Perspective

A Review of Therapeutic Ultrasound: Biophysical Effects

Almost 2 decades ago, it was pointed out that physical therapists tended to overlook the tenuous nature of the scientific basis for the use of therapeutic ultrasound. The purpose of this review is to examine the literature regarding the biophysical effects of therapeutic ultrasound to determine whether these effects may be considered sufficient to provide a reason (biological rationale) for the use of insonation for the treatment of people with pain and soft tissue injury. This review does not discuss articles that examined the clinical usefulness of ultrasound (see article by Robertson and Baker titled "A Review of Therapeutic Ultrasound: Effectiveness Studies" in this issue). The frequently described biophysical effects of ultrasound either do not occur in vivo under therapeutic conditions or have not been proven to have a clinical effect under these conditions. This review reveals that there is currently insufficient biophysical evidence to provide a scientific foundation for the clinical use of therapeutic ultrasound for the treatment of people with pain and soft tissue injury. [Baker KG, Robertson VJ, Duck FA. A review of therapeutic ultrasound: biophysical effects. *Phys Ther.* 2001;81:1351–1358.]

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The purpose of this review is to examine the biophysical basis for using therapeutic ultrasound. The focus will primarily be on the use of ultrasound to reduce pain and promote soft tissue healing, but this review will also address the effect of this modality on soft tissue extensibility. We investigated whether existing knowledge of the effects of ultrasound provides a conceptual argument for the use of this modality.

Biophysical Effects

To a large extent, the biophysical effects of therapeutic ultrasound have been examined through in vitro studies.[1–8] There is relatively little evidence that these changes occur in vivo, and extrapolation of these results to humans is therefore conjectural. At the molecular level, in vitro research can be useful in determining function; for example, in vitro mutagenesis is an effective method of ascertaining protein function.[3] However, in order to assess the effect of a modality such as ultrasound on an intact organism, the influence of regulatory mechanisms such as homeostasis must be taken into account.

In an in vivo condition, any change in the extracellular fluid initiates a protective reaction to minimize the effect on cells, tissues, and organs.[4] These protective mechanisms may be at least partly responsible for the discrepancy between the results of in vitro ultrasound studies and the findings of a small number of high-quality randomized controlled trials (see article by Robertson and Baker titled "A Review of Therapeutic Ultrasound: Effectiveness Studies" in this issue). This includes the absence of injurious effects despite the increased cell lysis observed following pulsed ultrasound in vitro. However, it has been suggested that further investigation of the hazards of ultrasound is necessary.[9] Harvey et al[5] and Ramirez et al[6] both reported cell destruction using 1-MHz pulsed ultrasound via underwater application at a dose equivalent to a space-averaged time-averaged (SATA) intensity of 0.08 W/cm^2. Similarly, Fahnestock et al[7] reported cell lysis or cell permeabilization following exposure of neuroblastoma cell lines to 1-MHz continuous ultrasound at a spatial peak dose of 1 W/cm^2. This cell damage occurred in vitro and was attributed to cavitation, which is usually not a factor in vivo at therapeutic intensities.[8] The World Federation for Ultrasound in Medicine and Biology has addressed this issue: "Because the probability of cavitation is much greater for in vitro conditions, one must be cautious in applying in vitro experimental results to the clinical situation."[8(p3)] Despite the similarity of the ultrasound doses used in the studies with lysis with doses used clinically, the absence of adverse signs and symptoms following the careful and proper application of ultrasound suggests that cell destruction occurring in vitro is not relevant clinically.[10] Dyson[10] argued against accepting the results of in vitro studies without in vivo confirmation. We believe that accepting untested assumptions of equivalence of in vitro and in vivo applications may result in inappropriate extrapolation from in vitro to in vivo conditions.[2]

Therapeutic ultrasound has traditionally been regarded as having a strong biophysical basis.

