SYSTEMATIC INTERVENTION COMPONENT ANALYSIS: DOSE-RESPONSE FOR THERAPEUTIC ULTRASOUND

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The Supervisory Committee certifies that this ***disquisition*** complies with North Dakota State University's regulations and meets the accepted standards for the degree of

DOCTOR OF PHILOSOPHY

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ABSTRACT

Therapeutic ultrasound has been well documented in the literature to affect human tissue. The four main parameters practitioners are able to influence are frequency, duty cycle, intensity, and treatment time. Alteration to one or more of these parameters will affect the total dose of acoustical energy delivered to the tissue resulting in a target tissue temperature increase or biophysical effect. The goal of this two-part study was to determine the appropriate energy dose of therapeutic ultrasounds needed to create a beneficial intervention when treating unhealthy human tissue. Prior to the investigation a non-systematic review was conducted to determine the dose-response and thermal outcome in laboratory studies. The first investigation used a systematic intervention component analysis (ICA) to determine the effectiveness and empirical relationship between the different parameters of an ultrasound intervention when treating unhealthy tissue. The second investigation included a four-part survey which addressed trends within parameter selection in the clinical setting and influences on clinical decision making. The first investigation findings indicated no one parameter had significant influence on the ultrasound treatment effectiveness. The second investigation findings indicated practitioners set a treatment goal of 2℃ and a mean predictive outcome between 1.85 and 2.56℃ regardless of the condition.

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LIST OF ABBREVIATIONS

BNR .....Beam nonuniformity ratio.

ERA.....Effective rating area.

ICA.....Intervention component analysis.

PROMs.....Patient reported outcome measure.

ROM .....Range of motion.

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CHAPTER I: INTRODUCTION

Therapeutic ultrasound is a dynamic and complex modality. The alteration to one or more of an ultrasound's treatment parameters will affect the total dose of acoustical energy delivered to the tissue. The main parameters used to adjust the ultrasound's acoustical wave production are frequency, duty cycle, and intensity. Other factors affecting the dose of acoustical energy are how the ultrasound is applied (treatment time, treatment area, or movement of the transducer) and the ultrasound manufacture standards, which include transducer effective radiating area (ERA) and beam nonuniformity (BNR).

An integrative non-systematic review was conducted to understand the different parameters and factors affecting the acoustical energy production and the application of acoustical energy to tissue. The search process emphasized the chronological development of the research by evaluating textbook citations, non-systematic primary literature database searches, and secondary reference exploration from the textbooks and primary literature. Specific trends emerged during the investigation of the question; what dose of acoustical energy is appropriate when treating unhealthy human tissue? First, there was a consistent trend of incomplete reporting of treatment parameters, which may have led to inaccurate assumptions of an ultrasound intervention. Secondly, there was dependence on animal-model-based research due to American Institute on Ultrasound in Medicine's[1] recommendation to thoroughly test therapeutic ultrasound interventions in animal-models before moving to human-models. Although animal-model-based results are valid in developing acoustical dose recommendations, animal-model-based results cannot provide relevant dose recommendations for humans due to biology, size, and treated tissue depth differences.[2]

Within the human-model-based literature, the lack of systematic evaluation makes it difficult to compare acoustical dose and the subsequent biophysical effects relative to the measured outcome of tissue temperature increase caused by the ultrasound treatment.[3-13] Furthermore, there is a lack of systematic evaluation of parameter alterations with little explanation for why specific parameters were selected between and within studies. Three surveys indicated clinical experience and undergraduate training strongly influenced practitioners' ultrasound parameter selection (frequency, intensity, duty cycle, time) in a clinical setting.[14-16] However, the rationale for parameter selection in the primary research has not been consistently outlined in the literature. Thus, there are limited conclusions that can be made about the logic or decision-making process researchers used during the methodology development for selecting the ultrasound parameters. Finally, systematic reviews that evaluate ultrasound effectiveness provide limited guidance to formulate a practical application of therapeutic ultrasound for appropriate parameter selection or modifications based on manufacturer standerds.[17]

The appropriate acoustical energy dose for targeting a specific biological effect remains unclear. Although there is a broad spectrum of primary literature, the lack of detail limits the practical clinical application. Literature trends need to be identified and further explored in a systematic intervention component analysis (ICA) to establish if a specific parameter could significantly influence the outcome when compared to other parameters. Additionally, identifying the ERA of the ultrasound unit used in each study enables the acoustical dose of the treatment to be determined. Thus, the examination of the dose-response relationship can occur for a given condition. To accurately understand the acoustical dose and predicted temperature outcome both the manufacture standards and practitioner's parameters must be known. Therefore, the individual components required for further evaluation are frequency, duty cycle,

intensity, treatment time, and ultrasound manufacture standards (ERA and BNR). Further investigation is needed to evaluate the current clinical application and practitioners' understanding of therapeutic ultrasound.

Statement of the Problem

There are some known biological effects as a result of ultrasound treatment. However, inconsistencies exist in the literature due to the lack of systematic evaluation of manufacture standards, parameter selection, and dose-response of acoustical energy to human tissue. Furthermore, the lack of systematic assessment may lead to the incorrect clinical application of therapeutic ultrasound with unknown harmful or ineffective results.

Purpose of the Study

The primary goal of phase one was to ascertain trends within parameter selection to evaluate the thermal effect of ultrasound on unhealthy human tissue. The primary purpose of phase two was to determine how clinicians are currently using therapeutic ultrasound and their understanding of parameter differences. The primary treatment parameters evaluated during both phases include frequency, duty cycle, intensity, treatment time, ERA, BNR, and total energy delivered during a single treatment. In addition, conditions examined were evaluate underlying symptoms of pathologies associated with tissue extensibility, pain management, muscle restriction, and scar tissue remodeling.

Research Questions

There were two primary research questions identified, "What parameters are critical for the therapeutic ultrasound to be effective when treating unhealthy tissue?" and "To what extent does the ultrasound manufacturer standards (ERA and BNR) influence the effectiveness of ultrasound when treating unhealthy tissue?"

Phase 1

Research Question 1

To what extent can the predicted tissue temperature increase based on the selected parameters (intensity, frequency, and time) accurately predict a significant treatment outcome.

(a) H_0: $r = r_0$ The null hypothesis is that the predicted tissue temperature increase is equally effective regardless of the tissue pathology.

H_A: $r \neq r_0$ The alternate hypothesis is that the predicted tissue temperature increase is different for at least one range of BNR, regardless of the tissue pathology,

Research Question 2

To what extent can parameters components predict the effectiveness of an ultrasound intervention success. Components include: (a) BNR (b) ERA (c) total energy delivered?

(a) H_0: $r = r_0$ The null hypothesis is that the reported or manufactured cited BNR are equally effective, regardless of the tissue pathology.

H_A: $r \neq r_0$ The alternate hypothesis is that the reported or manufactured cited BNR is different for at least one range of BNR, regardless of the tissue pathology.

(b) H_0: $r = r_0$ The null hypothesis is that the reported or manufactured cited ERA are equally effective, regardless of the tissue pathology.

H_A: $r \neq r_0$ The alternate hypothesis is that the reported or manufactured cited ERA is different for at least one range of ERA, regardless of the tissue pathology.

(c) H_0: $r = r_0$ The null hypothesis is that each condition group's predicted total energy delivered for "successes" treatments will be equal.

H_A: $r \neq r_0$ The null hypothesis is that each condition group's predicted total energy delivered for "successes" treatments will differ.

Phase 2

Research Question 1

To what extent do the selected parameters (intensity, frequency, duty cycle, and time) match the results of the non-systematic review and systematic review from phase one.

H_0: $r = r_0$ The null hypothesis is that the selected parameters are equal to those selected in the primary research.

H_A: $r \neq r_0$ The alternate hypothesis is that the selected parameters are different from those selected in the primary research.

Research Question 2

To what extent do the selected parameters (intensity, frequency, duty cycle, and time) match the predicted tissue temperature for the practitioner's treatment goal.

H_0: $r = r_0$ The null hypothesis is that the predicted tissue temperature increase is equal, regardless of the tissue pathology.

H_A: $r \neq r_0$ The alternate hypothesis is the predicted tissue temperature increase is different, regardless of the tissue pathology.

Research Question 3

To what extent do practitioners understand differences in ultrasound manufacture standards (ERA and BNR) that may affect the desired thermal outcome.

(a) H_0: $r \geq r_0$ The null hypothesis is that 75% or more of the participants understand the concept of BNR.

H_A: $r < r_0$ The alternate hypothesis is that less than 75% of the participants understand the concept of BNR.

(b) H_0: $r \geq r_0$ The null hypothesis is that 75% or more of the participants understand the concept of ERA.

H_A: $r < r_0$ The alternate hypothesis is that less than 75% of the participants understand the concept of ERA.

Significance

Phase 1

Prior systematic reviews that evaluated the effectiveness of ultrasound focused on condition/pathology instead of general biophysical effects of therapeutic ultrasound. Limited systematic reviews explored the acoustical dose delivered to the tissue. Further evaluation is necessary to identify the appropriate acoustical dose to cause a specific biophysical effect. Previous systematic reviews repeatedly concluded that the parameters varied widely between the included studies. However, limited exploration has been done to explain the rationale for the wide variation. Additionally, little consideration has been given to the effect BNR and ERA could have on the outcomes and overall effectiveness of the ultrasound treatment. There has been a documented difference between different ultrasound manufacturers' standers (BNR and ERA). Thus, manufacturers' standers should be considered when determining the effectiveness of a treatment. Another factor that had not been commonly addressed in previous systematic reviews was the technological advancements made in ultrasound design. Literature published between 1950 to 1995 cannot be compared to literature published after 1995 due to the technological advancement of the microchip. Therefore, this study aimed to evaluate the different components that may affect the ultrasound treatment outcome, identify the effective dose-response for unhealthy tissue, and identify trends that might assist in directing clinical practice.

Phase 2

There has been a documented difference between different ultrasound manufacturers' heating rates that may be due to the differences in manufacturer standers (BNR and ERA).[3-13] However, limited evaluation has been conducted into practitioners' understanding of manufacturer standers (BNR and ERA). Furthermore, prior survey-based research has not included manufacturer standers (BNR and ERA) as parameter variables. Therefore, the practitioners desired acoustical dose for the ultrasound treatment could not be determined. Previous survey-based research has reported wide variation in the treatment parameters (frequency, intensity, duty cycle, and treatment time) selected by practitioners, but there has been little investigation into how the chosen parameters affect a treatment outcome like tissue temperature increase or the total acoustical energy delivered to the tissue. Therefore, this study evaluated practitioners' selection of different parameter variables (frequency, intensity, duty cycle, treatment time, ERA, and BNR) related to specific biophysical effects that may affect the ultrasound treatment outcome.

Limitations

1. This study assumed that literature published after 1995 used an ultrasound unit manufactured between 1990 to 2022.
2. The systematic review assumed that although methodological heterogeneity between the different studies, the individual studies controlled for covariables that could affect the outcome.
3. The systematic review assumed that the remaining demographics do not influence the ultrasound treatment outcome apart from the diagnosed unhealthy human tissues,

4. Conditions examined looked at underlining symptoms of pathologies related to thermal effects of ultrasound: tissue extensibility, pain management, muscle restriction, scar tissue remodeling.
5. The systematic review did not control for the different studies' sample size statistically.
6. The survey assumed that there will be self-reporting bias from the participants regarding beliefs and practices of therapeutic ultrasound.

Delimitations

1. Studies included in the systematic review were published between 1995 and 2022.
2. Only studies that reported participants with specific diagnosed types of unhealthy tissue were included in the systematic review.
3. The systematic review was limited to randomized control trials or quasi-randomized controlled trials.
4. The survey population only included current practicing certified athletic trainers, who were 18-years or older at the time of the survey, and who fluently spoke English.

Assumptions of the Study

1. Accurate reporting of beam nonuniformity ratio and effective radiating area.
2. Correct calibration of an ultrasound unit will be equal to reported manufacturers' standards.

Definition of Terms

Absorption: The process of a medium collecting thermal energy and changing it to kinetic energy.

Attenuation: A decrease in the intensity of a wave due to the absorption, reflection, and refraction of energy.

Beam nonuniformity ratio (BNR): The ratio of the special peak intensity to the special average intensity.

Cavitation: The formation of gas-filled bubbles that cause pressure changes in tissue fluids during ultrasound application.

Duty cycle: The percentage of time the acoustical energy is being delivered.

Effective rating area (ERA): The surface area of the soundhead that transmits a soundwave.

Frequency: Applies to ultrasound is defined as the number of waves produced in one second.

Half value depth: Represents the depth in the tissues at which half the surface energy is absorbed.

Intensity: The strength of the sound waves at a given location within the tissue.

Law of Grotthus-Draper: Ultrasound will penetrate through tissues high in water content, absorbed in tissues high in protein, reflects off bone, or refracts through joints.

Microstreaming: A one-directional motion of fluid caused by the sound wave that is capable of moving ions and small molecules along and around cell membranes.

Power: The amount of energy produced by the transducer measured in watts (W).

Therapeutic ultrasound: The application of ultrasonic energy on biological tissues to produce physiological changes.

Thermal ultrasound: The transfer of energy that causes an increase in tissue temperature. A continuous output of ultrasonic energy or 100% duty cycle produces thermal effects during an ultrasound treatment.

Transducer: A device that converts one form of energy to another[2]. In the case of ultrasound, the device changes electrical energy into ultrasound waves. It is also known as the applicator or sound head that is moved on the treatment surface.

Treatment duration: The total number of consecutive ultrasound applications to the same area over the course of days or weeks.

Treatment parameters: Settings that are utilized for a specific goal for ultrasound treatment that include time, intensity, and frequency.

CHAPTER II: REVIEW OF LITERATURE

Properties of an Ultrasound Unit

Design of the Ultrasound Machine

Therapeutic ultrasound is a dynamic and complex modality that has been documented to affect biological tissue in several diverse ways. The origins of ultrasound trace back to 1880 when physicists Pierre and Eugene Curie first introduced the piezoelectrical effect by showing a direct correlation between the ability of certain materials to generate an electric charge in response to applied mechanical stress.[18] Mathematician Gabriel Lippman theorized a reverse piezoelectric effect, later confirmed by the Curie brothers, which hypothesized that applying an electric field to certain materials would cause the material to deform. Limited applications of piezoelectricity existed until 1917, when Paul Langevin developed an ultrasonic transducer for submarines.[18] In a 1920 French patent, Langevin documented that high-intensity ultrasound waves could kill fish in a tank immediately. Langevin further stated one experienced "a painful sensation on plunging the hand" into the tank where the high-intensity ultrasound was applied.[19] Between 1920 and 1960, independent research was conducted to explore ultrasounds effect on biological tissue in the United States, United Kingdom, Germany, and Japan. This research eventually led to the development of what is known today as a conventional therapeutic ultrasound unit.[20]

Conventional therapeutic ultrasound units are composed of two main parts, a generator, and transducer, that differ based on the year the machine was produced and the manufacturer. Typically, the generator contains a control panel, user interface, and a voltage-controlled oscillator. Piezoelectric conversion occurs in the transducer.[21] An ultrasound transducer requires

a crystal for the conversion of electrical energy into acoustical energy and a transducer plate to conduct the soundwave.

