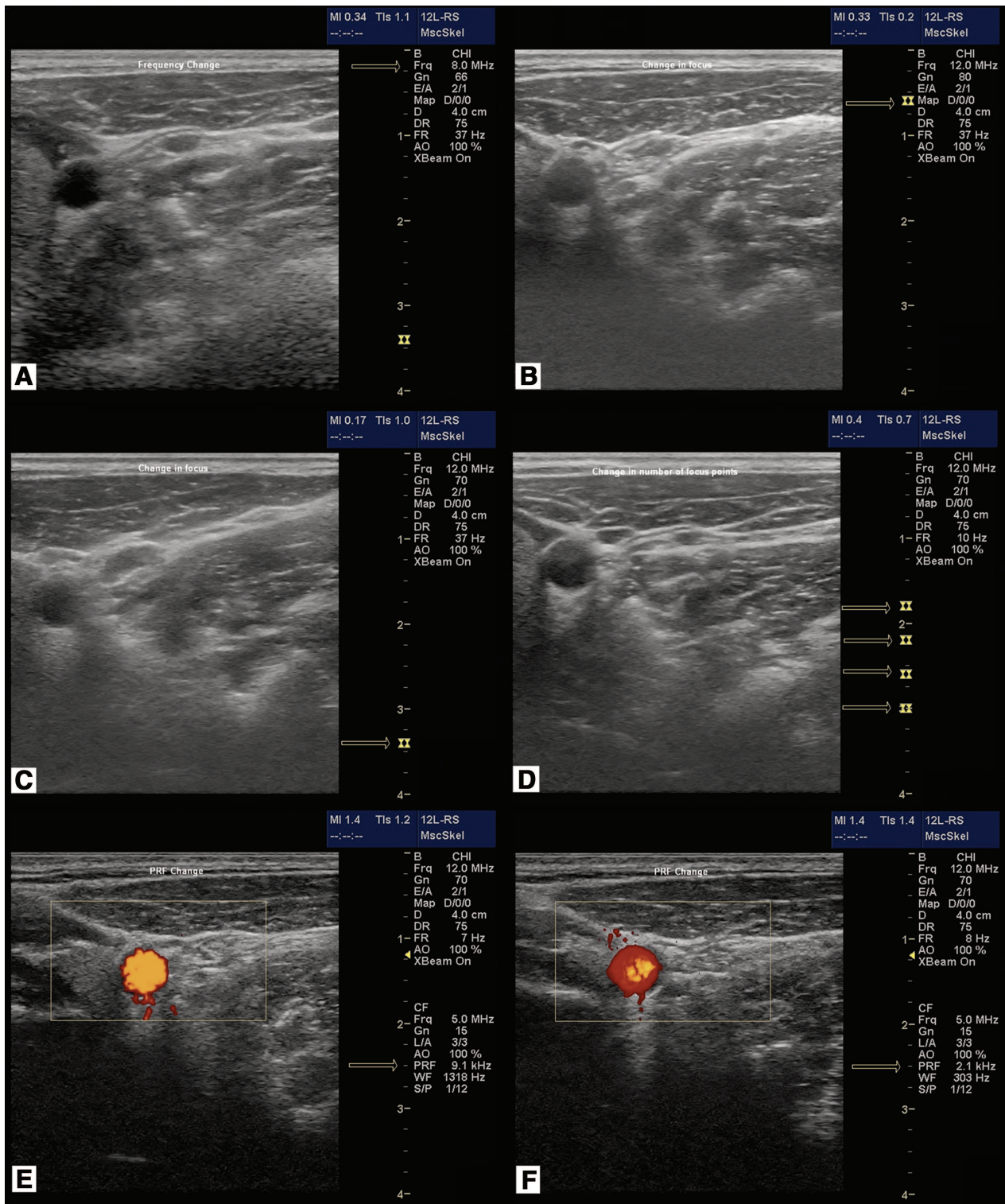


Fig. 3. Similar ultrasound images with a linear transducer showing alterations in thermal and mechanical indices with changes in various parameters. (A) The arrow pointing to the frequency and the appropriate indices is displayed at the upper right corner. (B and C) Change in the value of the indices can be noted when the focus point is moved to a deeper location. The arrow points to the location of the focus point. (D) Increasing the number of focus points increases the value of the indices. The arrows point to the focus points. (E and F) Decreasing the pulse repetition frequency from 9.1—2.1 kHz increases the thermal index.

ble oscillation. This action also causes microstreaming and may be associated with moderate bubble cavity growth that does not exceed twice the original bubble equilibrium radius. The short half-life of cavitation nuclei prevents most cavitation-related biologic effects unless ultrasound contrast agents are also present. Contrast agents markedly reduce the threshold intensity for cavitation and, to a lesser extent, also decrease the threshold pressure amplitude.