Biophysical effects of ultrasound are traditionally separated into thermal and nonthermal effects.[9,11] In our opinion, it is incorrect to assume that only one effect is present at any time and that physical therapy treatment may be classed as either thermal (that is, continuous wave exposure) or nonthermal (that is, pulsed exposure). The reality is that the 2 effects are not separable,[12] and indeed it is rarely true that one class of effects may be ignored completely. A notable exception is extracorporeal lithotripsy, which causes exclusively mechanical bioeffects.[13] For all other situations, it is best to assume that nonthermal effects will always be accompanied by some heating because the interaction between ultrasound and tissue is simultaneously thermal and mechanical and there is insufficient evidence as to whether there is a true threshold for bioeffects resulting from either mechanism.[14] Conversely, acoustic fields that give rise to heating are always accompanied by nonthermal effects.[14] Pulsing the ultrasound beam reduces the temperature rise proportionately to the pulsing ratio; it does not eliminate heating.[15] Neverthe-

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less, it is convenient to classify the effects of insonation as either thermal or nonthermal. Nonthermal effects are those usually associated with cavitation and its associated effects.[1] Thermal effects are those due to heating and are accepted as including increased metabolic activity and blood flow and an analgesic effect on nerves. An additional claim is increased collagen extensibility.[1,16,17]

Nonthermal Effects

Nonthermal effects have been divided by ter Haar[12] into cavitation and other mechanical effects. She contended that the beneficial effects of ultrasound were due to "nonthermal interaction mechanisms" rather than heating. The term "cavitation" appears to have been first used by Sir John Thornycroft in the early 20th century and was defined as the formation and life of bubbles in liquids.[18] The general term "cavitation" can be used to describe any bubble phenomenon, but it will be used here to denote acoustic cavitation: the behavior of bubbles within an acoustic field. Therefore, cavitation may be more specifically defined as "the formation of tiny gas bubbles in the tissues as the result of ultrasound vibration."[19(p159)]

Claims regarding the existence of in vivo cavitation at therapeutic intensities are usually based on 1 of 2 very similar studies,[20,21] which have not been replicated by other workers. These studies were on the guinea pig hind limb, and continuous and nonpulsed ultrasound was used. Although there is evidence of bubble nucleation in the body at the surgical doses used by extracorporeal lithotriptors,[13,22,24] it has proved difficult to demonstrate cavitation in vivo at the intensities used for therapeutic ultrasound.[25] Therefore, it is not generally accepted that cavitation occurs at these intensities. A major source of error in the studies by ter Haar and colleagues[20,21] may have been problems with the interpretation of B-scan images (a pulse echo ultrasound imaging technique) used to detect cavitation.[26] The tissues were immersed in saline, and a scanner was used to study bubble formation following decompression created by raising the ambient pressure.[20] However, it has been demonstrated that artifactual bubble echoes may be produced and mistaken for evidence of cavitation.[26] Nevertheless, gas bubbles have the potential to oscillate and cause damage under the influence of ultrasound. We believe that a great deal of caution needs to be exercised near air-filled cavities such as the lungs[25] and intestines.[27,28]

Like cavitation, *acoustic streaming* is as a major effect of insonation and is described as "localized liquid flow in the fluid around the vibrating bubble."[15(p112)] It is necessary to distinguish between "bulk streaming" and "microstreaming." Bulk streaming is far less mechanically powerful than microstreaming.[14] Bulk streaming occurs when an ultrasound beam propagates in a liquid and there is movement of the fluid in a single direction,[29] whereas microstreaming forms as eddies of flow adjacent to an oscillating source.[1] A major difference between bulk streaming and microstreaming is that bulk streaming occurs in vivo, but microstreaming does not.[30] This is because microstreaming is always associated with and secondary to cavitation,[1] which does not occur in vivo except in gas-filled cavities. Microstreaming is the only type of acoustic streaming with sufficient strength to alter membrane permeability and stimulate cell activity when it occurs at the boundary of the cell membrane and tissue fluid.[1]

There is no direct evidence that any purported clinical benefits of ultrasound are due to altered membrane permeability. These purported changes include increases in protein synthesis, mast cell degranulation, growth factor production, uptake of calcium, and fibroblast mobility.[1,11,31] Dyson[10] has suggested that these changes could account for the improved tissue repair that is alleged to follow ultrasound therapy. The only experimental evidence for ultrasonically altered membrane permeability, however, comes from studies of cell cultures for which there was good evidence that cavitation occurred. For example, Lota and Darling[32] reported changes in the permeability of the red blood cell membrane in a homogeneous ultrasonic field. This finding was based on detection of increased extracellular potassium following administration of 1-MHz continuous ultrasound at an intensity of 0.5 to 3 W/cm^2. These changes, however, could also have been the result of ultrasound causing further trauma.