The energy pathway from electrical socket to acoustical soundwave production is similar between ultrasound machines. Electrical energy travels from the electrical socket to the generator, where the energy is regulated to a specific therapeutic frequency. A basic oscillator is a circuit that only needs a trigger to start a regenerative feedback loop to produce a sinusoidal output waveform without an external signal source.[21] In an ultrasound unit, a voltage-controlled oscillator is coupled with the control panel and tuned to generate a sinusoidal output wave at a specific therapeutic frequency. The signal is transferred by a coaxial cable to metal plates attached to the crystal in the transducer. When the sinusoidal wave reaches the crystal, the piezoelectric effect occurs and the crystal compresses.[20-22] As the current alternates, the reverse piezoelectric effect occurs causing the crystal to expand. The rapid compression and expansion of the crystal produces acoustical waves.[20-22] A transducer plate acts as a conductor for the crystal which can transfer the acoustical sound waves produced by the crystal through a water-based medium into the tissue.[20-22]

Ultrasound generators may have variations in the design which affects the soundwave production. Within the generator, additional circuitry allows for further control of the soundwave. Machines manufactured after 1970 contain safety features to control power supply, which hold the electrical input proportional to acoustic deformation in the converter constant.[23] Units produced between 1983 and 1988 contained an analog servo feedback circuit which acted as a switch between the voltage-controlled oscillator and crystal. Typically, the feedback circuit was composed of three individual circuits: pulse duration and pulse period circuit, treatment time circuits, and power and intensity circuit.[24] During this time, the input from the control panel was

interrupted by the three circuits in the switch, and the applied input caused the oscillator to cycle on and off producing the desired pulsed soundwave. After 1988, the analog servo feedback circuit within the generators were replaced with a microprocessor, which enabled an operator to select various output modes, intensities, and durations.[25]

The design and quality of the components within the transducer can also have an effect on soundwave production. The portion of the transducer plate that is in contact with the crystal and emitting the soundwave is known as the effective radiating area (ERA).[22,26-28] The ERA will always be smaller than the total surface area of the transducer plate and receive at least 5% of the peak acoustical energy. Depending on the manufacturer, the transducer plate to crystal ratio may differ and effect the ERA.[29] Early ultrasound transducers used natural quartz crystals as the piezoelectric material.[20] However, natural materials have inherent imperfections which affected the ERA and beam nonuniformity ratio (BNR), thus creating inconsistencies in expansion and contraction of the crystal.[26] Therefore, manufacturers switched to a synthetic ceramic crystal. Although manufactured crystals have fewer imperfections, discrepancies in the ERA and BNR can exist between units. The acoustical energy emitted by a synthetic ceramic crystal will still not be uniform across the ERA, instead areas of high and low intensity exist. The total fluctuation of intensity across the ERA is known as the average spatial intensity (average spatial intensity = total watts / effective radiating area of the soundhead), and the peak spatial intensity is the area of highest intensity.[22,26-27]

A perfect 1:1 BNR does not exist as it is difficult to manufacture and maintain a consistent spatial intensity across the entire ERA of the transducer plate for the full duration of a treatment.[22,26-27] A low BNR means the crystal uniformly expands and contracts transmitting the vibrations evenly to the transducer plate for transition into tissue with limited spatial peak

intensity and limited areas of high intensity. A typically reported BNR is between 2:1 to 5:1, with anything 8:1 or greater considered unsafe.[30] The lowest BNR reported in the literature is a 1.4:1 with an Omnisound ultrasound unit.[31]

Transducer design has changed in complexity and differs based on the manufacturer. Prior to 1988, the size and operating frequency of the transducer was specific to the generator. Herzog and Knapp[32] developed interchangeable transducers to be matched to the voltage-controlled oscillator, allowing for the transducer size and output frequency to be adjusted. Depending upon the location and size of the treatment area, a large or small transducer may be necessary. Large transducers deliver large diameter ultrasound beams, which results in less attenuation or beam disruption when compared to a smaller transducer. However, if the transducer is too large and unable to remain in contact with the treatment area via the water-based medium, the beam will bounce and reflect off the uncoupled surface. Soundwaves cannot move through air; therefore, energy intended for the tissue bounces back or reflects into the transducer causing overheating and damage to the crystal.

Overheating was a common problem prior to manufacturers developing a temperature-based warning signal that indicated uncoupled conditions which required the operator to discontinue treatment. In 1993, Grzeszykowski[33] introduced the coupling meters that monitored changes to the ERA as the coupling conditions changed. Grzeszykowski[33] designed and patented the radiation dose control using the coupling meter with the Excel Tech Ltd manufacturer. The design of the radiation dose control allowed for adjustments based on the amount of power radiated by the transducer to the patient at any point during the treatment. A sensing circuit was included into the transducer design, which measured the instantaneous current through the transducer and an instantaneous voltage across the transducer. The information from the sensing

circuit was relayed to the microprocessor in the generator, which automatically self-calibrated to regulate the soundwave output.

In 1992, Castel et al[34] patented a hand-held transducer which housed the electrical controls and acted as the user interface. Three years later, the Omnisound hand-held electrical control included an automatic dose feature which allowed pre-programed parameters to be selected based on treatment goals.[35] The automatic dose controller was designed to calculate treatment frequency, intensity, and treatment time based on four input factors from the operator: tissue depth, desired temperature rise (1°, 2°, and 4°), the area of tissue to be treated, and the method of ultrasound coupling (i.e. gel or water immersion).[35]

Prior to 1995, ultrasound devices had transducers capable of only operating effectively at a single frequency. Working with Dynatronics, Hall and Selfridge[36] patented a single applicator which operated at 3 different frequencies (1, 2, and 3 MHz), eliminating the need for separate transducers for each frequency. Patent infringement may explain why other manufactures adapted this concept, but with only two frequencies (1 MHz and 3 MHz).

Ultrasound technology and design continue to evolve with new improvements to the generator circuitry, transducer, and patient/practitioner interface. Understanding the limitations and design of a specific unit when reviewing decades of research may be critical to understanding the gaps between available literature and clinical application. Literature from 1950 to 1995 may have valid data for the ultrasound units of that time; however, that literature may not be valid for ultrasound units manufactured after 1995.

Acoustical Soundwaves

An ultrasound machine transforms electrical energy into acoustical energy, which is then transferred to the tissue.[22,26-28] The first law of thermodynamics states energy transferred into a

tissue will cause an internal change resulting in a temperature increase.[37] As the acoustical soundwave travels through homogeneous tissue, the wave creates regions of high and low molecular density that alternates with the positive and negative peaks of the longitudinal sinusoidal wave.[38] When the crystal in the transducer compresses during the positive peak of the sinusoidal wave the tissue has a lower molecular density.[20,22,26-28] Inversely, the crystal expands during the negative peak of the sinusoidal wave, causing areas of higher molecular density.[20,22,26-28] The ultrasound beam provides the kinetic energy, while the molecular expansion and contraction introduces potential energy. Therefore, the soundwave causes the generation of acoustic vibration energy within the tissue. The sum of kinetic energy and potential energy is the total acoustic energy due to the acoustic disturbance or molecular movement, which is measured by an increase in temperature. The greater the molecular movements the greater the temperature increase.[37-38]

Kinetic energy from the sinusoidal wave is transferable since the acoustic beam is one directional and nonconservative.[38] The beams pathway will not be through homogenous tissue, but rather layers of different types of tissues. As the wave passes from one tissue type to the next, the beam will encounter different acoustic impedances.[38] A certain amount of the energy is refracted at the boundary of each cell, some amount of energy will be absorbed, and the remainder continues as a transmitted wave.[38] Refraction occurs by the bending of the soundwave as a result of a change in the speed of the wave as it enters a tissue that is a different density then the prior tissue. Absorption occurs as the soundwaves collect in the tissue, changing the potential energy into kinetic energy, and causing a temperature increase in the tissue.[37] The refection and absorption of energy results in energy attenuation, a loss of energy as the ultrasound beam moves through tissue, creating a reduction of the total energy.[38] Moreover, the half-value depth is often

used as a marker for tissue attenuation as it is the distance at which 50% of the ultrasound energy has been absorbed into the tissue. Complete reflection occurs when the wave cannot pass through the next tissue density. When the longitudinal wave hits a solid object like bone, the energy rebounds instead of refracting through. When the beam rebounds the wave changes from a longitudinal wave to a transverse wave where molecular displacement is perpendicular. A transverse wave is unable to travel through fluids.[22,26-27] Although, damage to the tissue can occur due to an accumulation of energy from transverse waves, treatments are often discontinued before damage occurs due to periosteal pain from localized heating. [22,26-27]

Altering the Acoustical Soundwave

Adjusting ultrasound parameters affects the delivery of the longitudinal sinusoidal wave and the dose of kinetic energy to the tissue. The four main parameters include: frequency, duty cycle, intensity, and treatment time. Other considerations affecting the parameters include the treatment area, transducer ERA and BNR, tissue type, the total treatment duration, and the movement of the transducer.

Frequency

Frequency, is the number of waves produced in one second and ranges from 1 to 3 megahertz (MHz).[22,26-27] The clinical selection of a specific frequency is primarily based on the target tissue depth with a secondary consideration of the thermal increase rate as a result of the treatment.[3,22,26-27] The half-value depth represents the depth in the tissues at which half the energy is absorbed.[21] Theoretically, 1 MHz has a half-value depth of 2.3 cm, allowing it to heat tissues 2.3-5 cm deep.[39] Three MHz has a half-value depth of 0.8 cm, for heating tissues up to 1.6-2.5 cm depths.[39]

The literature has explored if different types of tissues have a specific absorption rate of acoustical energy. The Law of Grotthus-Draper states ultrasonic energy will penetrate through tissues high in water content, absorb into tissues high in protein, reflect off bone, or refract through joints.[40] Tissues like blood and fat which have a high water and low protein content will transmit ultrasonic energy and absorb very little. In contrast, muscle has a lower water and a higher protein content and thus will absorb ultrasonic energy more efficiently than fat. In 2005, Hoogland[41] published a guide for ultrasound therapy based on the Sonopuls® 190 ultrasound unit. Hoogland outlined a formula for calculating the absorption coefficient for longitudinal waves with perpendicular incidence on homogeneous tissues. If the sound wave is traveling only through fat at a 1 MHz frequency, the half-value depth would be 5cm, compared to the half-value depth of muscles at 0.9 cm, and tendons the 0.62 cm. A general understanding of half-value depth as it relates to tissue type is necessary for understanding depth of penetration in relation to frequency and treatment tissue.

In 1995, Draper et al[3] examined the rate at which tissue temperature increased in response to an ultrasound treatment. The Omnisound 3000™, 4.1 cm^2 ERA and 1.8:1 BNR, was used to deliver four separate treatments per subject at intensities of 0.5, 1.0, 1.5 or 2.0 W/cm^2. Twenty-four subjects were split into two treatment groups, 1 MHz and 3 MHz. Internal tissue temperatures were measured every 30 seconds by two independent thermistor needles inserted into the medial muscle belly of the left triceps surae. The 3 MHz group had the thermistor needles inserted to depths of 0.8 cm and 1.6 cm. Due to the 1 MHz slower attenuation, the thermistor needles were inserted to 2.5 cm and 5 cm. Intensity selection was randomized during each trial with time off to allow tissue to return to baseline temperature. The remaining parameters were consistent for both ultrasound groups; 10-minutes treatment time, treatment area

was 2x the ERA, and 2-3 cm/s transducer velocity. A significant difference between the frequency was noted for the tissues heating rate when the other parameters were controlled, 1 MHz [$F_{3,33}$= 131.57, $P < .001$] and 3 MHz [$F_{3,33}$ = 41.59, $P < .001$]. A heating rate of 0.58°C/min occurred with the 3 MHz frequency compared to a 0.16°C/min heating rate with a 1 MHz frequency. Furthermore, the 3 MHz frequency heated significantly faster than the 1 MHz frequency for all intensities. Additionally, no significant difference existed between the two depths (half-value and 2-times the half-value), suggesting that Draper et al[3] may not have adjusted for the different tissue types in the area to be treated or tissue differences between subjects.

To investigate a deeper half-value depth, Hayes et al[4] re-examined the thermal change for 1 MHz and 3 MHz at a 2.5 cm depth. Eighteen subjects were given a 1 MHz or 3 MHz treatment with a 1.5 W/cm^2 intensity or a sham treatment with the machine turned off. The treatment duration lasted until one of the following criteria was met: total treatment duration of 10 minutes, the intramuscular temperature remained stable for a full minute, subject discomfort occurred, a 4°C temperature increase occurred, or an absolute intramuscular tissue temperature of 40°C was reached. Hayes et al[4] used the Theratouch 7.7 ultrasound unit with a 5.5:1 BNR and 5 cm^2 Therapy Hammer transducer with a 5 cm^2 reported ERA. The transducer was moved at a rate of 3-4 cm/s during each trial. Tissue temperatures were recorded every 10 seconds by Type-T thermocouples inserted into the medial triceps surae. In the group that received the 3 MHz treatment, an increase of 4°C was reached at 3.35 ± 1.23 minutes, but absolute intramuscular tissue temperature of 40°C was reached at 4.13 ± 1.69 minutes. An acoustical intensity of 1.5 W/cm^2 with 3 MHz frequency heated at a rate of 1.19°C per minute, whereas the 1 MHz

frequency heated at a rate of 0.13°C/min. The 1 MHz ultrasound differed from the theoretical 0.9°C/minute increase calculated based on a heating rate method based on Draper et al.[3]

Frequency and depth of wave penetration share an inverse relationship. The 1 MHz frequency can penetrate up to 5 cm, while 3 MHz reach depths of 2 cm to 3cm.[3] Although 3 cm has been reported in the literature for 3 MHz frequency, textbooks[22,26-27] recommend 3 MHz for tissues up to 2-2.5 cm depths. This variation may be due to variation within body composition; however, this was not addressed within the literature. Draper et al[3] found 3 MHz heated three times faster than 1 MHz, which is significantly different from Hayes et al,[4] who found 3 MHz heated 10 times faster than 1 MHz. The Dynatron manual[42] states 2 MHz should be used for medium depth tissue around 2.6 cm; however, limited research exists regarding the depth and rate of heating at a 2 MHz frequency. The appropriate frequency selection depends on target tissue depth, the desired thermal increase, and the rate at which the temperature increase occurs.

Intensity

While the frequency options are limited by the machine design, the intensity or strength of the soundwave typically has a wider range of available selections. Intensity is expressed as W/cm^2. Watts (W) represents the average power output or spatial average intensity (SAI) of the centimeter squared (cm^2), which represents the ERA of the transducer. The acoustical intensity in most ultrasound machines may be modified by 0.1 W/cm^2. Depending on the unit, the intensity may be able to be increase up to 4.0 W/cm^2.[14] A direct relationship exists between intensity and tissue temperature during continuous duty cycle treatments. As the intensity increases, there is a corresponding thermal increase in the tissue.[22,26-28] The Draper et al[3] results demonstrated this direct relationship when using the Omnisound 3000™. Thermal change was demonstrated between all four intensities (0.5, 1.0, 1.5, and 2.0 W/cm^2). Draper et al[3] reported

0.5 W/cm^2 intensity at a 1 MHZ frequency increased tissue temperature by 0.04°C/min; 1.0 W/cm^2 intensity at the same frequency increased tissue temperature by 0.16°C/min; 1.5 W/cm^2 caused an increase of 0.33°C/min; and 2.0 W/cm^2 increased at 0.38°C/min. Similar results were observed with the 3 MHz frequency which demonstrated an increase in tissue temperature of 0.3°C/min with 0.5 W/cm^2 intensity; 1.0W/cm^2 produced a 0.58°C/min increase; 1.5 W/cm^2 increased at 0.89°C/min; and 2.0 W/cm^2 increased by 1.4°C/min. Draper et al[3] demonstrated the linear relationship between an increase in intensity and a corresponding increase in tissue.