Measurement of Mechanical Effects

The mechanical index describes the relationship between cavitation formation and acoustic pressure and is defined as the ratio of the peak rarefactional negative pressure adjusted for tissue attenuation and square root of the frequency (mechanical index = $P_{r,3}/\sqrt{f}$).⁴⁵ The mechanical index was originally formulated based on the threshold for acoustic cavitation in water and blood, and hence may not specifically consider the type of tissue in which this process occurs.^{46–48}

Safety Standard

The Food and Drug Administration mandated standards for ultrasound output exposure levels based on compliance with Output Display Standard (fig. 3). The Food and Drug Administration's track 1 describes recommended acoustic outputs (in mW/cm²) for devices in which output indices are not specifically displayed. In contrast, the Food and Drug Administration's track 3 raised the upper limits of ultrasound exposure for equipment in which acoustic output and the thermal and mechanical indices are available to facilitate monitoring¹⁷ (table 5). Manufacturers are also required to provide detailed information to the Food and Drug Administration about the spatial-peak temporal-average intensity, spatial-peak pulse-average intensity, the frequency range, and the focal length of each new ultrasound transducer before the equipment can be marketed. Notably, many ultrasound users remain unaware of the significance of Output

Table 5. FDA Recommendations on Acoustic Output Exposure Levels

Use —	$I_{SPTA,3}$ (mW/cm ²)		$I_{SPPA,3}$ (W/cm ²)	MI
	Track 1	Track 3	Tracks 1 and 3	
Peripheral vessel	720	720	190	1.9
Cardiac	430	720	190	1.9
Fetal imaging and other	94	720	190	1.9
Ophthalmic	17	50 and $TI \leq 1$	28	0.23

The limits vary depending on the on-screen display of the indices. Track 1 limits are used when there is no display of indices. Track 3 limits are used when there is a visual display of indices. FDA = Food and Drug Administration; $I_{SPPA,3}$ = derated spatial-peak, pulse-average intensity; $I_{SPTA,3}$ = derated spatial-peak, temporal-average intensity; MI = mechanical index; TI = thermal index.

Display Standard despite its important clinical ramifications. For example, a European survey of clinicians, sonographers, and midwives revealed that fewer than one-third were able to define thermal or mechanical index, and only one-fourth knew how to adjust the acoustic output levels of an ultrasound device.⁴⁹ Similarly, 79% of ultrasound users in the United States were unable to identify the display location of thermal or mechanical indices in the equipment that they use on a regular basis.⁵⁰

Limitations of Safety Standard

Many ultrasound device manufacturers compute acoustic output characteristics based on computer modeling and not actual measurement in tissue. Quality control measurements seldom identify significant variations between model predictions and measured output values, but predictions of acoustic output most often exceed measured values, thereby providing an additional margin of safety.⁵¹ Nevertheless, acoustic output predictions may not be directly correlated with changes in tissue temperature under all clinical conditions because of tissue characteristics and their specific response to ultrasound energy. Estimations of changes in tissue temperature based on National Council for Radiation Protection and American Institute of Ultrasound in Medicine/National Electrical Manufacturers Association recommendations for Output Display Standard may differ from the actual temperature measurements because calculations use acoustic power and not intensity; absorption and attenuation coefficients are determined assuming the presence of a continuous fluid column in the ultrasound beam; and the beam focus is assumed to be the site of maximal temperature rise.⁵² These assumptions may not entirely reflect clinical reality. Underestimates of temperature rise may also occur with heating of the transducer itself or as a consequence of nonlinear propagation (table 6). In addition, differences in calculated acoustic output and subsequent temperature rise may be observed using National Council for Radiation Protection compared with American Institute of Ultrasound in Medicine/National Electrical Manufacturers Association estimates; temperature rises predicted based on National Council for Radiation Protection calculations were 15% greater and those based on American Institute of Ultrasound in Medicine/National Electrical Manufacturers Association estimates were 30%

Table 6. Causes for Underestimation between Calculated (Based on Indices) and Actual Pressure and Temperature in Tissues

Use of acoustic power and not intensity
Significant transducer heating
Using absorption and attenuation coefficients assuming there is fluid in the path
Long fluid path
Temperature calculated at the focus of the beam may not be the actual area of greatest temperature rise
High amplitude pulses
Significant nonlinear propagation component

less than the actual measured temperatures.⁵² In general, Output Display Standard underestimates the *in situ* temperature changes by approximately 8%.⁴⁸

Limitations of the mechanical index in Output Display Standard also occur and include field alterations in different tissues that may fail to correlate with displayed values; underestimation of pressures at higher acoustic output levels or in the presence of poorly attenuating medium; failure to display pressures when examining the lung; and failure to account for the role of positive pressures on lung hemorrhage.^{45,47}