Mast cell degranulation and increased membrane permeability have usually been observed in vitro where it is possible to readily produce microstreaming, which could be responsible for the observed cell damage. Not only is mechanical trauma a known cause of mast cell degranulation, it can also cause increased passive cell membrane permeability.[33] Furthermore, damage to the basement membrane initiates angiogenesis.[34,35] Although microstreaming does not occur in vivo, we believe that the possibility of direct mechanical trauma from insonation cannot be discounted. We contend that it is highly unlikely that membrane damage will occur at the intensities used in clinical practice,[36] and the lack of reports of detrimental clinical effects reinforces the view that cell lysis is not occurring. Therefore, despite ultrasound being used in a manner similar to its clinical application, the in vitro experiments described have little relevance to clinical practice.

Other mechanical effects are considered to be created by small oscillation of particles due to the movement of ultrasound waves through tissues.[1] Any displacement,

however, will depend on the acoustic pressure amplitude or intensity, which will be small. Consequently, small-particle oscillation is usually not seen as a cause of the biophysical effects of ultrasound. Free radical formation has also been suggested as a potential source of cell damage with ultrasound.[37,38] However, because there is no good evidence of cavitation occurring in vivo, the evidence for free radical formation secondary to ultrasonic cavitation in solutions in vitro is not relevant in this context.[39]

Blood cell stasis is a nonthermal effect of ultrasound that has been attributed to the behavior of red blood cells in a standing wave field.[10] These effects are strongest when the standing wave is "stationary." This occurs when a standing wave is set up in a medium that has very low acoustic attenuation, such as water, with a perfect reflector perpendicular to the ultrasound beam.[40] Such conditions can be closely approximated in in vitro experiments. They are much less likely to occur in vivo where the forces tending to cause cell stasis are much weaker. Consequently, the blood cell stasis observed in vitro by Dyson[10] is unlikely, in our view, to occur in clinical practice.

Hogan et al[41] claimed that pulsed ultrasound can promote circulation independently of a heating effect. In their frequently cited study on ischemic rat muscle,[41] they claimed that 5 minutes of 2.5 W/cm^2 (spatial peak, time averaged; equivalent to a SATA intensity of 0.15 W/cm^2 according to the World Federation for Ultrasound in Medicine and Biology[39]) of ultrasound on alternate days for a period of either 1 or 3 weeks improved arteriole blood flow. This dose was chosen because a similar intensity was used by Dyson et al[42] (a SATA intensity of 0.2 W/cm^2) for the treatment of people with varicose ulcers. Hogan et al[41] found vasoconstriction of small arterioles (30 μm in diameter) following insonation. This slight constriction did not reduce blood flow below that measured in control subjects. Therefore, there was no discrepancy with the results of a previous study by the same authors.[43] The previous research demonstrated that insonation of normal muscle resulted in vasoconstriction and decreased blood flow.[43] In a more recent study by Rubin et al,[44] using the same duration and intensity of ultrasound as Hogan et al,[41] the researchers found that pulsed ultrasound produced no change in blood flow.

Whether ultrasound causes growth of new blood vessels is controversial.[44] Angiogenesis occurs briefly under some circumstances such as during wound healing.[34] Hogan et al[41] found that ultrasound promoted angiogenesis. These results were supported by the work of Young and Dyson.[45] However, when Rubin et al[44] attempted to replicate Hogan and colleagues'[41] research by also applying pulsed ultrasound to the rat cremaster muscle using 2 (0.15 and 0.31 W/cm^2) of the 4 intensities (0.08, 0.15, 0.31, and 0.62 W/cm^2) used by Hogan et al, angiogenesis did not occur. Therefore, there is no clear proof that angiogenesis is promoted by ultrasound in the animal model.