Leonard et al[5] evaluated thermal changes during a 10-minute continuous ultrasound using 1 MHz frequency for the same four intensities (0.5, 1.0, 1.5, and 2.0 W/cm^2) used by Draper et al.[3] The Rich-Mar Theratouch 7.7 ultrasound device was used, which had a manufacturer reported 5.5:1 BNR and a 4.5 cm^2 ERA. Each subject took part in four different ultrasound intensity treatments, 24 hours between each treatment. The tissue temperature for the medial calf was collected every 10 seconds with type T thermocouples inserted to a depth of 4 cm. A total of 19 subjects were included in the study. However, four subjects discontinued the 2.0 W/cm^2 intensity trial, and one subject discontinued the 1.5 W/cm^2 trial due to discomfort. A statistically significant difference occurred among the four different intensities ($F_{3,36} = 3.94$, $P = .014$, $1-\beta = .795$). Specifically, the 1.0 W/cm^2 demonstrated an increase of temperature of 1.9°C (35.4°C baseline to 37.3°C). Whereas 2.0 W/cm^2 increased by 0.7°C (35.4°C baseline to 36.1°C), which was expected to heat at a greater rate than the 1.0 W/cm^2 intensity. There is limited explanation for the unexpected difference, further research into why 1.0 W/cm^2 heated at a greater rate than 2.0 W/cm^2.

An increase in intensity does not appear to relate to treatment depth. Three MHz had no significant differences in maximum temperature reached between 0.8 cm and 1.6 cm tissue depth

for the intensities evaluated ($F_{1,11} = 3.60$, $P = .084$).[3] Furthermore, there was no significant difference between to 2.5 cm and 5 cm depths with 1 MHz ($F_{1,11} = .00$, $P = .987$).[3] Draper et al[3] indicated that an increase in intensity relates to an increase in temperature. Three MHz frequency at a 0.5 W/cm^2 intensity increased tissue temperature by 0.3°C/min and at a 2.0 W/cm^2 intensity tissue temperature increased by 1.4°C/min.[3] One MHz frequency at a 0.5 W/cm^2 intensity increased tissue temperature by 0.04°C/min and at a 2.0 W/cm^2 intensity there was an increase of 0.38°C/min.[3] However, Leonard et al[5] showed that the 1 MHz frequency at an intensity of 1.0 W/cm^2 increased intramuscular tissue greater than the 2.0 W/cm^2 intensity at a uniform depth of 4 cm. Further research is needed to explore why the temperature did not increase as predicted. One area for further exploration is the variation in the BNR between the Omnisound 3000™ (1.8:1 BNR) and the Rich-Mar Theratouch 7.7 (5.5:1 BNR). However, it is unknown if other manufacturer differences occur in other ultrasound units that would influence intensity's relationship to thermal change.

Duty Cycle

Ultrasound machines can produce the acoustical frequency continuously or for a set percentage of time during a treatment called a duty cycle. The duty cycle is the fraction of time the ultrasound machine generates waves over one second and is represented as a percentage or as a ratio of energy production and off period.[22,26-27] Limited ultrasound machines allow the clinician to enter any percentage from 1-100. Most manufacturers allow for specific duty cycles in pre-programmed settings, such as 20, 50, and 100%.[25,35]

Limited literature exists evaluating the thermal effect of the pulsed duty cycle. A study by Gallo et al[6] compared the intramuscular temperature change after a pulsed ultrasound versus continuous ultrasound with mathematically equivalent spatial average temporal average (SATA)

intensity. The Omnisound 3000™ was used with a reported 3.8 cm^2 ERA and 3.6:1 BNR. The intramuscular temperatures in the medial gastrocnemius were evaluated at a 2 cm depth. A cross-over design was used for the 16 subjects with a rest period between each 10-minute trial. One trial evaluated 3 MHz, 1.0 W/cm^2, 50% duty cycle for treatment parameters and the other trial used 3 MHz, 0.5 W/cm^2, at 100% duty cycle. The two treatment protocols should theoretically produce identical temperature changes by maintaining the same time and frequency but modifying the intensity and duty cycle. The 100% duty cycle at a 0.5 W/cm^2 intensity produced a 2.8°C ± 0.8 temperature increase, and the 50% duty cycle at 1.0 W/cm^2 intensity produced a 2.8°C ± 0.7 temperature increase. When comparing pulsed to continuous duty cycles no significant differences were reported across the variables; a statistical comparison of the duty cycle reported an intercept of 0.078°C ($t = 0.31$, $P = .76$), difference in slopes was 0.034°C/min ($t = 1.33$, $P = .19$), and for difference in quadratic effect was 0.00095°C/min^2 ($t = –.42$, $P = .68$). Therefore, a relationship can be inferred between intensity and duty cycle relates to tissue temperature increase.

Duty cycle and spatial average intensity (SAI) work to produce a specific therapeutic effect. SATA intensities are determined by multiplying SAI by the duty cycle.[26] If the SATA is equivalent between two treatments with the same treatment duration and frequency, the heating outcomes should be identified as reported by Gallo et al.[6]

Effective Radiating Area (ERA) and Beam Nonuniformity Ratio (BNR)

Due to the design and crystal quality of the unit, ERA and BNR have a relationship to the heating rates of various ultrasound machines. Federal regulations require manufacturers to print ERA and BNR directly on the transducer. In addition, the Food and Drug Administration Department of Health and Human Services[30] has established performance standards for ultrasonic

radiation-emitting products. The 2018 standards state continuous wave waveform ultrasound unit shall not exceed ≥ 20% error for all emissions ≥10% of the maximum emission. This error translates to a possible 50% differential between two ultrasound transducers of the same make and model.

Johns et al[43] compared the intra-manufacturer and inter-manufacturer differences in ERA, power, and SAI for new transducers. Six different transducer manufacturers (Chattanooga 78047, Dynatron 300-5, Mettler ME7513, Omnisound 3000™, Rich-Mar C-4, and XLTEK UL-5) were included in the study for a total of 66 transducers. The transducers were calibrated to within ± 15% of the manufacturer's guidelines. A standardized electrical supply was used to power the transducers to eliminate variability in manufacturer design. Measurements of SAI, ERA, and power were analyzed for variance. Intra-manufacturer variability in SAI ranged from 16% to 35%, and inter-manufacturer variability ranged from 22% to 61%. Five of the six manufacturers had a difference between the manufacturer's stated ERA and the measured ERA. The Omnisound 3000™ was the only transducer aligned with the manufacturer's ERA. The wide range of variability could account for the inconsistent reported biological effects and overall ultrasound effectiveness as a therapeutic intervention within the literature.

The beam nonuniformity ratio is calculated by taking the average spatial intensity of the ultrasound beam across the ERA and dividing by the peak spatial intensity of the ultrasound beam (BNR = spatial peak intensity / average spatial intensity). Fluctuation within the ERA will affect the reported BNR. The studies previously discussed note ultrasound units reported different BNRs. When using the Omnisound 3000™[34] lists the BNR as <5:1, which implies differences exist between units. Individual BNR are a product of proper calibration. Draper et al[3] and Chan et al[44] reported a BNR of 1.8:1 compared to Gallo et al[6] with a 3.6:1 BNR. Miller et al[7]

reported differences in BNR were different frequencies where used, 1 MHz had a 2:1 BNR and 3 MHz had a 3:1 BNR. Therefore, BNR should be not only a factor between manufactures but within manufacturers.

While the reported BNR are different between Draper et al[3] and Miller et al,[7] this appears to cause a limited impact on the reported thermal increase. Miller et al[7] examined the temperature differences 2x ERA with 1 MHz and 3 MHz frequencies. The Omnisound 3000™ was used with a 5 cm^2 transducer and a reported 2:1 BNR for 1 MHz and 3:1 BNR for 3 MHz. Two thermocouples were inserted into the triceps surae muscle group to measure the thermal change at the midpoint and outer edge of the treatment area. A 2.5 cm depth was used for the 1 MHz treatment group and 1.0 cm depth for the 3 MHz treatment. Ten subjects completed the protocol, which used continuous ultrasound at 1 MHz with a 1.5 W/cm^2 intensity for 10 minutes, followed by the 3 MHz at 1.0 W/cm^2 for 10 minutes with a minimum of 48 hours between treatments. The 1 MHz elicited a tissue temperature increase of 2.62°C at the center of the treatment area but only increased by 1.58°C at the outer edge. In the 3 MHz trial, the treatment protocol produced a 5.88°C temperature increase at the midpoint but only a 3.64°C increase at the outer edge of the treatment area. Draper et al[3] reported a temperature increase of 0.58°C/min while Miller et al[7] 0.588°C/min for 3 MHz frequency at a 1.0 W/cm^2 intensity with a difference of 1.2 BNR. In the 1 MHz with a 1.5 W/cm^2 trial, Miller et al reported a 0.262°C/min compared to Draper et al[3] temperature increase of 0.3°C/min. However, a 0.2 BNR difference was reported between the studies. The difference in BNR could explain the difference in temperature increase. A low BNR means the crystal expands and contracts uniformly, transmitting the vibrations evenly. The larger difference in BNR seen with the 3 MHz should have resulted in a similar discrepancy. There

may be a further relationship that must be considered between frequencies and BNR to thermal effect than previously explored.

Similar to the SAI and duty cycle relationship, the quality of the BNR and ERA affects the SAI. These quality changes, in turn, affects the thermal outcome of a specific treatment.[6] Any variation within the BNR and ERA can affect the thermal outcome even between the same manufacturer using the same treatment duration, frequency, and duty cycle.[31]

Treatment Area

There is a direct relationship between the ERA, treatment area, and the increase in tissue temperature which is elicited by an ultrasound treatment. Chan et al[44] examined two different treatment areas to explore this relationship based on the reported 4.5 cm^2 ERA. A 4-minute ultrasound was performed at a 3 MHz frequency and 1.0 W/cm^2 intensity with the Omnisound 3000™, 4.1 cm^2 ERA, and a 1.8:1 BNR. The trial which used a treatment area 2x the ERA, reported an increase in patella tendon temperature by 8.3°C ± 1.7°C (2.06°C/min ± 0.43). However, in the trial which used the treatment area 4x the ERA there was an increase temperature of 5.0°C ± 1.0°C (1.25°C/min ± 0.25). Results suggested that the treatment areas should be limited to 2x the ERA to maintain consistent temperature increase within the tissue.

To further support the importance of treatment size, Garrett et al[31] examined an increased treatment size and the subsequent thermal changes in muscle tissue. Garrett et al[31] compared the heating rate between an ultrasound and a drum diathermy. To accurately compare the diathermy to ultrasound, the ultrasound treatment area was 40x the ERA (200 cm^2 surface area/5 cm^2 head). Sixteen subjects participated in the study and had three thermistor microprobes inserted into the medial aspect of the triceps surae muscle at a depth of 3 cm and spaced 5 cm apart. Ultrasound was administered with the Omnisound 3000™, 4.1 cm^2 ERA and 1.4:1 BNR, at a 1 MHz

frequency and 1.5 W/cm^2 intensity for 20 minutes. After the tissue returned to its baseline temperature, a 20-minute pulsed short-wave diathermy treatment was administered with 800 bursts per second, 400 microsecond burst duration, 850 microsecond interburst interval, peak root mean square amplitude of 150 W per burst, and an average root mean square output of 48 W per burst. Results indicated diathermy heated the calf muscle significantly more than ultrasound ($F_{1,75} = 409.59$, $P < .0001$). Diathermy had an average temperature increase of 3.02 ± 1.02, 4.58 ± 0.87, and 3.28 ± 1.63 at the thermistor microprobes sites. The average temperature increase for the ultrasound was 0.17°C ± 0.40°C, 0.09°C ± 0.56°C, and -0.43°C ± 0.41°C at the thermistor microprobes sites. Theoretically, the Omnisound 3000™ with parameters of 1 MHz at 1.5 W/cm^2 for 20 minutes should have elicited a 6°C thermal increase if the treatment area was 2-3 times the ERA.[3] Therefore, it could be assumed that the diminished thermal change has a link to the large treatment area.

Miller et al[7] examined the temperature differences with a treatment area 2x the transducer head size using both 1 MHz and 3 MHz frequencies. The Omnisound 3000™ was used with a 5 cm^2 transducer and a reported 2:1 BNR for 1 MHz and 3:1 BNR for 3 MHz. Two thermocouples were inserted into the triceps surae muscle group to measure the thermal change at the midpoint and outer edge of the treatment area to a 2.5 cm depth for the 1 MHz treatment group and 1.0 cm depth for the 3 MHz treatment. Ten subjects were included in the study. The first treatment was a continuous 1 MHz frequency at 1.5 W/cm^2 intensity for 10-minutes. A minimum of 48 hours was required between treatments. The second ultrasound treatment used continuous 3 MHz frequency at 1.0 W/cm^2 intensity for 10-minutes. Results indicated a temperature increase of approximately 2.62°C (0.262°C/min) at the midpoint and 1.58°C (0.158°C/min) at the outer edge of the 1 MHz treatment area. At 3 MHz, a similar phenomenon occurred at the center of the treatment area; the

tissue temperature increased 5.88°C, but the outer edge 3.64°C increased. The conclusion was that the center of the selected treatment area would receive the highest concentration of acoustical energy if the treatment was performed at a consistent rate and pattern.

In summary, the literature[7,31] suggests an inverse relationship between treatment size and thermal change; the rate of thermal change decreases as the treatment size increases. The recommendation for selecting a treatment size is to treat an area two to three times the transducer ERA or twice the size of the transducer plate for consistent and predictable thermal change at the center of the treatment area.[22,26-27]

Transducer Velocity

Early therapeutic ultrasound protocol recommended a stationary transducer during treatments. However, Haar et al[45] evaluated blood vessels and myometrium of a mouse uterus. Both a control tissue and mouse tissue were exposed to a static 3 MHz frequency at 2 W/cm^2 intensity for 15 minutes. The control and experimental tissues were excised from the mouse immediately after irradiation or after a delay of 10 or 20 min. The static ultrasound tissue showed damage to the blood vessels in the mouse tissue sample, specifically the endothelial cells of the uterine vessels, and in some cases extravasation of erythrocytes occurred. Kerr et al[46] also evaluated damage that occurred during the static ultrasound but in the veins of a pig's ear. Treatment was conducted with 0.75 MHz and1.5 W/cm^2 intensity for an undisclosed length of time. The veins were then examined under an electron microscope. Notable gaps developed between the endothelial cells and showed fine perforations in the cell membrane. Extensive blood clots were found in which erythrocytes became more spherical and damaged the membrane. Following Haar et al[45] and Kerr et al[46] publications, the recommendation has been to continuously move the transducer during all ultrasound treatments.