It is important to note that current Food and Drug Administration guidelines do not account for exposure duration, which may be of considerable importance during training because the time required to acquire diagnostic information is longer. To overcome this potential problem, a graphic display of the exposure time and acoustic outputs have been proposed to facilitate trainees' awareness of this issue.²¹

Current Recommendations

It is clear that modern ultrasound devices may produce acoustic outputs that are capable of causing biologic effects in experimental animals.^{47,53–55} Several national and international organizations have published guidelines and consensus reports that highlight the need for concern about such biologic actions, encourage prudence in the use of diagnostic ultrasound, and recommend safety education. Detailed recommendations regarding exposure times at various ranges of index values are available from the British Medical Ultrasound Society.[‡]

The American Institute of Ultrasound in Medicine concluded that there are no significant effects of ultrasound unless exposure duration is prolonged. Most of these recommendations currently involve obstetric imaging and fetal safety. The American Institute of Ultrasound in Medicine 2008 consensus report[§] noted that a transient increase in temperature of 18°C for a 0.1-s exposure was required to damage nonfetal tissue, but prolonged (≤ 50 h) temperature increases $\leq 2^\circ\text{C}$ did not produce injury. The duration of ultrasound exposure appears to be important when the adverse effects of moderate increases in temperatures (2–6°C) are considered. Notably, specific episodes of ultrasound-in-

duced thermal damage have yet to be reported in humans.⁵⁴ For example, the incidence of fetal malformations has remained constant despite the widespread use of obstetrical ultrasound. The British Medical Ultrasound Society,^{||} European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB),[#] Australian Society for Ultrasound in Medicine (ASUM),^{**} and World Federation of Ultrasound in Medicine and Biology (WFUMB)^{††} recommend limiting the ultrasound acoustic power and exposure duration during two-dimensional imaging.⁵³

The World Federation of Ultrasound in Medicine and Biology and the European Federation of Societies for Ultrasound in Medicine and Biology further recommend limiting the ultrasound exposure duration during Doppler mode sonography (fig. 4). The World Federation of Ultrasound in Medicine and Biology also suggests caution during imaging of febrile patients, as increase in body temperature may theoretically potentiate the ultrasound-induced thermal injury.⁵³ The American Institute of Ultrasound in Medicine recommends following the ALARA (as low as reasonably achievable) principle if the mechanical index is more than 0.4 when gas-containing bodies are exposed to ultrasound,⁵⁶ but there is virtually no possibility of mechanical biologic effects if gas-containing structures are not encountered. Because of the greater potential for tissue temperature increase when encountering bone, the exposure time is determined by the thermal indices specific to bone and cranium according to the British Medical Ultrasound Society recommendations[‡] of 2009 on exposure time during the use of ultrasound imaging. Ultrasound imaging is not recommended when the displayed thermal index bone (TIb) or thermal index cranium (TIc) are more than 6 and 3, respectively. (table 7) Whenever bone is encountered less than 1 cm from the skin, thermal index cranium (TIc) should be used. The British Medical Ultrasound Society also cautions about the potential for cavitation at mechanical indices more than 0.7 when using microbubble contrast agents.

Known Biologic Effects

Cellular Effects of Ultrasound

Thrombus formation after ultrasound-induced endothelial damage was one of the earliest demonstrations of its biologic effects.⁵⁷ Ultrasound facilitated an influx of calcium ions in fibroblasts,⁵⁸ and this action may have resulted from a mechanical effect on ion channels.^{59,60} Acoustic microstreaming was the postulated mechanism by which ultrasound caused efflux of intracellular potassium ions.⁶¹ Cell necrosis was shown to increase when nonlethal hypotonicity (146 mOsm) was combined with low-intensity ultrasound (0.5 W/cm^2).⁶²

Ultrasound (20 MHz) was also shown to inactivate several enzymes and causes free radical production, both of which may initiate cellular injury.⁶³ Alterations in antioxidant enzyme concentrations may either protect against or further exacerbate ultrasound-induced free radical damage. For example, ultrasound exposure in the Doppler mode (3

‡ The British Medical Ultrasound Society [http://www.bmus.org/policies-guides/pg-safety03.asp]. Accessed April 24, 2011.

§ The American Institute of Ultrasound in Medicine [http://www.aium.org/publications/statements.aspx]. Accessed April 24, 2011.

|| British Medical Ultrasound Society [http://www.bmus.org/policies-guides/pg-safetystatements.asp]. Accessed April 24, 2011.

European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) [http://www.efsumb.org/guidelines/2008safstat.pdf]. Accessed April 24, 2011.

** Australian Society for Ultrasound in Medicine (ASUM) [http://www.asum.com.au/site/policies.php]. Accessed April 24, 2011.