Although there is in vitro evidence of stimulation of fibroblast proliferation with ultrasound,[5,6] there is no good evidence that this occurs in vivo. In addition to proliferation, Harvey et al[5] and Ramirez et al[6] also described damage to fibroblasts treated with therapeutic levels of 1- and 3-MHz ultrasound. This finding was supported by the work of De Deyne and Kirsch-Volders,[46] who described in vitro fibroblast changes similar to those outlined by Harvey et al[5] and Ramirez et al.[6] Other effects have also been observed in in vivo studies, such as changes in the plasma membrane[11] and in intracellular organelles such as lysosomes and mitochondria.[1]

Despite claims of membrane and intracellular changes in vitro, the results of treating soft tissue injuries in animals with ultrasound are contradictory.[6] For example, although Byl et al[47] found increased collagen deposition following pulsed ultrasound treatment (0.1–0.3 W/cm^2 SATA, 1 MHz) of wounded pigs, Turner et al[48] found no alteration in healing following insonation (0.2 W/cm^2 SATA, 3 MHz) of repaired cockerel tendon, which has a similar degree of collagen cross-linkage to that found in human tendon. However, in this instance, there is at least the possibility that the disparity between the results of Byl et al[47] and Turner et al[48] may be due to the difference in frequency used.

The results of 2 studies by Enwemeka and colleagues[49,50] do not decrease the confusion noted by Ramirez et al[6] regarding the effect of ultrasound on in vivo soft tissue healing. This confusion is due to an inadequately explained lack of correlation between the results of Enwemeka and colleagues' studies[49,50] regarding the effect of 1-MHz ultrasound on the tensile stress (force per unit area) of rabbit tendons. They attributed this disparity in results between the 2 studies[50,51] to variation in ultrasound intensity (1.0 W/cm^2 and 0.5 W/cm^2, respectively). However, if this were the case, it is unclear why there was no similar interstudy disparity regarding tensile strain and tensile strength, both closely related to tensile stress.[49,50]

Thermal Effects

Although there is evidence for insonation causing a rise in tissue temperature,[52] the extent of tissue heating is dependent on a number of variables. Heating is intensity dependent. Reduced heating occurs for pulsed ultrasound as opposed to continuous ultrasound, the reduc-

tion being approximately proportional to the on:off pulse ratio.[15] A study on human muscle by Draper et al[53] has shown that, following 10 minutes of 1-MHz continuous ultrasound at an intensity of 1.5 W/cm^2 with a 20-cm^2 transducer applied to a skin area of 80 cm^2, the temperature in the gastrocnemius muscle at a depth of 3 cm was increased by 5°C. These researchers emphasized the necessity of limiting the area treated, and they considered it necessary to give ultrasound for at least 7 or 8 minutes in order to achieve a rise in temperature.

In vivo studies using continuous ultrasound (1 MHz, 2.5 W/cm^2) applied to the pig hip joint showed that the anterior aspect of the fibrous capsule was heated to 41°C after 1 minute and reached between 43° and 44°C after 2 or 3 minutes. Although lower-intensity ultrasound (1.5–2.0 W/cm^2) resulted in a temperature rise of only 1 degree above the pretreatment mean temperature of 39.8°C,[54,55] which approximates the normal resting temperature of the pig leg,[55] an intensity of 3.0 W/cm^2 was required to obtain a temperature increase of between 41° and 44°C.[16] Similarly, ter Haar and Hopewell[55] found that, on occasion, it was necessary to increase the ultrasound intensity from 1.5 W/cm^2 to 3.0 W/cm^2 (frequency of 0.75 MHz) to achieve heating of skin and deeper tissues. They reported that, in some cases, an intensity of 3.0 W/cm^2 was necessary to raise skin temperature in the pig thigh above 35°C, with the rise in temperature being greatest at the fat/muscle interface and not deeper as might be expected using this frequency.

Homeostatic mechanisms will tend to counteract the rise in temperature of tissues exposed to heating. The success of homeostasis in restoring normal temperature depends on the balance between heat gain and heat loss. Any alteration in temperature automatically initiates a reaction in an effort to restore normal temperature.[4,56] However, it is apparent that homeostatic control was unable to prevent the rise in tissue temperature recorded by Draper and colleagues.[53,57] This is because local and general homeostatic mechanisms are only partially successful in quickly reversing the effect of a rise in temperature.[4] The resultant tissue temperature following heating will primarily depend on the extent of conduction into surrounding tissues and dissipation by blood perfusion.[15,24] Dissipation by blood perfusion is highly variable and difficult to estimate, but is known to be poor in fatty tissue and tendon.