Although there has been the recommendation to move the transducer, the velocity or rate at which it should be moved is unclear. Draper et al[3] demonstrated a direct relationship between continually moving a transducer and decreased heating rates in the tissue. The details of the full study have been outlined previously. However, the results indicated a 35% lower temperature change than initially theorized by Haar.[3,47] Based on the research conducted by Haar[47] in 1978, an intensity of 0.25 W/cm^2 at a frequency of 1 MHz would produce about 1°C increase if the transducer were held stationary over a poorly vascularized area of soft tissue for 5 minutes. Although intensity of 0.25 W/cm^2 was not examined by Draper et al,[3] a 1 MHz with an intensity of 0.5 W/cm^2 reported an increase of 0.04°C/min in muscle tissue or an estimated 0.2°C increase over a 5-minute treatment. The difference may be attributed to the change from a stationary transducer to a moving transducer. A stationary transducer has a concentrated treatment area of 1x ERA, where ultrasonic energy would continue to accumulate kinetic. Depending on the treatment location, tissue vascularity could further compound the accumulation of kinetic energy and the subsequent tissue temperature increase. As previously stated an inverse relationship exists between treatment size and thermal change, as the treatment size increases the thermal change decreases.[43-44] Therefore, if the ultrasound transducer is continuously moved compared to stationary, there would be a subsequent increase in the treatment area, which would explain the thermal decrease.

Only one study has been performed to examine the effect of transducer velocities on tissue heating. Weaver et al[8] evaluated three different transducer velocities (2-3, 4-5, and 7-8 cm/sec) applied to the medial triceps surae. The Omnisound 3000™, with a 2.1:1 BNR and manufacturer reported 5 cm^2 ERA, delivered 10-minute treatments at a 1 MHz frequency and 1.5 W/cm^2 intensity. Eleven subjects received consecutive ultrasound treatments at the given

velocity (2-3, 4-5, and 7-8 cm/sec) controlled with a metronome. A template twice the transducer head width was used to create a treatment area size that would be consistent across subjects. Although the three treatments were conducted consecutively, the subject's muscle temperature had to return to within 0.3°C of the pre-treatment for 5 minutes after each trial before the next trial could begin. There was a significant main effect for treatment time (F1,10 = 155.68, P <0.00001). A significant thermal increase was reported with an average increase of 5.1°C, pre-treatment 37.8°C ± 0.8°C to post-treatment thermal 42.9°C ± 1.9°C. However, no significant effect was seen for transducer velocity ($F_{2,20} = 0.07$, $P = 0.93$) and no significant interaction was found ($F_{2,20} = 0.33$, $P = 0.72$).

There is evidence that the static delivery of acoustical energy can cause damage to tissue, and the continuous movement of the transducer can limit the adverse effects.[45-46] No significant difference has been reported in the rate of heating between velocities ranging from 2-8 cm/sec.[8] However, a formal recommendation should not be made based off of only one study with no parameter variation in the treatment protocol. Further research is needed to investigate different parameter variations on transducer velocity and tissue damage.

Treatment Time

The final primary parameter to consider is treatment time, the least defined in the literature. For this review, the treatment time will be operationally defined as the total time the tissue is receiving active ultrasound energy in a single application. Selection of the appropriate treatment time is dependent on several factors: desired thermal change,[3,22,26-27] intensity,[3,5] frequency,[3-4] and treatment area.[3,7,44]

The method commonly used in clinical practice to calculate a predicted tissue temperature increase during treatment, using a known frequency and intensity to determine the

heating rates per minute (Table 1).[3] The heating rates per minute are then multiplied by the treatment's total time, which equals the total predicted thermal change. The treatment time is adjusted to reach a specific tissue temperature increase (1°C, 2°C, or ≥ 4°C).

Table 1. Temperature Increase Per Minute [3,22,26-27]

Intensity (W/cm^2)	1MHz	3MHz
0.5	0.04°C	0.3°C
1.0	0.2°C	0.6°C
1.5	0.3°C	0.9°C
2.0	0.4°C	1.4°C

The literature highlights treatment times reliance on tissue type and other parameters. In the clinical setting, De Brito Vieira et al[29] examined the use of therapeutic ultrasound among 55 clinical physical therapists. Survey results indicated the participants understood ERA. Furthermore, participants demonstrated knowledge of the relationship between the treatment time and the rate of heating. However, the typical treatment time regardless of condition or other parameter settings ranged between 2-4 minutes. This discrepancy in knowledge and clinical application, led De Brito Vieira et al[29] to determine that the knowledge exhibited by the respondents was not entirely satisfactory regarding the rationale for ultrasound parameter selection.

Although the interconnection between treatment time and other parameters is clear in the literature, the time the tissue is exposed to acoustical energy has not been considered a factor in the literature. Further research is needed to determine if treatment duration has a significant effect on tissue response other than as a factor for delivering a specific thermal increase.

Treatment Duration

Like treatment time, selecting the appropriate treatment duration depends on additional factors not clearly defined in the literature. Treatment duration is operationally defined as the

total number of consecutive ultrasound applications to the same area over the course of days or weeks.[26] The first text to recommend limiting ultrasound treatments was published in 1964 by Summer and Patrick,[48] which stated the actual number of treatments of ultrasound would variable depending on the condition. However, the total number of ultrasound treatments should be limited due to a concern in the reduction of erythrocytes and leukocytes and an ensuing loss of body weight. No references or other evidence to support these claims were in the 1964 textbook at publication. Research conducted between 1974 and 1989 led to the recommendation for moving the transducer to avoid adverse effects like cell damage caused by the transducer held in a static position.[45-46] However in 1991, Gann[49] stated ultrasound should be discontinued after three or four applications if there were no positive clinical effects. This recommendation was made based on the Summer and Patrick[48] 1964 text.

The implication of a cumulative dose-response is unclear, with no guidance for safe clinical application. Limited evidence supports or discredit the recommended a specific treatment duration. Therefore, further research is needed to examine the hematologic changes in healthy tissue and address the appropriate treatment duration for the optimal biophysical effect.

Biophysical Effect

Considerations for safety and effective outcomes of an ultrasound treatment may be condition specific. The ultrasound wave delivered to the tissue elicits non-thermal or mechanical effects regardless of the vibration rate of the molecules. The pulses of acoustical energy cause microstreaming and cavitation, which are the result of the mechanical movement of the soundwave on the cells or fluid around the cells.[50-51] The biological effect of microstreaming is caused by a one-directional movement capable of affecting ions and small molecules along and around cell membranes. In addition, cavitation occurs as the sound waves pass through the

tissue, and compression and refraction occur in the tissues causing microscopic gas bubbles to contract and expand.[50-51] Early non-thermal studies completed by Dyson et al[51] and Haar et al[45] reported that if an animal blood vessel is exposed to static waves, the blood cells will pack together into bands spaced at half-wavelength intervals. These bands will remain stationary while the blood plasma continues to flow, and cells can move from band to band in the same direction as normal blood flow. Starkey[27] advises using a pulsed output (20% to 25% duty cycle) with typical intensities or using a continuous (100% duty cycle) and a low-output intensity (below 0.3 W/cm^2) in treatments where the practitioner only wants to elicit mechanical changes.

Unlike mechanical changes, which will occur in all ultrasound treatments, thermal ultrasound treatments have a measurable outcome. The internal tissue temperature increase is the measurement of kinetic energy transfer between acoustical beams interacting with the tissue. Early research into thermal ultrasound indicated tissue temperature had to reach 39.6°C or higher to display physiologic thermal changes.[52-54] Due to differences in the individual's baseline muscle temperature when referring to thermal effects of ultrasound, relative change from baseline is the gold standard for evaluating thermal change. Therefore, mild heating can be considered an increase of 1°C, moderate heating is an increase of 2°C to 3°C, and an increase $\geq$ 4°C is considered vigorous heating.[26-27] Thermal ultrasound recommendations in textbooks[26-27] are correlated to physiological effects. Tables 2 and 3 describe the effects and temperature increase necessary to obtain the desired effect.

Table 2. Temperature Increases Theorized to Bring About Desired Effect[26]

Temperature increase	Effect
1.8°F (1°C) (mild heating)	Increase metabolism, reduces mild inflammation
3.6-5.4°F (2-3°C) (moderate heating)	Reduce pain and muscle spasms, increase blood flow
7.2°F (4°C) (vigorous heating)	Increase ROM and tissue extensibility

Table 3. Temperature Increase Required to Achieve Specific Therapeutic Effects During Ultrasound Application[27]

Classification of ultrasound	Temperature increase	Used for thermal effects
Mild	1°C	Mild inflammation Accelerating metabolic rate
Moderate	2-3°C	Decreasing muscle spasm Decreasing pain Increasing blood flow Reducing chronic inflammation
Vigorous	4°C	Tissue elongation, scar tissue reduction Inhabitation of sympathetic activity

Inconsistencies occur in textbook recommendations[22,26-28] regarding thermal effects and the subsequent biophysical changes. Textbooks[26-27] agree that mild heating can increase metabolism and affect inflammation. Furthermore, the textbooks[26-27] consistently state that moderate heating could reduce pain, muscle spasm and increase blood flow. However, Starkey[27] reported that moderate heating can also reduce chronic inflammation. According to Knight and Draper,[26] vigorous heating affects tissue extensibility and range of motion. Starkey[27] agreed that vigorous heating affects tissue extensibility but it may also affect scar tissue reduction and inhibition of sympathetic activity. The difference may be due to publication date or relevant literature; however, no specific citations were given for the recommendations.

Tissue Extensibility

The recommended thermal increase of 4°C has been well established within the literature to affect tissue extensibility.[26-27] Davis' Law describes how soft tissue models according to imposed demands similar to stretching. A relationship exists between low force long-duration stretching and increasing tissue temperature to produce significantly greater residual elongation in tissue.[52]

Early research into tissue extensibility focused on the length-tension curve of a tendon, which was represented by a normal distribution with resting length on the x-axis versus the tension or force development on the y-axis.[53] An outside tension placed on the tissue will increase in potential force development until the force generation potential peaks, followed by a decreased potentiation force with further stretch until tendon failure.[53] In 1954, Gersten[54] conducted the first study to evaluate the length-tension ratio related to ultrasound effect on increased tendon extensibility. Gersten[54] treated frogs' Achilles tendons with Ringer's solution (commonly composed of sodium chloride, potassium chloride, calcium chloride, and sodium bicarbonate in the concentrations to match the body's natural fluids). The Birtcher model U ultrasound unit with a 7 cm^2 transducer plate was used during the experimental trials. The tendons in the experimental group were exposed for 3-minutes to a stationary pulsated ultrasound treatment at a 1 Mc (0.000001 MHz) and a frequency between 1 and 3 W/cm^2 intensity. The controlled tendons received no ultrasound or sham treatment. The length-tension curves were found by attaching one end of the tendon to a steel bar, which was attached to four strain gauges, and the other end of the tendon was clamped to a moveable steel bar. By moving the steal bar, the final length of the tendon was measured using calipers. The resting length had a reference value of 100, and the absolute tension was measured in grams. The tension at the final altered length was measured by the strain gages coupled with an amplifier. The results indicated that the length-tension ratio had a linear relationship to temperature. As the temperature increased, the extensibility did as well. Furthermore, the results indicated a progressive thermal increase as the intensity increased (Table 4). Also, a progressive increase occurred in tendon extensibility as ultrasound intensity increased. Although the parameters do not align with modern

frequency recommendations and the subject tissue is non-human, the results demonstrated that a thermal effect may be needed if the treatment goal is to increase the extensibility of the tendon.

Table 4. Intensities Effect in Frog Tendons[54]

Intensity	Thermal change	Absolute Tension	Length Tension Ratio
1.0 W/cm^2	39.6°C ± 0.22	0.29g	0.35
2.0 W/cm^2	43.4°C ± 0.21	0.50g	0.50
3.0 W/cm^2	47.5°C ± 0.76	1.92g	1.92

Stretching Window

In 1995, three studies examined different aspects of tissue extensibility. All three studies used the Omnisound 3000™ with a 5 cm^2 transducer plate, reported 1.8:1 BNR, and reported 4.5 cm^2 ERA.[9-10,44] Draper and Ricard[9] examined the optimal stretching window in 20 human subjects. The methodology is based on vigorous heating, causing an increase in tissue extensibility. Thermistors were placed in the left triceps surae muscle belly at a 1.2 cm depth. The intermuscular thermistor recorded thermal change. Ultrasound was applied using a template two times the ERA at a frequency of 3 MHz and 1.5 W/cm^2 intensity for 6 minutes on average. All treatments were discontinued once the tissue reached a 4°C intramuscular increase resulting in different treatment times between trials. The baseline temperature was recorded as 33.8 ± 1.3°C, which increased to 39.1 ± 1.2°C following the ultrasound application. Therefore, the average intermuscular increase was 5.3ºC with a thermal decay of 18 ± 3.5 minutes post-treatment for the tissue temperature to return to baseline. The tissue temperature dropped a degree at different time points, reported in minutes: seconds: 1°C = 1:20; 2°C = 3:22; 3°C = 5:50; 4°C = 9:13; 5°C = 14:55; 5.3°C = 18:00 (baseline). Once temperatures reached baseline, the tissue temperature continued to drop at a rate of 0.08 ± 0.05°C per minute until stabilized at a temperature below the baseline. Therefore, the tissue was at an optimal temperature for

extensibility, approximately 3.3 minutes following the conclusion of the ultrasound treatment. Furthermore, the window may be extended to 5.5 minutes if the stretch is applied during the heating process.

Rose et al[10] conducted a study using the same methodology and sample size as Draper and Ricard.[9] The difference in the study by Rose et al[10] was that a 1 MHz frequency was used and the intramuscular thermistors were inserted to 2.5 cm and 5 cm depth to adjust for the frequency half-value depth. Ultrasound was applied 2x the ERA using a 1.5 W/cm^2 intensity for an average treatment time of 10-12 minutes (treatment was discontinued once the temperature had increased 4°C at a depth of 2.5 cm). Post-treatment thermal decay took 21.4 ± 4.8 minutes before the tissue returned to baseline. At the 2.5 cm depth, the tissue temperature decay was reported in minutes: seconds for the following times: 1°C = 2:34; 2°C = 6:35; 3°C = 12:10; and 4°C = 21:14. At the 5 cm depth, the tissue temperature decay was reported: 1°C = 2:31; 2°C = 6:50; 3°C = 14:32; and 4°C = 27:49. The observed difference between the two depths indicated that deeper tissue cooled slower than superficial tissue after a 1 MHz ultrasound. Furthermore, the thermal decay of 1 MHz ultrasound was slower than 3 MHz. Limited conclusions can be made about tendon elasticity as neither Rose et al[10] or Draper and Ricard[9] formally evaluated a change in length-tendon ratio.