†† World Federation of Ultrasound in Medicine and Biology (WFUMB) [http://www.wfumb.org/about/statements.aspx]. Accessed April 24, 2011.

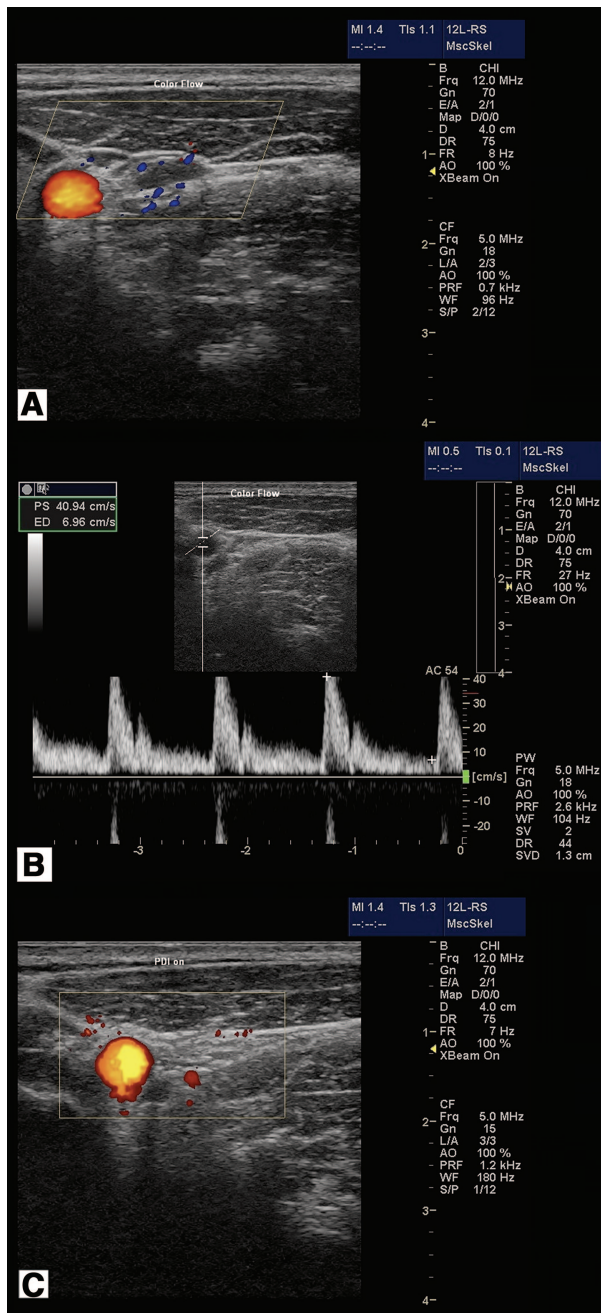


Fig. 4. Ultrasound images with different Doppler features showing alterations in the thermal and mechanical indices. (A) Color flow Doppler image increasing indices. (B) Pulsed wave Doppler image decreasing indices. (C) Power Doppler image increasing indices.

MHz) may increase antioxidant enzyme activities in the rat fetal liver and brain. Conversely, antioxidant enzyme activity decreased in the fetal brain tissue due to its higher lipid concentration after B-mode ultrasound exposure (4 MHz).⁶⁴ Interestingly, these paradoxical results were achieved with outputs within Food and Drug Administration limits. Heat-shock proteins are constitutively expressed in neural cells, prevent or correct polypeptide folding, and may protect neurons against injury.⁶⁵ A rapid temperature rise associated

Table 7. Recommended Exposure Times for Nonobstetric and Nonfetal Ultrasound Imaging at Various Thermal Indices in Bone and Cranium

Maximum Exposure Time	TI _B	TI _C
5 s	5.0–6.0	Not recommended
15 s	4.0–5.0	Not recommended
1 min	3.0–4.0	2.5–3.0
4 min	2.5–3.0	2.0–2.5
15 min	2.0–2.5	1.5–2.0
30 min	—	1.0–1.5
60 min	1.5–2.0	0.7–1.0
120 min	1.0–1.5	—

Adapted with permission from the 2009 recommendations provided by the British Medical Ultrasound society at their Web site: <http://www.bmus.org/policies-guides/pg-safety03.asp>. Accessed April 24, 2010.