Changes in blood flow due to heating at clinically acceptable doses are probably confined to the skin.[58,59] In a recent study using duplex ultrasound scans (with the option of gray-scale or Doppler mode) to measure saphenous vein cross-sectional area, heat stress (via a thermal suit perfused with water at 49°C) resulted in doubling of the cross-sectional area and, therefore, blood volume in this vein.[60] An increase in blood flow gave a rapid turnover of warm blood, which assisted cooling.[60] In muscle, the use of radioactive tracers in human subjects showed that heating agents, including ultrasound, do not cause an increase in blood flow that is comparable to that caused by even moderate exercise.[61] This finding was confirmed recently using venous occlusion plethysmography and laser Doppler flowmetry before and after the administration of continuous ultrasound (1.5 W/cm^2 for 5 minutes).[62] A reasonable explanation for the discrepancy between these studies and studies demonstrating that muscle blood flow increased with heating[63,64] is that the latter studies used only plethysmography to measure blood flow. This technique, however, does not measure tissue-specific changes in blood flow in tissues such as muscle.[62]

Robinson and Buono[62] noted that researchers using the xenon-33 washout technique to measure muscle blood flow concluded that continuous ultrasound at an intensity of 1.5 W/cm^2 given for 5 minutes to the forearm did not increase blood flow. There is still a possibility, however, that ultrasound at higher intensities may increase muscle blood flow. For example, although no increase in muscle blood flow was found at tolerable ultrasound intensities,[65] increased muscle blood flow did occur at intolerable ultrasound intensities (high-intensity continuous ultrasound is intolerable due to pain caused by excessive heating).[63] The contention that high temperatures are necessary to increase muscle blood flow is supported by a study using microwave heating to achieve temperatures in excess of 44.5°C.[66] Muscle blood flow increased from a pretreatment value of 10 mL/min/100 g to 44 mL/min/100 g. However, this increase was far less than the increase from 2 to 4 mL/min/100 g at rest to 80 mL/min/100 g of muscle achieved with extreme exercise.[56] Moreover, given the intolerably high intensity of ultrasound required, this increase is not achievable clinically using ultrasound.

Increased cellular activity due to heating is a more difficult issue to address. The type of cell affected by an increase in temperature is usually not specified, and the justification for speculation regarding cell activity is often erroneously attributed to van't Hoff's "law."[19] By far the most significant difficulty with the concept of increased cellular or enzymatic activity is the implication that this process will accelerate healing. Unfortunately, there is no evidence to connect these 2 events. Indeed, as previously mentioned, the evidence from randomized clinical trials suggests that insonation does not affect the rate of healing.[67–72]

Given the widely held belief that ultrasound increases collagen tissue extensibility, it is surprising to find that,

by 1997, there was only one in vivo study of the effect of heating with ultrasound on ligament extensiblity.[73] This investigation was performed on human knees, and the authors concluded that therapeutic ultrasound at clinically accepted doses (1.5 W/cm^2 at 1 MHz for 8 minutes) slightly increased the extensibility of the lateral and medial collateral ligaments, but this increase was not significant. The paucity of in vivo studies is in contrast to a number of in vitro studies on the effect of insonation on collagenous tissue extensibility, usually of rat tail tendon.[74,75] Although these studies showed increased extensibility with heating, this increase was very small and, we believe, of dubious relevance to humans. Reed and Ashikaga[73] suggested that the discrepancy between the results of in vitro experiments and their in vivo study may have been due to the effect of blood flow on heat dissipation.

Conclusions

Randomized controlled trials and other forms of clinical research provide evidence for the evaluation of modalities.[76] Although understanding the physiological effects of interventions does not justify their use, it is often helpful for clinicians. Alleged physiological responses to the biophysical effects of therapeutic ultrasound, in our view, have been pivotal in the widespread adoption of this form of treatment even in the absence of clinical studies.

This review indicates that the biophysical effects of ultrasound are unlikely to be beneficial. This conclusion is based on the absence of evidence for a biological rationale for the use of therapeutic ultrasound.

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