Due to the dense collagen makeup and low vascularization of tendons, it was theorized[36] that tendons would heat up faster and subsequently cool at a slower rate than muscle. Chan et al[44] used the Omnisound 3000™ with a 4.1 cm^2 ERA, 5 cm^2 transducer, and a 1.8:1 BNR, at a 3 MHz frequency and 1.0 W/cm^2 intensity to evaluate the change in the tendon. The continuous ultrasound treatment was limited to 4 minutes. Chan et al[44] evaluated two different radiuses based on the reported 4.5 cm^2 ERA. Eight subjects received an ultrasound treatment at 2x the

ERA, which increased the patella tendon temperature by 8.3°C ± 1.7°C (2.06°C/min ± 0.43). Another 8 subjects received a treatment 4x the ERA, which increased patella tendon temperature by 5.0°C ± 1.0°C (1.25°C/min ± 0.25). The tendon heated 3.45 times faster than predicted based on the muscle temperatures increases outlined in Draper et al.[3] The law of Grotthus-Draper explains that tendons are high in protein and absorb energy.[40] Additionally, tendons do not have the vast blood supply seen in muscles, thus making tendons less efficient at removing excess absorbed energy. However, the rate of thermal decrease was only significantly different during the first 5-minute interval post-treatment (2x the ERA = 0.9°C ± 0.3°C and 4x the ERA = 0.5°C ± 0.2°C). Therefore, the same 3.3-minute stretching window could apply to both muscles and tendons.

The literature supports a 3.3-minute stretching window for both muscles and tendons following an ultrasound treatment if tissue extensibility is the primary goal.[26-27,44] The literature supports the use of 3 MHz at 1.5 W/cm^2 for an average time of 6-minutes when treating muscle tissue. However, the parameter selection needs to be reduced or modified to continuous 3 MHz for 4 minutes at 1.0 W/cm^2 when treating tendon tissue. The available literature has limitations, including tissue type, sample size, and ultrasound manufacture standards (BNR and ERA). Only Chan et al[44] evaluated tendon tissue, the remainder of the literature evaluated the calf muscle. Further research is needed to explore if there is a difference in the stretching window due to modifications in parameter selection.

Range of Motion

Increased range of motion can be considered a measurable outcome of increased tissue extensibility. Ultrasound has been documented to cause a 4°C intramuscular increase, and the tissue temperature remains elevated in the therapeutic range for 3.3 minutes before decay

occurs.[9-10] However, the range of motion associated with the increase in tissue extensibility was not assessed by Draper and Ricard[9] or by Rose et al.[10] Within the literature there are limited studies that evaluated ultrasounds effect on range of motion as it relates to tissue extensibility.

To further understand the effect of thermal ultrasound on the range of motion, Knight et al[55] observed the cumulated effect of multiple ultrasound treatments over 6 weeks for ankle range of motion. Ninety-seven participants were randomly divided into 5 groups. All intervention groups were required to perform a 20 second static runner's stretch with a 10-second rest period 3 days per week, every other day, for 6 weeks for a total of 18 interventions. Group 5 received continuous ultrasound from a Sonopuls 434 unit set to 1 MHz frequency at 1.5 W/cm^2 intensity for 7-minutes prior to each static stretching session. The Sonopuls 434 with a 6.2 cm^2 transducer head and a manufacturer-reported 5.0 cm^2 ERA. The size of the treatment area was not indicated but was around the plantarflexor muscles.

Although no statistically significant differences were reported between the groups, the ultrasound group showed the greatest improvement in both active and passive dorsiflexion at the end of the 6-week intervention, as seen in Table 5. A p-value was not reported by Knight et al,[55] which limits replication and comparison of the study. Moreover, the lack of significant effect may have been due to a low thermal change due to the selected parameters. With an assumed treatment area of 2-3x the ERA, the predicted intermuscular thermal change elicited was $\leq$ 2.1°C in the plantar-flexor muscles.[3] It is unclear how adjusting the parameters would impact the study's outcomes. It may be argued that a significant effect might have been seen if internal tissue temperature reached vigorous heating of $\geq$ 4°C. Further research is needed to understand the effect of ultrasound on range of motion related to residual elongation in tissue.

Table 5. 6-Week Post Intervention Mean Differences Between Pretest and Posttest Measurements (in degrees)[55]

Group	AROM dorsiflexion	PROM dorsiflexion
Control (group 1)	1.11°	1.39°
Static stretching (group 2)	4.10°	6.11°
Active warmup (group 3)	4.16°	4.21°
Superficial heat (group 4)	4.38°	4.90°
Ultrasound (group 5)	6.20°	7.35°

Scar Tissue

Another suggested biophysical effect is the reduction of scar tissue with the application of ultrasound when a 4°C increase in tissue temperature is achieved. The literature supports the use of non-thermal ultrasound to increase tendon strength and collagen synthesis until 5 days post-injury.[56-57] However, little is known about the effect's ultrasound has on tissue after 7 days post-injury and through the remainder of the collagen remodeling process, where scar tissue may occur. The remodeling phase post-injury starts around day 8 and continues up to a year post injury. Collagen synthesis continues for at least 4 to 5 weeks after the initial injury.[58] The initially laid down collagen is fragile compared to the original tissue. At 1 week, a wound has only about 3% of its final strength. At 3 weeks, the strength improves to about 30% and 80% after 3 months. The initial collagen is reabsorbed, and thicker well-organized collagen is deposited in its place. These changes are accompanied by increased tensile strength, indicating a positive correlation between collagen fiber thickness, orientation, and tensile strength.[58]

To understand the effects of ultrasound on collagen fibril arrangement, Okita et al[59] focused on collagen fibril arrangement in the endomysium in immobilized limbs. The 17 rats in the experimental group had their legs immobilized for 4 weeks, receiving 24 ultrasound or sham treatments. The Ultrasound US-3 (Itoh Physiotherapy and Rehabilitation Ltd, Tokyo, Japan) was

used to deliver a continuous 15-minute 1 MHz frequency at a 1.0W/cm^2 intensity (3°C predicted thermal change based on the heating rate formula from Draper et al[3]). The process was repeated with the sham group, but the machine was turned off with the transducer head moved over the triceps surae muscle. The researchers reported a 6°C change in tissue temperature; however, no movement or stretch was applied to the tissue during the 4-week trial. Dorsiflexion was significantly decreased in all groups when compared to the control group. However, the ultrasound group reported higher dorsiflexion (81.3 degrees $\pm$ 6.1) than immobilization only (68.5 degrees $\pm$ 11.1) and sham groups (63.8 degrees $\pm$ 5.3). Electron micrograph of the collagen fibril revealed that the control and ultrasound groups had arranged along the longitudinal axis of the muscle fibers. In contrast, the immobilization and sham groups had fibers arranged in a circumferential pattern. However, there was no notable change in histological structure. It should be noted that prior immobilization studies have found the formation of cross-links which form in intramuscular collagen.[60] Okita et al[59] concluded that thermal ultrasound inhibited the formation of cross-links that negatively affected the muscle contracture, which produced scar tissue. In other terms, ultrasound may help limit the adverse side effects of immobilization. However, the mechanism that causes the change in collagen alignment is yet to be determined, and further research is needed into the mechanical effect or thermal effect of immobilized tissue.

Starkey[27] recommends > 4°C increase in tissue temperature to reduce scar tissue complications during healing. However, there is limited evidence support in the literature to recommends > 4°C. Rather a 6°C tissue temperature change was used in Okita et al[59] methodology. Furthermore, there is limited literature on collagen fibers past one week, which examined an increase in tissue temperature. Moreover, a human model should explore potential detrimental effects caused by an increase of 6°C.

Pain Management

There is a consistent recommendation for moderate heating, between 2-3^{o}C tissue temperature, to reduce pain due to the biophysical effect of ultrasound. However, Starkey recommends vigorous heating $\geq$ 4^{o}C, which inhibits sympathetic activity.[27] Theoretically, ultrasound applied at various intensities may affect nerves conduction through stimulation or inhibition. There are two main types of nociceptors, C-fibers and A-fibers, found in the human body. The A-fibers can be further categorized into A-alpha, A-beta, and A-delta. A-delta fibers are associated with acute pain and response to heat or weaker stimulus intensity. C-fibers respond to strong stimulus, associated with dull, longer-lasting pain. C-fibers are also considered polymodal and react to chemical, thermal stimuli, and mechanical stimuli resulting from physiological changes in the body like hypoxia.[61] One possible way ultrasound reduces pain is through sensory information from an A-beta fiber, stimulated by touch and vibration, which will inhibit the signal from A-delta and C-fibers from transmitting to higher centers in the brain. However, the literature on pain management varies widely in theories to explain pain threshold and pain control.

Nerve Conduction

In 1981, Halle et al[62] suggested that the mechanical effects of ultrasound did not play a significant role in affecting the nerve conduction latency linked to the thermal effects. Halle et al[62] used thermistors to evaluate the temperature change of the 10 subjects' forearms. Subjects were randomly assigned the order to receive an ultrasound and infrared treatment with a minimum of 3 days separated by 2 sessions. Nerve conduction latencies were recorded on a Teca Model TE4 or Teca Model B-2 EMG recorder. The stimulating and recording electrodes were placed along the superficial radial nerve, and a ground electrode was secured to the palmar

aspect of the wrist. The active electrode was placed over the superficial terminal branch of the radial nerve with the dispersive electrode attached over the belly of the first dorsal interosseous muscle. A 20-gauge thermistor was inserted between the two stimulating electrodes. A baseline was recorded for subcutaneous temperature and nerve conduction latencies, which used a stimulus of supramaximal intensity and a duration of 0.1 msec to create an action potential. The brand of ultrasound unit was not specified; parameters included: 1.0 W/cm^2, 1 MHz, continuous duty cycle for an average of 13.2 minutes. The intervention was discontinued once tissue increased by 1.2°C. A nonluminous infrared lamp, 66 cm, was administered for an average time of 7.5-minutes and was discontinued once tissue increased by 1.2°C. The treatments were interrupted after each 0.3°C increase to record the nerve conduction latency. The nerve conduction latency was significantly ($P < .001$) shorter when the nerve was heated to a temperature $\geq$ 1.2°C, however no significant difference between ultrasound and infrared was identified (Ultrasound group $t = 7.00$, $df = 9$; infrared group $t = 5.84$, $df = 9$).

Kramer[63] studied the association between a rise in tissue temperature and large afferent nerve conduction velocity. Nineteen subjects were included, each received six separate continuous ultrasound treatments, each at a different intensity: 0.5 W/cm^2, 1.0 W/cm^2, 1.5 W/cm^2, 2.0 W/cm^2 and 2.5 W/cm^2. The Burdick UTI 4300 ultrasound was used at a frequency of 0.87 MHz for 5 minutes over the ulnar nerve in the proximal forearm, which was 4.5x the ERA. The nerve conduction velocities varied between intensities (minutes/second): 0.5 W/cm^2 (2.23 m/s), 1.0 W/cm^2 (2.78 m/s), 1.5 W/cm^2 (3.15 m/s), 2.0 W/cm^2 (4.47 m/s) and 2.5 W/cm^2 (2.97 m/s). All intensities were significant for increased nerve conduction velocities ($P < 0.01$) except for 0.5 W/cm^2 ($p < 0.05$). The results indicated intensities above 0.5 W/cm^2 produced significant increases in nerve conduction velocity.

To further understand motor and sensory latencies, Moore et al[64] compared continuous and pulsed ultrasound effects on the median nerve. Five ultrasound treatment parameter protocols were included: (1) 1 MHz, 1.0 W/cm^2, continuous, 8 minutes; (2) 1 MHz, 1.0 W/cm^2, 50% duty cycle, 8 minutes; (3) 3 MHz, 1.0 W/cm^2, continuous, 8 minutes; (4) 3 MHz, 1.0 W/cm^2, 50% duty cycle, 8 min., (5) placebo, 0.0 W/cm^2, 8 min. All treatments were given on the same day with the Omnisound 3000™, a 2.0 cm^2 transducer with a reported l.5 cm^2 ERA and 3:l BNR for l MHz and 4:l BNR for 3 MHz. The treatment area was 6 cm in length by 4 cm in width to not exceed three times the ERA. The soundhead was moved at approximately 2 cm/sec during the treatment. The thermistor for subcutaneous temperatures was inserted into the mid-portion of the treatment area, medially to the palmaris longus tendon, above and medially to the median nerve. The nerve conduction was recorded using a Cadwell Sierra LT, 2 Channel Electromyograph (EMG) machine. Following each treatment condition, the subcutaneous tissue was returned to within 0.1^{o}C of baseline before beginning the next treatment. There were significant interactions for motor latencies [F (16,224) = 52.77, P < .001], sensory latencies [F (16,224) = 41.10, P < .001 J, and subcutaneous temperatures [F (16,224) = 52.77, P < .001]. Continuous ultrasound produced expected thermal effects, which caused a decrease in median nerve distal sensory latency and median nerve distal motor latency. The 3.0 MHz treatment produced faster temperature and latency changes than 1.0 MHz (Table 6). Pulsed ultrasound produced a similar change as the sham ultrasound for both intensities in median nerve distal sensory latency and median nerve distal motor latency. Moore et al[64] concluded alterations in nerve conduction are related to thermal effects, not by non-thermal or mechanical effects.

Table 6. Distal Motor and Sensory Mean Latency with Mean Temperature Change [64]

Group parameters (frequency, intensity, duty cycle, time)	Distal motor latency[a]		Distal sensory latency[a]		Tissue Temperature[b]	
	Pre	Post	Pre	Post	Pre	Post
1 MHz, 1.0 W/cm², 100%, 8 minutes	3.961 (0.234)	3.912 (0.222)	3.129 (0.192)	3.041 (0.190)	32.033 (0.708)	32.493 (0.948)
1 MHz, 1.0 W/cm², 50%, 8 minutes	3.963 (0.281)	4.047 (0.276)	3.163 (0.157)	3.233 (0.138)	32.053 (0.674)	30.887 (0.650)
3 MHz, 1.0 W/cm², 100%, 8 minutes	3.918 (0.204)	3.783 (0.208)	3.139 (0.138)	2.984 (0.126)	32.027 (0.708)	33.893 (0.701)
3 MHz, 1.0 W/cm², 50%, 8 minutes	3.935 (0.207)	4.033 (0.207)	3.132 (0.180)	3.201 (0.181)	32.047 (0.691)	31.033 (0.603)
placebo, 0.0 W/cm², 8 minutes	3.933 (0.233)	4.112 (0.223)	3.147 (0.178)	3.291 (0.166)	32.020 (0.719)	30.267 (0.713)

[a]All latency values are expressed as mean (msec) and (standard deviation)
[b]All temperature values are expressed as mean in (°C) and (standard deviation)

There is evidence to support ultrasounds' effect on increasing nerve conduction velocity with a subcutaneous temperature increase. The literature supports 3 MHz frequency, 1.0 W/cm^2 intensity, and 100% duty cycle for 8-minute treatment time.[64] These parameters supported by the literature for pain control would cause a predicted increase of 4.8°C based on the heating rate per minute.[3] Further research is needed to determine if increasing nerve conduction will assist or inhibit pain control.

Pain Threshold

The literature allows for a few possible explanations for ultrasound as a pain regulation. One explanation for an increase in pain threshold is due to thermal receptor activation from the tissue temperature increase. Mardiman et al[65] conducted a within-subject experiment, that evaluated pain threshold following an ultrasound treatment. The pain threshold was measured on both subject's arms (one for control and one for experimental) using a pressure dolorimeter. The pressure dolorimeter produced a dull, aching pain similar to many musculoskeletal conditions. The pain threshold was tested for a baseline and 2-minutes post-intervention. The Therasonic

Mark 3a with a 5 cm^2 transducer was used to deliver a continuous treatment of 1.1 MHz at 1.0 W/cm^2 for 5 minutes, estimated to elicit a thermal change of 1°C.[3,22,26-27] Eleven subjects reported warmth during the experimental ultrasound treatment. The results indicated a significant ($P < 0.05$) increase in pain threshold from baseline (1.53 $kg/cm^2 \pm 0.08$) to post-intervention (1.93 ± 0.12 kg/cm^2) treatment only on the dorsal aspect of the experimental arm. There were no changes to pain threshold of the control arm on the treatment site (1.49 ± 0.07 - 1.56 ± 0.08 kg/cm^2), in the experimental arm in an untreated site (1.95 ± 0.12 - 1.96 ± 0.13 kg/cm^2), or control arm in an untreated site (1.85 ± 0.13 - 1.94 ± 0.13 kg/cm^2). A possible explanation the researchers' proposed for the increase in pain threshold included heat activation of large diameter fibers (A-alpha and A-beta), limiting the dull pain (C-fibers) from transmitting to the second-order neurons.