TI_B = thermal index bone; TI_C = thermal index cranium.

with ultrasound exposure (30 min at 1.2 W/cm²) increases heat-shock protein production,⁶⁶ and may therefore produce a neuroprotective effect. When combined with systemic hyperthermia, ultrasound-induced temperature increases may contribute to the development of congenital malformations in experimental animals,⁶⁶ but such effects do not occur in the fetus when temperatures remain less than 39°C after ultrasound exposure.⁵² Ultrasound may also affect cell regeneration. Repetitive ultrasound exposure reduced leukocyte production in monkeys *in utero*.⁶⁷ Similarly, a decrease in somite numbers was noted when embryo cultures were exposed to ultrasound for 15 min at 40°C.⁶⁶ Synaptic vesicles clumped when exposed to ultrasound (300 W/cm²) for 0.5–3 s.⁶⁸ A nonthermal mechanism of injury was proposed to be responsible for these effects.

Genetic Effects of Ultrasound

A small increase of sister chromatid in Chinese hamster ovary cells when exposed to high-intensity ultrasound exchanges was observed, but these observations could not be verified in another study.⁶⁹ Mutations in various cell lines have been reported after ultrasound exposure, presumably because of increased free radicals production and their action on nuclear material.⁷⁰ Low-frequency ultrasound may cause free radicals formation by inertial cavitation that may contribute to nonspecific DNA degradation through double-strand helical fractures.⁶³ Ultrasound-induced free radical production is reduced in the presence of carbon dioxide and may offer protection against such genetic damage.⁶²

Previous demonstrations of aberrations within human chromosomes *in vitro* were observed with ultrasound exposure for 1–2 h, but subsequent experiments including repeated exposures at higher ultrasound intensities failed to replicate these data.^{71–73} Additional experiments examining the effect of ultrasound on the frequency of sister chromatid exchanges in human and mammalian cell lines have not been uniformly supportive.^{74–80} A collaborative investigation be-

tween laboratories led to a standardized technique using an ultrasound intensity of 35 W/cm² for 4 min.⁸¹

It remains unclear whether ultrasound contributes directly to genetic aberrations. Chromosomal aberrations, enhanced sister chromatid exchange, and other mutations has been investigated extensively as possible consequences of ultrasound exposure, but whether these actions lead to meaningful physiologic consequences is controversial.

Fetal Effects of Ultrasound

Ultrasound exposure was initially thought to cause neurobehavioral responses indicative of transient neurologic injury, but subsequent work has not supported this hypothesis.⁸² Developmental delay occurred in reflex responses of rats whose mothers had received ultrasound (20 W/cm²).⁸³ Rats exposed to ultrasound also showed a substantially different vocalization compared with normal rats,⁸⁴ but immobilization stress may have been a contributing factor for this difference in response that could not be completely excluded from the analysis.⁸² Prenatal ultrasound exposure did not cause gross developmental abnormalities in monkeys with the exception of an increase in muscle tone.⁸⁵ Similarly, reflex activity and behavior in offspring of rats continuously exposed to high-intensity (20–30 W/cm²) ultrasound were normal except for a small increase in aggregate of errors of commission in the Cincinnati water maze (a neuropsychiatric test for learning behavior).⁸⁶ Alterations in adult negative geotaxis and reflex suspension were also observed with exposure to ultrasound.⁸⁷ Despite these collective findings, another study found no statistically significant alterations in postnatal behavior or delays in acquisition of reflexes after prenatal ultrasound exposure (less than 1,500 W/cm²).⁸²

There is limited information available about the biologic effects of ultrasound in humans, and most of the studies or published data to date pertain to fetal exposure or therapeutic ultrasound. The relative safety of ultrasound has been well established based on its use in the obstetric population over several decades. Nevertheless, national and international advisory groups continue to urge caution with the use of ultrasound, especially the Doppler mode. A retrospective matched cohort study of 1,907 children whose mothers had undergone Ultrasound-guided amniocentesis was studied, at birth and at 1-yr follow-up. Children exposed to ultrasound *in utero* had abnormal grasp and tonic neck reflexes compared with those who were not, but no other differences in motor, sensory, or other reflex responses were observed between groups. Notably, ultrasound exposure occurred during late gestation in this study and may likely not reflect direct teratogenic effects as a result.⁸⁸ Stark *et al.* retrospectively reviewed and compared the pregnancy and delivery records of children with and without *in utero* ultrasound exposure over a 4-yr period.⁸⁹ The authors reported that the incidence of dyslexia was modestly increased in children exposed to *in utero* ultrasound. However, two subsequent studies failed to confirm these findings.^{90–92} Similarly, an initial

report of speech delays in children exposed to ultrasound *in utero* were not verified in later studies.^{93,94} Multiple ultrasound exposure *in utero* was associated with a small increase in the incidence of low birth weight compared with a single exposure, but this difference was not statistically significant, and was eliminated as the children developed.⁹⁵ The authors subsequently followed the growth, development, and behavior of the children for another 8 yr. They reported a delay in language and speech development at 1 yr in ultrasound-exposed children, but no other significant differences were observed between groups. This finding was most likely related to parenting and not to ultrasound exposure *per se* because the difference was not observed during later development.⁹⁶ The results of these epidemiologic studies clearly requires qualification because ultrasound devices available then had lesser acoustic output. The studies were also performed before Output Display Standard was established. Nevertheless, the American Institute of Ultrasound in Medicine consensus report concluded that there was insufficient evidence of a direct causal link between ultrasound exposures *in utero* and subsequent biologic consequences in neonates and children.⁵⁴

Neural Effects of Ultrasound

Neurons are sensitive to the adverse effects of ultrasound. Cerebral tissue has a relatively low absorption coefficient, but the temperature of the cranium increases during ultrasound exposure and raises the temperature of the adjacent brain through a conduction mechanism.⁹⁷ This phenomenon is particularly important in the fetus when using a Doppler ultrasound mode, which is a stationary mode with the potential for producing the greatest temperature increases in bone. In addition to these indirect thermal effects, ultrasound also causes direct neural effects. For example, high-intensity focused ultrasound was previously used to produce destructive lesions in the brain. Fry *et al.* demonstrated that focused ultrasound was capable of causing reversible suppression of neural transmission.⁹⁸ Direct exposure of the brain to high-intensity (150–1,500 W/cm²) ultrasound was also shown to produce thermal and cavitation effects as indicated by neural apoptosis.^{99,100} Ultrasound exposure to the lumbar plexus causes hind limb paralysis in experimental animals.¹⁰¹ Hind limb paralysis was observed at room temperature after a 4.3-s ultrasound exposure (35 W/cm²) to the lumbar area, but more prolonged exposure duration (7.3 s) was required to produce similar neurologic damage at cooler temperatures (1–2°C).¹⁰¹ Histologic analysis revealed neuronal and myelin destruction in the spinal cord, and axonal degeneration, chromatolysis, pyknosis with intact mesenchymal structures, and clumping of myelin in the peripheral nerves and cauda equina.¹⁰² These data indicated that ultrasound-induced neural injury was temperature dependent. An increase in the peak rarefactional pressures or the pulse repetition frequency also worsens these adverse effects.^{103,104} The rapid onset of spinal cord injury suggested that cavitation was the most

likely mechanism because thermal damage requires adequate time for temperature rise and most often occurs at an ultrasound focal point at which maximum temperature increase is known to occur.^{99,103,105} Nevertheless, there is some experimental evidence suggesting that myelin is especially sensitive to ultrasound. Such effects impair neural conduction through disruption of contact processes, periaxonal enlargement, and direct alterations in myelination.¹⁰⁶ Studies examining the effects of ultrasound on myelin and nerve conduction velocity in conscious animals may be difficult to interpret because animal restraint also changes myelin formation.¹⁰⁷ Reversible changes in conduction velocity and compound action potential have been reported during the use of ultrasound. Smaller unmyelinated fibers are most susceptible to these effects. The compound action potential decreases with repeated pulses of ultrasound.^{108,109} A direct relationship between acoustic intensities and conduction velocity has also been demonstrated *in vitro*. Sodium and potassium channels open with increases in temperature during ultrasound exposure, thereby affecting conduction velocity. An increase in ultrasound intensity (2–3 W) inactivates stretch-sensitive channels and decreases the compound action potential. Mechanical effects (*e.g.*, radiation pressure) may also play a role in ultrasound-induced changes in ion channel function through stretch-sensitive channels.^{110–112} Highly focused ultrasound decreased presynaptic activity and increased dendritic field potentials in hippocampal slices.¹¹³ Auditory evoked potentials were also transiently suppressed after ultrasound exposure in the diagnostic range.¹¹⁴ In contrast to these studies suggesting that high-intensity ultrasound may cause neural dysfunction, exposure to lower intensity may cause beneficial effects. Rat tibial nerves exposed to therapeutic ultrasound intensities between 0.5 and 1 W/cm² demonstrated more rapid recovery of nerve conduction velocity and compound action potential after a crush injury¹¹⁵ concomitant with functional improvement.^{116,117} Injured nerves exposed to therapeutic ultrasound also showed histologic evidence of regeneration including increased nerve fiber density, prominent Schwann cell nuclei, and previous myelin formation compared with nerves that had not been exposed to ultrasound.¹¹⁸