To further understand the change in pain threshold, Schuhfried et al[66] evaluated supramaximal stimulation intensity of the superficial branch of the radial nerve. Twelve subjects were included in the study. The sensory antidromic nerve conduction velocity and sensory nerve action potential of the radial nerve in the forearm were assessed. Furthermore, the current intensity was increased slowly until the amplitude of the recorded potential reached a plateau to establish the supramaximal stimulation intensity. For conduction velocity determination, the latencies from the stimulation site to the onset of the initial negative deflection of the sensory nerve action potential were measured. The subjects received an ultrasound treatment and a placebo treatment on two days with a week between the treatments. A Sonostat 133 GBO (Medizintechnik, Rimbach, Germany) with 2.5 cm^2 transducer was used to deliver a 20% pulsed 3 MHz frequency at 1.0 W/cm^2 intensity for 5-minutes to the radial side of the forearm. A significant increase (6 ± 4 m/s, $P = 0.05$) in supramaximal stimulation intensity was detected. No

significant differences were found for sensory antidromic nerve conduction velocity and sensory nerve action potential. Schuhfried et al[66] hypothesized if nerve conduction velocity remained unchanged after a non-thermal ultrasound treatment, there could be an increase in the depolarization threshold (hyperpolarization).

Based on the current literature, an ultrasound protocol with a thermal outcome of 1℃ can be used to increase pain threshold. [65] Further research into pain threshold is needed to assess diverse treatment protocols that illicit different tissue temperatures.

Blood Flow

Textbooks[26-27] recommend moderate heating of 2°C to 3°C to stimulate an increase in blood flow. The literature addressing the effects of therapeutic ultrasound on blood flow can be divided into two time periods: early (1953-1995) and modern (1995 – present). Early studies employed occlusion plethysmography, which can identify a change in the volume of blood by alterations in the size of arteries or veins.[67-69] Modern technology used to identify changes in blood flow includes near-infrared spectroscopy and doppler ultrasound. Near-infrared spectroscopy measures changes in intramuscular hemodynamics and oxygen dynamics to determine changes in blood concentration. The limitation of near-infrared spectroscopy is that it can only detect 20 to 30 mm below the skin surface.[70] Doppler ultrasound uses acoustical waves sent into the tissue via a transducer. However, the high-frequency ultrasound waves bounce off the red blood cells sending waves back to the receiver, which provide information about the rate and volume of blood flow.[71] The difference in the outcome measures make it difficult to compare results between studies however there are limited conclusions that can be identified.

Blood Flow with Plethysmography

In 1953, Bickford and Duff[67] pioneered research in ultrasounds' effect on blood flow. Venous occlusion plethysmography was used to estimate blood flow rate during an ultrasound treatment in 26 humans. The Siemens Sonostat Universal Ultrasonic Generator, able to produce 0.2 W/cm^2 to 5.3 W/cm^2 at a set frequency of 0.8 MHz, was used to perform the ultrasound treatments with a 10 cm^2 transducer. However, parameter standards had yet to be established in the literature; therefore, the ultrasound treatments evaluated in the study varied in intensities, ranging from 2.0 to 3.5 W/cm^2, and the treatment time between 10 to 15 minutes. The specific combination of intensity and time was not outlined by Bickford and Duff.[67] There was no significant change in blood flow with the 2.0 W/cm^2 intensity. However, 3.0 to 3.5 W/cm^2 intensities produced an increase in blood flow (3.0-4.3 ml/100ml/min) with an intramuscular temperature increase of 1.8^{o}C at the 1.5 cm depth and 2.1^{o}C at the 3 cm depth. While Bickford and Duff[67] reported an increase in both blood flow and tissue temperatures, they concluded the increase in blood flow was not sustainable due to the subjects' severe and deep boring pain.

In 1991, Baker et al[68] explored blood flow increase and the lasting effects from different thermal therapies. An unknown number of human subjects reported for 7 separate sessions: 20-minute ice pack, an ice massage to the point of numbness, 5-minute ultrasound, an ice massage to the point of numbness followed by 5-minute ultrasound treatment, a 20-minute moist hot pack, and a 20-minute moist hot pack followed by a 5-minute ultrasound treatment, and control. Except for the control session, blood flow was measured with plethysmography up to 45-minutes after the application of the modality. The 5-minute ultrasound treatment using the Medcosonolator ultrasound at a 1.5 W/cm^2 intensity had no frequency specified. An increase occurred in blood flow following the moist hot pack and combination of the moist hot pack

followed by ultrasound compared to the control group. However, applying hot pack prior to an ultrasound treatment did not result in a significant increase in blood flow compared to just a moist hot pack. Additionally, ultrasound alone and ice followed by ultrasound had an increase in blood flow over the control.

In 1995, Robinson and Buono[69] followed the same protocol as Bickford and Duff[67] to evaluate blood flow in the forearm during an ultrasound treatment. However, data was collected with a strain-gauge plethysmograph, a blood perfusion monitor, and a laser-doppler flowmeter to measure changes in the blood flow. Twenty subjects received an ultrasound treatment of 1.5 W/cm^2 intensity at 1.0 MHz frequency for 5 minutes with the Chattanooga Intellect 205 with a 5 cm^2 transducer. The control arm was treated identically to that for the treatment arm, except the ultrasound machine was not turned on. The results of the conclusion of Bickford and Duff,[67] in that intensities below 2.0 W/cm^2 had no significant difference ($P < .05$) in the blood flow 30 minutes post-treatment (Table 7).

Table 7. Mean Forearm, Skin and Muscle Blood Flow Pre and Post Ultrasound Application[69]

Location of blood flow	Pre-treatment[a]	2 min post[a]	30 min post[a]
Forearm ultrasound	4.8 (2.2)	5.9 (3.1)	5.0 (2.2)
Forearm control	4.6 (2.2)	5.2 (2.6)	4.6 (2.2)
Skin ultrasound	2.0 (0.9)	3.1 (1.8)	2.2 (1.3)
Skin control	2.1 (0.9)	3.3 (2.2)	2.5 (0.9)
Muscle ultrasound	2.8 (2.2)	2.8 (3.1)	2.8 (1.8)
Muscle control	2.4 (1.8)	1.8 (2.2)	2.1 (1.8)

[a]Expressed as mean (standard deviation) and are in milliliters per 100 milliners per minute

This may have been due to parameters selection, which when calculated equaled a maximum possible increase of 1.5°C.[3,22,26-27] The parameters used do not reach the 2°C to 3°C recommended to increase blood flow.

Blood Flow with Modern Technology

To further understand the extent of the biophysical effect of ultrasound on blood flow, researchers used innovative evaluation outcome measures. Morishita et al[70] explored the effects of ultrasound on the intramuscular local blood circulation of the upper trapezium. The 11 subjects completed three treatment protocols (ultrasound, placebo, and control). Near-infrared spectroscopy was used to determine oxygenated, deoxygenated, and total hemoglobin concentrations in intramuscular tissue (20 to 30 mm depths) and surface temperature of the treatment area. Measurements were recorded at 10 minutes before the intervention, 10 minutes into the trial, and 20 minutes after trial. The EU-940 (Ito Co., Ltd. Japan) ultrasound unit was used to deliver 3 MHz frequency at a 1.0 W/cm^2 intensity with a 100% duty cycle for 10 minutes and 2x ERA treatment area. The placebo treatment was identical to the ultrasound, except the ultrasound machine was not turned on. The control group was instructed to rest, and no treatment was performed. The oxygenated ($F(2, 10) = 51.96$, $P < 0.01$) and total hemoglobin ($F(2, 10) = 52.91$, $p < 0.01$) levels were significantly higher in the ultrasound group than in the placebo and control groups 20 minutes after ultrasound. The results demonstrate the presence of a significant interaction in skin surface temperature and ultrasound ($F(2, 14) = 165.39$, $P < 0.01$). Morishita et al[70] concluded that therapeutic ultrasound provided a continuous increase of intramuscular local blood circulation and oxygen dynamics for at least 20-minutes after the conclusion of the treatment. The extent of increased blood flow reported by Morishita et al[70] could have a relationship with the high thermal change, the parameters selected would have a predicted 6℃ tissue temperature increase.[3]

To further understand ultrasound's effect on artery dilation, Strand[71] evaluated the blood flow of the brachial artery following an ultrasound. Blood flow was measured with the Phillips

HD11 XE Diagnostic Ultrasound System reported in time-averaged mean velocity (cm/sec) pre-treatment and following ultrasound treatment. Thirty subjects received a continuous ultrasound treatment with 3 MHz frequency at 1.0 W/cm^2 intensity for 5-minutes with the Dynatron Solaris® 700 Series ultrasound, which had a reported 5 cm^2 ERA and 6:1 BNR. A significant difference (t(29)= -2.6, P = 0.015) between blood flow before ultrasound application (11.19 $\pm$ 11.56) and following ultrasound application (16.48 $\pm$ 9.41) was reported. The 47% increase in blood flow of the brachial artery immediately after ultrasound treatment supports the continued use of ultrasound as a method to stimulate an increase in blood flow.

Although textbooks[26-27] recommend moderate heating of 2-3℃, further research is needed to determine whether there is a relationship between temperature increase and blood flow velocity. Positive effects on blood flow were seen with a predicted a 3℃[71] and 6℃[70] increase. If the only treatment goal is only to increase blood flow, practitioners have freedom in parameter selections. However, the ideal blood flow velocity or arterial dilation to facilitate healing is unknown, and it is unknown what velocity of blood flow or artery dilation is ideal for facilitating healing.

Muscle Spasm and Trigger Points

A muscle spasm involves a contraction of the whole muscle. Textbooks[26-27] consistently state that moderate heating between 2-3℃ can reduce muscle spasms. However, there is limited literature addressing muscle spasms treated with ultrasound.[72] Due to the contractile mechanism of both muscle spasms and trigger points, research into trigger points may be an available alternative to overcome the limitation in the literature.

In 1998, Gam et al[73] completed an intervention study in an out-patient clinic evaluating the effect of ultrasound in conjunction with massage and exercises in treating chronic trigger

points. A 4-week treatment protocol was used with a total of 8 treatment sessions. Subjects were randomized into three groups: group 1 received an ultrasound, massage, and exercise (20 subjects); group 2 received a sham-ultrasound, massage, and exercise (18 subjects); group 3 was control and received no treatment (18 subjects). The Sonopuls 590 (Enraf Nonius) was used to deliver the 25% pulsed ultrasound treatment for 3-minutes per trigger point at 100 Hz or $1x10^{-6}$ MHz, for an average total treatment time 15-minutes; no specific intensity was given. No differences were found between groups in the visual analog scale scores, analgesic usage, or global preference. However, the myofascial trigger point and index scores showed a significant reduction in the number and tenderness of myofascial trigger points for groups 1 and 2 compared to the control group 3 ($P < 0.05$). There was no standalone ultrasound treatment, limiting the ability to evaluate the ultrasound's impact on the trigger points. Furthermore, no difference between ultrasound (group 1) and sham ultrasound (group 2) was found. One explanation for the lack of difference was the low frequency used in this study. There was not adequate information to calculate a tissue temperature change, but due to the low frequency and treatment time, it would be unlikely a thermal change occurred.

To further understand ultrasounds' effect on myofascial trigger points, Ay et al[74] conducted a randomized, double-blind placebo-controlled study to assess the effect of a nonsteroidal anti-inflammatory medicated ultrasound treatment compared to ultrasound or placebo ultrasound therapies on trigger points. Phonophoresis is an ultrasound treatment technique with a medicated coupling medium instead of the water-based coupling medium traditionally used. The 60 subjects were randomly assigned to one of three groups: diclofenac phonophoresis, ultrasound, or sham. The study was conducted over 3 weeks. All subjects completed the same isometric-isotonic neck exercises paired with back extensor stretching

exercises and 15 total ultrasound treatments during the trial. The model for the ultrasound unit was not stated, but the brand was a Chattanooga device with a 5 cm^2 transducer. All ultrasound and phonophoresis treatments consisted of a 10-minute treatment time with 1 MHz at a 1.5 W/cm^2 intensity. Based on the textbooks[3,22,26-27] prediction models, the thermal increase would be $\leq$ 3°C. The following outcome assessments were taken before and after each of the 15 treatment sessions: mean pain score, range of motion of the neck, number of trigger points, algometric measurement and disability, pain severity (visual analog scale and Likert scale), and the neck pain disability index. At the end of the therapy, a statistically significant decrease in the number of trigger points for both phonophoresis and ultrasound groups ($P = 0.0001$) was found compared to pre-treatment measures. However, no difference in the number of trigger points was observed between phonophoresis and ultrasound post-treatment groups ($P = 0.142$). Statistically significant improvements were reported in both phonophoresis and ultrasound groups regarding visual analog scale and Likert pain severity ($P = 0.0001$) compared to pre-treatment measures. Furthermore, there was no improvement in pain outcome measures for the control group ($p = 0.180$, $p = 0.564$). Cervical ROM was increased significantly in phonophoresis and ultrasound groups ($P < 0.05$) after treatment. The control group detected significant increases in cervical lateral flexion and rotation ($P < 0.05$) but no improvements in cervical flexion-extension ($P = 0.083$). There was no difference between phonophoresis and ultrasound in cervical ROM after therapy ($P > 0.05$). A decrease was found in the disability index scores for neck pain in both phonophoresis and ultrasound groups when compared to pretreatment score ($P = 0.0001$). However, no difference was detected between phonophoresis and ultrasound after therapy ($P = 0.946$). Although the intervention of ultrasound treatments is combined with stretching exercises,

ultrasound and phonophoresis treatments that cause a $\leq$ 3°C tissue temperature increase was shown to be effective in the treatment of myofascial trigger points when compared to the control.

To further understand if pairing other medications with ultrasound are as effective for the treatment of myofascial trigger points as ultrasound or manual therapies, Sarrafzadeh et al[75] evaluated three interventions on the upper trapezius. Sixty subjects were split into four groups: control, pressure release, hydrocortisone phonophoresis, and ultrasound. The pressure release group received 90-seconds of ischemic pressure on each identified trigger point, the phonophoresis and ultrasound group received a 5-minute pulsed ultrasound treatment at a 1 MHz frequency with a 1.2 W/cm^2 intensity. In addition, the phonophoresis group had 1% hydrocortisone added to the conduction medium. Six treatments were given on separate days. A significant reduction in pain intensity occurred in all experimental groups ($P < 0.001$). Furthermore, phonophoresis and pressure release had a significant reduction in pain when compared to ultrasound ($P < 0.001$). Pain pressure threshold increased significantly in all experimental groups ($P < 0.001$). However, the pressure release group had a significantly greater pain pressure threshold than the ultrasound group ($P < 0.001$). Significant increases in contralateral lateral flexion and ipsilateral lateral flexion were also reported for all experimental groups ($P < 0.001$). Sarrafzadeh et al[75] demonstrated that hydrocortisone phonophoresis and pressure release may be superior to stand alone ultrasound treatment for treating myofascial trigger points. However, there is support for ultrasound as it was superior to the control. The available parameters make estimating thermal change difficult because the pulsed duty cycle was unknown, but a 100% duty cycle would be expected to cause a < 1.5°C increase. Therefore, a pulsed ultrasound treatment would be unlikely to reach the textbooks[26-27] recommended 2-3^{o}C temperature increase for treating muscle spasms.