Therapeutic ultrasound increases tissue temperature in an intensity-dependent fashion and may cause an increase in nerve conduction velocity.^{119,120} Therapeutic ultrasound over the ulnar nerve up to an ultrasound intensity of 1.9 W/cm² caused a decrease in temperature and nerve conduction velocity. When the ultrasound intensity exceeded 1.9 W/cm², an increase in temperature and conduction velocity was noted. An additional increase was noted with decrease in the area of ultrasound exposure.¹²¹ The ultrasound-induced effects on nerve conduction seems to follow a bimodal distribution with a nadir in conduction velocity between intensities 1–2 W/cm², and increases in conduction velocity above and below this intensity range (*i.e.*, ≤ 0.5 W/cm² and ≥ 3 W/cm²).¹²² The decreases in conduction velocity secondary

to ultrasound exposure has been explained as being similar to a micromassage action.¹²³ Using a Biothesiometer (Biomedical Instrument Company, Newbury, Ohio) to measure vibration threshold, a temporary increase in vibration threshold was noted after the application of therapeutic ultrasound (1.25–1.5 W) over the ulnar nerve of healthy volunteers.¹²⁴ A previous study had shown an increase in pain threshold with the application of ultrasound over the ulnar nerve.¹²⁵ Ultrasound-induced biologic consequences have not been reported in patients during use for regional anesthesia. The lack of effects in this setting may be related to attenuation of thermal effects by coupling gel, the use of B-mode ultrasound, frequent transducer movement and adjustment during nerve localization, conduction of heat by the needle, or dissipation of heat by blood vessels close to nerve bundles. Importantly, regional anesthesia using ultrasound guidance appears to be relatively safe.

Ocular Effects of Ultrasound

Avascular structures containing large amounts of collagen, including the cornea and lens of the eye, are efficient absorbers of ultrasound energy and have the potential to increase in temperature during prolonged ultrasound exposure. Ultrasound is used clinically in ophthalmology for diagnostic imaging and phacoemulsification; focused, higher intensity ultrasound may also be used for destruction of intraocular lesions (intraocular tumors). Early work by Zeiss in 1938 demonstrated that ultrasound (10 W/cm² for 2–4 s) causes vitreous humor liquefaction. Prolonged exposure also produces cataracts. Transient chemosis, conjunctival injection, corneal clouding, lens opacities, reduction in intraocular tension, or permanent destruction of the ciliary body were all reported after focused ultrasound exposure (3 and 7 MHz at peak intensities of 58 W/cm² and 135 W/cm²).¹²⁶ Similar lesions were also produced at intensities close to 1 W/cm².¹²⁷ Higher intensity, focused ultrasound is capable of damaging the ocular structures to different degrees depending on the duration of exposure and the intensity.¹²⁸ These data suggested that focused ultrasound may be therapeutically useful for destruction of intraocular pathology.

Diagnostic ultrasound imaging may also be for the detection of intraocular pathology, identification of foreign bodies, examination of retinal artery blood flow, and measurements of axial lengths of the globe.¹²⁹ Notably, in contrast with the findings described previously, ultrasound exposure of rabbit eyes for durations of 1–4 h at diagnostic intensities of 33.7 mW/cm² did not produce ocular damage.¹²⁹ High-frequency ultrasound (more than 50 MHz) is used for imaging the anterior chamber. At these frequencies, there is a theoretic concern for thermal effects, within the focal plane, but this energy is rapidly dissipated. In addition, the typical exposure duration is usually only a few seconds, thereby preventing thermal consequences from occurring. Experiments performed at higher order of magnitudes than those required

clinically attest to the ocular safety of ultrasound exposure at these frequencies.¹³⁰

Phacoemulsification uses high-intensity ultrasound (1,000 W/cm²) in short bursts (a few seconds) to fragment and emulsify the lens during cataract surgery. Reports of corneal endothelial damage secondary to the use of ultrasound during phacoemulsification have been attributed to the release of free radicals due to cavitation.^{131–134} However, the aqueous humor is rich in antioxidants, including ascorbic acid, and the lens has a coating of glutathione, another effective antioxidant. These endogenous antioxidants provide some endothelial protection. Conversely, irrigant solutions used to dissipate heat and facilitate removal of debris inadvertently also wash away natural antioxidants.¹³⁵ The corneal endothelial cells also do not replicate under normal circumstances. Thus, corneal endothelial damage remains a known risk of phacoemulsification.

Ultrasound also enhances delivery of agents (dye) applied to the corneal surface. Increasing intensities (0.19–0.56 W/cm²) of ultrasound caused transient disruption of superficial corneal layers resulting in increased delivery of dye transfer. Notably, a 5-min exposure at an ultrasound intensity of 0.56 W/cm² caused an increase in the corneal temperature to 43°C. Both thermal- and cavitation-related mechanisms are thought to be responsible for this effect.¹³⁶ As a result, the concern for intraocular damage prompted the Food and Drug Administration to limit ocular exposure to a spatial peak, temporal average intensity (I_{SPTA}) of 50 mW/cm² and a spatial peak, pulse average intensity (I_{SPPA}) of 28 W/cm². Similarly, the British Medical Ultrasound Society recommended limiting thermal and mechanical indices to less than 1 and 0.7, respectively, during ocular exposure to ultrasound.