Therapeutically, the thermal effects of ultrasound could benefit trigger points and range of motion restriction caused by muscle spasms. For example, reduction in trigger points and pain were reported using the parameters of 1 MHz frequency at an intensity between 1.0 W/cm^2 to 1.5 W/cm^2 intensity for 5 to 10 minutes. Nevertheless, further exploration is necessary to understand the full effect of thermal ultrasound on muscle spasms.

Manufacturer Inconsistencies

The design of the ultrasound machine has evolved due to manufacturer differences and patented technology. Although a variety of ultrasound designs exists, many of the parameter recommendations are based on literature that evaluated a specific unit. This limits generalizations about expected thermal change and acoustical dose between ultrasound manufacturers. Furthermore, several studies do not list a manufacturer or details about the unit used in the study, specifically ERA and BNR. Therefore, it is prudent to consider the potential impact that various ultrasound manufacturers may have on the literature. In addition, noting the publication date compared to manufacture standards has changed over time.

Heating Rates

As mentioned above, Draper et al[3] investigated the rate at which tissue temperature increased in response to ultrasound treatment. Twenty-four subjects were split into two treatment groups of 1 MHz and 3 MHz and received four separate treatments with different four intensities (0.5, 1.0, 1.5, or 2.0 W/cm^2). The remaining parameters were consistent for both ultrasound groups: 10-minute treatment time, treatment area 2x the ERA, and 2-3 cm/s transducer velocity. The Omnisound 3000™ with a 4.1 cm^2 ERA and a 1.8:1 BNR was used for all treatments. Internal tissue temperatures of the medial muscle belly of the left triceps surae were measured at two depths based on the frequencies' half-depths. Three MHz was evaluated at 0.8 cm and 1.6

cm depths. One MHz was measured at 2.5 cm and 5 cm depths. This foundational study demonstrated the linear relationship between an increase in intensity and a corresponding increase in tissue temperature (Table 1). Thus, the method used currently in clinical practice to calculate a predicted tissue temperature increase uses a known frequency and intensity to determine the heating rates per minute. The heating rates per minute are then multiplied by the total minutes the treatment is delivered.

Following the publication of Draper et al[3] in 1995, the assumption was that the heating rates found with the Omnisound 3000™ could be applied uniformly across all ultrasound machines if the machines were calibrated correctly. However, Kimura et al[76] explored the effect of changing the angle of the transducer and noted the increase in temperature was not the expected increase previously outlined by Draper et al[3]. Kimura et al[76] completed four trials with the transducer placed at four different application angles (90°, 80°, 70°, and 60°) and used two different ultrasound units, Excel UltraMax and a Mettler Sonicator 720. The BNR or ERA was not specified for either ultrasound unit; however, the ultrasound power output was tested on an ultrasound power meter to ensure proper calibration within 1%. There were no subjects included in the study instead the ultrasound was applied to a plexiglass box that housed a phantom tissue. A thermocouple was inserted into this phantom tissue directly opposite the ultrasound transducer. All trials used the same continuous ultrasound treatment at 1 MHz frequency at 2.0 W/cm^2 intensity for 5 minutes. The phantom tissue temperature was recorded in 1-minute intervals. The thermal effects were noted to be greatest with 90° and 80° angles of application. However, the 90° angle of application failed to follow the predicted heating rate in the Excel UltraMax and a Mettler Sonicator 720 (Tables 8 and 9). Furthermore, despite appropriate calibration and identical treatment protocols, the two ultrasound devices yielded significantly

different tissue temperatures ($P < .05$). Due to the limitation of manufacture information, ERA and BNR, and the unanimity subject population, the study supported the need for further research into ultrasound device-specific output and calculation of treatment dosage.

Table 8. 90° Angle of Application in Phantom Tissue[3, 76]

Intervals	Expected (Omnisound 3000™)[a]	Excel UltraMax[b]	Mettler Sonicator 720[b]
1 minute	0.4°C	0.475°C (0.287)	0.525°C (0.340)
2 minutes	0.8°C	0.475°C (0.206)	0.6°C (0.236)
3 minutes	1.2°C	0.5°C (0.163)	0.725°C (0.238)
4 minutes	1.6°C	0.625°C (0.126)	1.175°C (0.171)
5 minutes	2.0°C	0.8°C (0.141)	1.475°C (0.275)

[a]Expected interval increase is based on textbook[22,26-27] recommendations, original data had a reported mean of 0.34°C (0.18) per min.[3.]
[b]Values are expressed as mean (standard deviation)

Table 9. 80° Angle of Application in Phantom Tissue[3,76]

Intervals	Expected (Omnisound 3000™)[a]	Excel UltraMax[b]	Mettler Sonicator 720[b]
1 minute	0.4°C	0.375°C (0.435)	0.650°C (0.661)
2 minutes	0.8°C	0.400°C (0.432)	1.100°C (0.638)
3 minutes	1.2°C	0.475°C (0.411)	1.375°C (0.695)
4 minutes	1.6°C	0.625°C (0.443)	1.675°C (0.727)
5 minutes	2.0°C	0.825°C (0.499)	2.025°C (0.680)

[a]Expected interval increase is based on textbook[22,26-27] recommendations, original data had a reported mean of 0.34°C (0.18) per min.[3]
[b]Values are expressed as mean (standard deviation)

Several studies have been performed comparing the thermal increase of different manufacturers to understand the heating rates of various units. Holcomb and Joyce[11] compared the Omnisound 3000™ and Forte™ 400 (Chattanooga Group, Inc, Hixson, TN) ultrasound units. The Omnisound 3000™ had a reported 3.7:1 BNR with a 4.9 cm^2 ERA, compared to the Forte™ 400 with a 2.3:1 BNR with a 4.6 cm^2 ERA. The 10 subjects in this study had a temperature probe inserted to 1.2 cm depth into the medial belly of the triceps surae. Two ultrasound trials were

performed on each subject. Between trials, the tissue temperature was allowed to return to baseline. The treatment order was counterbalanced. The treatment area was 2x ERA, and treatment time was limited to 10-minutes or until tissue temperatures reached 6°C above baseline. Both ultrasound treatments used a 3 MHz frequency at a 1.0 W/cm^2 intensity and a 100% duty cycle. Tissue temperatures were monitored continuously and recorded every 30 seconds. A significant main effect was observed for the ultrasound unit ($P < .001$), with the Omnisound 3000™ producing a higher temperature increase (5.81°C ± 0.41) than the Forte™ 400 (3.85°C ± 0.75). The Omnisound 3000™ showed a temperature increase of 0.58°C per minute as expected based on Draper et al[3] research. The Forte 400 Combo had a 0.39°C/min increase, lower than the predicted 0.6°C. The possible reasons for the discrepancy in heating rates could be a gross difference in ultrasound design or standard manufacturer parameters (ERA and BNR). It is unknown if the lower heating rate of the Forte 400 Combo could be explained by the smaller (0.3 cm^2 difference) ERA, even though the Forte 400 Combo presented with a lower BNR (1.4:1 difference).

The same year (2003) of the Holcomb and Joyce[11] publication, another study was published by Merrick et al[77] to compare the heating rate of Omnisound 3000™ to both the Dynatron 950 (Dynatronics, Salt Lake City, UT) and the Excel Ultra III (XLTEK, Oakville, Ontario, Canada). The Omnisound 3000™ had a manufacturer reported 3.9:1 BNR and a 6.7 cm^2 ERA. The Dynatron 950 had a manufacturer reported < 6.1:1 BNR and a 5 cm^2 ERA. The Excel Ultra III had a manufacturer reported < 4:1 BNR and a 5 cm^2 ERA. The 6 subjects in the study received a separate treatment with each device, given 24-48 hours apart. For each of the 3 treatments, thermocouples were inserted into the medial triceps surae at a 1.6 cm depth. All 3 ultrasound treatments used a 3 MHz frequency with 1.5 W/cm^2 intensity at a 100% duty cycle for

a 10-minute treatment time and a treatment area 2x transducer ERA. The Omnisound 3000™ was able to reach the 4°C tissue temperature increase by the 6th minute ($F_{2,10} = 14.1$, $P = .001$). However, at the end of the 10-minute treatment, neither the Dynatron 950 nor the Excel Ultra III reached the 4°C increase. A significant difference was found for the temperature increase between the Omnisound 3000™ and the other two units ($F_{2,10} = 12.2$, $P = .001$), but no difference was found between the Dynatron and Excel units. Therefore, if the goal was to have a 4°C increase in tissue temperature for a specific therapeutic effect to occur, the literature only supports the Omnisound 3000™ for the current parameter selection (3 MHz, 1.5 W/cm^2, 100%, 10-minute). The main differences reported between the ultrasound units were the manufacturer standards (ERA and BNR). The Omnisound 3000™ had a 1.7 cm^2 larger ERA and 2.2:1 lower BNR than the Dynatron 950 and a 0.1:1 lower BNR than the Excel Ultra III. Further examination is necessary to understand the impact of ERA and BNR on heating rates to allow practitioners to adjust other parameters to reach the intended therapeutic effect.

A year later, Hayes et al[4] and Leonard et al[5] published studies which explored heating rates with different ultrasound manufacturers. Hayes et al[4] conducted a study with the Theratouch 7.7 ultrasound device (Rich-Mar, Inola, OK), which re-examined the thermal change for 1 MHz and 3 MHz at a 2.5 cm tissue depth. Eighteen subjects were given a 1 MHz or 3 MHz treatment at a 1.5 W/cm^2 intensity. The treatment duration lasted until one of the following criteria was met: total treatment duration of 10-minutes, the intramuscular temperature remained stable for a full minute, subject discomfort occurred, 4°C temperature increase occurred, or absolute intramuscular tissue temperature of 40°C was reached. The Theratouch 7.7 ultrasound unit with a 5.5:1 BNR and 5 cm^2 Therapy Hammer transducer with a 5 cm^2 reported ERA was moved at a 3-4 cm/s rate. Results revealed inconsistent temperature changes between

frequencies: the 1.5 W/cm^2 with 3 MHz heated at a rate of 1.19°C/min and the 1 MHz ultrasound heated at a 0.13°C/min rate. This result was notably different from the predicted temperature increase of 0.3°C/min (1 MHz) and 0.9°C/min (3 MHz).[3]

Leonard et al[5] used the Rich-Mar Theratouch 7.7 ultrasound device to evaluate thermal changes during a 10-minute continuous ultrasound at 1 MHz frequency for the same four intensities (0.5, 1.0, 1.5, and 2.0 W/cm^2) used by Draper et al.[3] Leonard et al[5] inserted thermocouples into the medial calf to a 4 cm depth to evaluate tissue temperature increase. The Theratouch 7.7 had a reported manufacturer 5.5:1 BNR and a 4.5 cm^2 ERA. The treatment area was 2x ERA. Four separate ultrasound trials were administered to each of the 19 subjects, 24 hours between each treatment. Four subjects from the 2.0 W/cm^2 intensity and one from the 1.5 W/cm^2 groups discontinued treatment because of discomfort during the sessions. Statistically significant differences occurred among the four different intensities ($F_{3,36} = 3.94$, $P = .014$, $1-\beta = .795$). Specifically, the 1.0 W/cm^2 increased to 37.3°C from 35.4 ± 0.7°C baseline, which is a predicted temperature increase of 0.16°C/min. Furthermore, 2.0 W/cm^2 increased to 36.1°C from 35.4 ± 0.7°C baseline, which would be a predicted temperature increase of 0.07°C/min. Due to the different tissue depths evaluated, it is difficult to compare heating rate reliability of the Theratouch 7.7 between Hayes et al[4] and Leonard et al.[5] Furthermore, due to the difference in tissue depth evaluated, the results from the Theratouch 7.7 cannot be clearly compared to the heating rates identified by Draper et al.[3]

To explore possible model differences, Gange et al[12] examined the heating capability of the Dynatron Solaris 708, which had a reported manufactured 5 cm^2 ERA and a 6:1 BNR. Thirty participants had 3 thermocouples inserted to different depths (1.0, 1.75, and 2.5 cm) into the medial triceps surae. Once the intramuscular temperature remained stable for 1-minute the

ultrasound treatment started with the following parameters: 3 MHz frequency, 1.0 W/cm^2 intensity, and 100% duty cycle for 20-minutes or until the tissue temperature increased to 4°C at all three issue depths. After 20-minutes, the average tissue temperature increased across all depths by 3.60°C ± 1.86, or rate of 0.18°C/min. Three of the treatments were discontinued due to subjects reporting feelings of uncomfortable heating. There was a significant main effect of depth ($F_{2,52} = 29.76$, $P < .001$), and depths 1.0 cm and 2.75 cm had a significant pairwise differences (P= .001). At the 1.0 cm depth, temperature increased 4.22°C ± 1.58 in 6-minutes at a 0.70°C/min rate. Furthermore, at the 1.75 cm depth the temperature increased by 3.91°C ± 1.94 in 10-minutes at a rate of 0.39°C/min. The temperature at 2.5 cm depth, could not achieve a 4°C temperature increase during the 20-minute treatment time. The Dynatron Solaris 708, however achieved 3.91°C ± 1.94 at a 1.75 cm depth, with the selected parameters (3 MHz frequency, 1.0 W/ cm^2 intensity, 100%, and 20-minutes).[12] Gange et al[12] results differ from that reported previously on a different unit in which the Dynatron 950 was unable to reach the 4°C increase at a 1.6 cm depth with the selected parameters (3 MHz frequency, 1.5 W/cm^2 intensity, 100% for a 10 minute).[11] Due to the differences in parameter selection, a comparison between the two Dynatron models is difficult. It should be noted that both the Dynatron 950 and Dynatron Solaris 708 reported the same manufacturer standards of 5 cm^2 ERA and a 6:1 BNR. Therefore, further research is needed to determine if significant variability occurs within manufacturing or if updated parameter recommendations should be examined based on each new model due to possible technological improvements.