Pulmonary Effects of Ultrasound

Lung hemorrhage after ultrasound is probably the most extensively studied example of acoustic cavitation,⁴⁵ but the current definitions of mechanical index do not accurately predict the clinical occurrence of lung hemorrhage in susceptible patients.⁴⁷ The hemorrhage itself originates from the microvasculature of the visceral pleura and not from the alveoli or bronchioles *per se*.¹³⁷ Nevertheless, ultrasound-induced lung hemorrhage produces alveolar injury and congestion in alveolar capillaries. The mechanism of ultrasound-induced lung hemorrhage may not be directly related to inertial cavitation because frequency dependence or augmentation by contrast agents do not occur.^{138,139} Tissue characteristics of pleural interface with lung, magnitude of lung deflation, and the peak ultrasound rarefactional pressure are the primary determinants of lung hemorrhage.^{140–142} Peak compressional pressure amplitudes during pulsed Doppler are also capable of producing lung hemorrhage, as the threshold for lung hemorrhage is lower than other nongas-containing tissues, and emphasize that currently available diagnostic ultrasound devices may theoretically produce such injury.¹⁴² The

relative absence of pulmonary collagen and elastin increases the susceptibility to ultrasound-induced pulmonary hemorrhage.⁵⁴ In contrast with experimental animals, humans do not appear to develop lung hemorrhage as a result of ultrasound exposure.⁴⁷ Nevertheless, neonates and patients with pulmonary disease may be theoretically vulnerable to this process. Notably, ultrasound-induced lung hemorrhage in animals is not associated with profound hypoxemia, and spontaneous restoration of pulmonary histology and function occurs within a few weeks of the inciting event.^{143,144} Indeed, hemolysis, endothelial cell damage, and cardiac myocyte necrosis have been reported during cardiovascular ultrasound applications as microbubble contrast agents decrease the threshold for cavitation.^{145–150}

Ultrasound-induced lung hemorrhage has been widely reported in experimental animals, but perhaps rather surprisingly, humans do not appear to be susceptible to this form of nonthermal injury.¹⁵¹ The lungs of 50 patients undergoing transesophageal echocardiography during coronary artery bypass graft surgery were examined intraoperatively for nonthermal injury. The mechanical index of the transesophageal echocardiography probe was 1.3 and the ultrasound exposure duration was 18 ± 14 (mean ± SD) min. None of the patients developed lung hemorrhage. This study suggested that diagnostic ultrasound may not cause lung hemorrhage in humans, but interpretation of the findings is limited by the small size and because the upper limit of mechanical index established by the Food and Drug Administration (1.9) was not approached.¹⁵¹

Limitations of Studies Examining Biologic Effects of Ultrasound

Many potential limitations of studies examining the biologic effects of ultrasound studies have been identified and interpretation of these investigations requires a consideration of these possible constraints. Core temperatures of experimental animals are different from those of humans, and extrapolation of thermal injury data from animal models to humans may be difficult. Most studies implicating the potential neonatal effects of ultrasound have not been consistently confirmed. For example, restraint required for ultrasound examination in the conscious animals is a known teratogen.¹⁵² The presence of unrecognized maternal or congenital disease or toxin exposure may also confound interpretation of studies of ultrasound biologic effects. Dichotomous results often appear in the literature as well. For example, ultrasound may produce either excitation and inhibition of neural circuits depending on intensity or exposure duration.¹¹³ The National Center for Devices and Radiologic Health compiled the reported biologic effects of ultrasound before 1985, but interpretation and extrapolation of these results to humans is difficult because experimental models and methods varied substantially between studies.¹⁵³ Lack of standardized ultrasound exposure protocols or the use of baseline anesthesia are

also important factors to consider when interpreting the findings of studies of ultrasound biologic effects.

Conclusions

The potential for ultrasound to cause adverse effects in experimental animals is well established, but whether similar effects also occur with humans in susceptible tissue (*e.g.*, neural) requires further investigation. After more than a decade of ultrasound imaging in regional analgesia and pain medicine interventions, there have been no major reports of harm secondary to its use. One could postulate that humans are resistant to ultrasound-related biologic effects and, if at all such effects do occur, they are likely to be either quite subtle or of sufficient rarity to escape detection. Currently, it is reasonable to conclude that ultrasound imaging, as used in current regional anesthesia and pain medicine interventions and when limited according to the current Food and Drug Administration regulations, appears to be associated with minimal risk of meaningful tissue injury to the patient. Nevertheless, use of higher intensity ultrasound combined with longer duration of exposure, may unmask detrimental effects. Awareness of the possible biologic consequences of ultrasound and the factors associated with their occurrence may permit the clinician to balance optimal visualization and the risk of ultrasound-related complications.

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