To further explore possible manufacturer and model differences in Chattanooga units. Smith[13] used methodology based on the Gange et al[12] study. The Chattanooga Intelect® Legend XT had a manufacturer reported 5 cm^2 ERA and a 5.0:1 BNR. Twenty-five subjects had three

thermocouples inserted to different depths (1.0, 1.75, and 2.5 cm) into the medial triceps surae. Once the intramuscular temperature remained stable for 1-minute, the ultrasound treatment started with the following parameters: 3 MHz frequency, 1.0 W/ cm^2 intensity, 100%. The treatment was discontinued if one of the following criteria was met: treatment time reached 15-minutes, tissue temperature increased to 4°C at all 3 tissue depths, 45°C temperature was reached at any depth, or the subject requested the treatment be terminated. After 6-minutes at the 1.0 cm depth, the temperature increased on average to 4.10 °C, at a rate of 0.68°C/min. At 8-minutes the temperature increased on average to 4.17°C at a 1.75 cm depth, at a 0.52°C/min rate. At the 2.5 cm depth, the temperature did not reach a 4°C increase, at 15-minutes, the mean temperature was 37.62°C ± 2.08, or a temperature increase of 3.07°C. There was a significant main effect of depth ($F_{1.56,\ 35.82} = 79.64$, P = 0.003). The 1.0 cm and 2.5 cm had a significant pairwise differences (P = 0.026) as did 1.75 and 2.5 cm (P = 0.008). Limited comparisons could be reached between the Chattanooga model used by Holcomb and Joyce[11] and Smith[13]. However, intra-manufacturer differences may exist, and there are differences in manufacturer standards for BNR and ERA. The Chattanooga Intelect® Legend XT achieved 4.10°C at a 1.0 cm depth, with the selected parameters (3 MHz frequency, 1.0 W/cm^2 intensity, 100%, and 6-minutes).[13] The Chattanooga Forte™ 400 achieved a 3.85°C ± 0.75 increase at 1.2 cm depth, with the selected parameters (3 MHz frequency, 1.0 W/cm^2 intensity, 100%, and 10-minutes).[11] The difference may be due to the 0.2 cm depth difference, or a variation within the Chattanooga manufacturer standards or possible technological advancement between the production of the Chattanooga Forte™ 400 and Intelect® Legend XT. Furthermore, there can be no clear comparison of either study to Draper et al[3] due to the influence tissue depth may have on the results, as seen in Table 10.

There are several limitations and inconsistencies in the literature, resulting from inadequate reporting and systematic evaluation of parameters. To confidently compare the rate of heating between 1 MHz and 3 MHz at a specific depth, several factors needed to be reported in the primary research: frequency, intensity, duty cycle, treatment time, baseline and post-treatment temperature or total temperature increase, and a treatment area of 2-3x ERA. Due to limitations in reported methodology, only a few studies could be assembled for a comparison of the different heating rates between ultrasound manufacturers (Tables 10 & 11).

Table 10. 3 MHz Rate Per Minute Heating for 100% Duty Cycle in Muscle Tissue

Study	Manufacturer	BNR	ERA (cm^2)	Depth (cm)	Intensity (W/cm^2) [a]			
					0.5	1.0	1.5	2.0
Draper et al,[3] 1995	Omnisound 3000	1.8:1	4.1	0.8	0.3	0.58	0.82	1.5
				1.6	0.31	0.58	0.96	1.3
Hayes et al,[4] 2004	Theratouch 7.7	5.5:1	5	2.5			1.19	
Gallo et al,[6] 2004	Omnisound 3000	3.6:1	3.8	2	0.28			
Miller et al,[7] 2008	Omnisound 3000	3.6:1	5	2.5		0.59		
Draper and Ricard,[9] 1995	Omnisound 3000	1.8:1	4.5	1.2			0.88	
Holcomb and Joyce,[11] 2003	Omnisound 3000	3.7:1	4.9	1.2		0.58		
	Forte 400	2.3:1	4.6	1.2		0.39		
Gange et al,[12] 2018	Dynatron Solaris 708	6:1	5	1		0.7		
				1.75		0.39		
				2.5		NA		
Smith,[13] 2019	Intelect Legend XT	5.0:1	5	1		0.68		
				1.75		0.52		
				2.5		0.21		

[a]Mean values (given or calculated with available data) expressed in °C/min

Table 11. 1 MHz Rate Per Minute Heating for 100% Duty Cycle in Muscle Tissue

Study	Manufacturer	BNR	ERA (cm^2)	Depth (cm)	Intensity (W/cm^2) [a]			
					0.5	1.0	1.5	2.0
Draper et al,[3] 1995	Omnisound 3000	1.8:1	4.1	2.5	0.04	0.16	0.40	0.4
				5	0.06	0.16	0.31	0.34
Hayes et al,[4] 2004	Theratouch 7.7	5.5:1	5	2.5			0.13	
Leonard et al,[5] 2004	Theratouch 7.7	5.5:1	4.5	4		0.16		0.07
Miller et al,[7] 2008	Omnisound 300	3.6:1	5	2.5			0.26	
Weaver et al,[8] 2006	Omnisound 3000	2.1:1	5	5.08			0.51	
Rose et al,[10] 1995	Omnisound 3000	1.8:1	4.5	2.5			0.36	
				5			0.32	

[a]Mean values (given or calculated with available data) expressed in °C/min

Further research is needed on different ultrasound manufacturers with a systematic approach to evaluating parameters. Fluctuations within the BNR may influence the tissue temperature, however in the current literature, even when the same ultrasound device was used, there was no pattern in tissue depth evaluation. It is critical to understand that the evaluated depth of each study was different, as seen in Table 10 and Table 11. A systematic evaluation approach of different frequencies should follow half-value depth recommendation or a standardized metric. Moreover, future studies with multiple depths should consider the thermocouple placement as the literature has shown that the midpoint of the treatment area heats at a greater rate than the periphery.[7]

Calibration

The assumption has been previously made that the heating rates outlined by Draper et al[3] could be generalized for all ultrasound machines if the units were calibrated, although the literature has suggested this concept to be inaccurate.[4-5,11-13,76-77] Calibration is still a necessary consideration to the operation of the ultrasound machine. A standard calibration will check power output, electrical safety, and timer accuracy.

To further understand the need for regular calibration, Artho et al[78] examined the calibration of 83 ultrasound units at four different intensity levels (0.5, 1.0, 1.5, and 2.0 W/cm^2). All ultrasound units were actively being used in clinical facilities, measurements of power output and timer accuracy were collected over a 3-month period. A Bio-Tek Digital Ultrasound Wattmeter (model UW-2) was used to test the power output. A perfect correlation coefficient (r) of 1.0 was obtained for the Wattmeter, with zero variance for any repeated measurements based on a pilot test-retest protocol. Therefore, only one measurement per intensity setting and timer interval was obtained. The time was examined with a stopwatch. The difference between the

ultrasound unit (indicated time) and the actual time recorded on the stopwatch (measured time) was recorded for every ultrasound unit tested using the formula: [(measured time - indicated time)/indicated time] X 100. Results showed that 39% of the ultrasound units were outside the calibration standard ±20 percent error for at least one intensity level. Of the 32 machines outside the standard, 26 (31%) were outside the standard for two or more settings, and three (4%) produced no output at any of the settings. This variability highlights the need for regular calibration in research and clinical practice.

Additionally, calibration of the ultrasound unit should be completed before using a new ultrasound unit even if it is directly from the manufacturer. As mentioned above, Johns et al[43] evaluated 66 new transducers (Chattanooga 78047, Dynatron 300-5, Mettler ME7513, Omnisound 3000™, Rich-Mar C-4, and XLTEK UL-5) to determine if intra-manufacturer and inter-manufacturer differences in ERA, power, and SAI existed. All transducers were calibrated to within ± 15% of the manufacturer's guidelines. Intra-manufacturer variability in SAI ranged from 16% to 35%, and inter-manufacturer variability ranged from 22% to 61%. Five of the six manufacturers had a difference between the manufacturer's stated ERA and the measured ERA. The Omnisound 3000™ was the only transducer to aligned with the manufacturer's ERA. The wide range of variability could account for the inconsistency in reported biological effects and overall ultrasound effectiveness as a therapeutic intervention within the literature.

Furthermore, the annual calibration of an ultrasound machine may not guarantee that the machine is operating within the required limits during different parameter selections. Therefore, further research is necessary to address different manufacturers at different parameter settings to evaluate the effectiveness and safe delivery of acoustical energy.

Dosage Response

The traditional method for estimating the dosage of acoustical energy delivered during an ultrasound treatment has been to examine the heating rate, which is a measurable outcome of the energy applied to the tissue. However, the literature presents another method for mathematically estimating the acoustical energy dosage including ERA.

A systematic review published in 2001 by Robertson and Baker[17] examined dosage variables, ultrasound application, treatment area, and treatment duration to evaluate how changes to one variable might affect the treatment outcome. There were 16 randomized controlled trials that met with methodological inclusion criteria. Calculations were done to enable comparisons of dosage between studies. To calculate the ultrasound energy delivered, Robertson and Baker[17] used the following formula, total energy (in joules) = watts per square centimeter × applicator size (in square centimeters) × time (in seconds). Several assumptions were made about the transducer head size and treatment area to compare dose-response as the information was not reported. Results showed that trials that used 3 MHz frequency had outputs ranging from 30 J to 180 J. At 1 MHz frequency, the output range was from 600 J to 11,600 J. Total energy per unit area had a wide range from a low of 2 J/cm^2 with a frequency of 3 MHz to a high of 150 J/cm^2 with a frequency 1 MHz ($\bar{X}$=55.79 J/cm^2, 95% CI=19.8–84.3). Differences in the energy density used to suggest that comparable areas are not treated with similar dosages. This may be due to parameter or ultrasound manufacturer differences.

Alexander et al[79] performed a systematic review evaluating ultrasound treatment protocols to determine whether specific treatment parameters were associated with improvements in soft tissue shoulder impairments or function. Eight of the 727 potentially relevant randomized controlled trials met the inclusion criteria. From the 8 trials the spatial

average–temporal average (SATA, W/cm^2), the energy density per treatment (J/cm^2), total energy delivered during a single treatment (J), and total exposure to ultrasound over the entire duration of the study (hours) were calculated. The total energy delivered per session had a wide range. The lowest was 181 J for 6 treatments and resulted in a total exposure of 1,085.4 J which was about 1/100 of the average for the studies that were included in the review. The highest total energy delivered per session was reported as 6,114 J for a total energy exposure of 216,028 J. However, clinical application of this information is limited in part due to the wide variety if conditions included in the study. For clinical application, it may be helpful to understand dose-response as it relates to a generalization associated to known thermal responses (tissue extensibility, muscle spasm, trigger points, and pain management) instead of a specific condition (shoulder impairment, carpal tunnel, etc.). Alexander et al[79] concluded that ultrasound benefited around 107,289 J total energy exposure when treating a soft tissue shoulder impairment. Clinical application of this information is limited. However, future application of total energy deliver during a treatment may lead to defining treatment durations for generalized thermal response in tissue.

Robertson and Baker[17] as well as Alexander et al[79] considered the dose of therapeutic energy instead of thermal change as an intervention outcome. This method allows variation in parameter selection and manufacture differences to be considered. However, both reviews only examined ultrasound treatment of musculoskeletal injury, not considering tissue type or treatment goals.

Applying this method to the heating rate model might explain possible variation in tissue temperature increase. The primary variable would be the ERA. However, there is limited observable evidence of ERA's impact on the tissue temperature (Table 12). Therefore, either the

ERA was incorrectly reported or BNR plays a larger role in the variation. A method for factoring BNR into the dose-response effect would improve the statistical model.

Table 12. At 2.5 cm the Energy Density, Total Energy, and Rate Per Minute Heating for 1 MHz Frequency, 1.5 W/cm^2 Intensity, 100% Duty Cycle in Muscle Tissue.

Study	Brand	BNR	ERA (cm^2)	SATA (W/cm^2)	Energy density (J/cm^2)	Total energy (J)	Rate per min heating (°C/min)
Draper et al,[3] 1995	Omnisound 3000	1.8:1	4.1	150	90000	369000	0.40
Rose et al,[10] 1995	Omnisound 3000	1.8:1	4.1	150	90000	369000	0.364
Miller et al,[7] 2008	Omnisound 3000	2.0:1	5	150	90000	450000	0.262
Hayes et al,[4] 2004	Theratouch 7.7	5.5:1	5	150	90000	450000	0.13

Clinical Application Surveys

Evaluation of Parameter Selection

Due to ultrasounds' wide clinical use and the various combinations of parameters and manufacturer differences, the evolution of parameter selection and clinical application may further assist in continued research into dose-response. The literature addressing the use of therapeutic ultrasound can be divided into two time periods due to technology and parameter recommendations based on heating rate literature: early (1953-1995) and modern (1995 – present). Early studies had limited information about heating rates until 1978 when Haar[47] indicated an intensity of 0.25 W/cm^2 at a frequency of 1 MHz would produce an increase in temperature of about 1°C if the transducer were held stationary over a poorly vascularized soft tissue area for 5-minutes. Modern heating rates were established by Draper et al[3] in 1995 for different frequencies (1 MHz and 3MHz) paired with specific intensities (0.5, 1.0, 1.5 or 2.0 W/cm^2).

Early Surveys

Robinson and Snyder-Mackler[80] surveyed the factors that influenced the frequency of different electrotherapeutic modalities in physical therapy clinics in the late 1980's. A total of 45% of the 490 distributed surveys were completed. Results indicated that 50% of the physical therapists used ultrasound 10 or more times per week and out of the 8 modalities, none approached ultrasounds' high level of use within clinical practice. Lindsay et al[81] conducted a survey of 105 physiotherapy clinics to further examine the access and used of electrotherapeutic modalities. A total of 70% of the clinics responded to the questionnaire comprised of closed and open-ended questions. Participants indicated that 100% had access to an ultrasound machine, and 93% indicated that ultrasound was used at least once per day. However, neither Robinson and Snyder-Mackler[80] nor Lindsay et al[81] evaluated specifics regarding how or why ultrasound was being used.

Roebroeck et al[82] conducted a large-scale epidemiological case-referent survey between 1989 and 1992 to examine the use of ultrasound in a clinical setting. In 52% of the 3,957 participants, ultrasound comprised a relatively large part of the clinical treatment. Furthermore, ultrasound usage occurred in higher incidence during short duration rehabilitation (3weeks or less) than in long-duration rehabilitation (greater than 6 weeks). Furthermore, practitioners used ultrasound predominantly for pain reduction (66.4%) followed by a reduction in swelling (15.3%) and alleviation of other impairments (12.2%). However, the survey did not address the specific parameters. Therefore, the survey is unclear about the potential effects of the treatments.

Early surveys do not address parameter selection; it is critical to recognize that at the time there was limited evidence regarding parameter manipulation and thermal outcomes. However, it

is essential to note that despite the lack of evidence, ultrasound was widely used and was the dominant electrotherapeutic modality in physical therapy clinics in the 1980's and 1990's.

Modern Surveys

In 2002, seven years following Draper et al[3] publication, Warden and McMeeken[83] distributed 355 questionnaires to sports physiotherapists which addressed demographics, ultrasound usage, and treatment dose. A total of 171 questionnaires were completed, with only 1% of the respondents indicating that ultrasound was not part of their practice. Of the therapists who indicated the use of ultrasound, 75% indicated that it was part of the treatment plan for both acute and chronic conditions with the median treatment time of 5-minutes. Furthermore, when evaluated separately, 86% applied ultrasound on acute conditions with intensities ranging from 0.51 to 1.5 W/cm^2, 81% indicated the use of pulsed duty cycle, and the treatment time varied between 2 to 10 minutes. When asked about chronic conditions, 88% reported ultrasound was used with intensities between 1.01 to 2.0 W/cm^2, and the treatment time varied between 3 to 20 minutes. However, Warden and McMeeken[83] did not address the frequency as a parameter therefore, the temperature outcome could not be assessed.

Wong R et al[14] conducted a 77-item survey which addressed the frequency of ultrasound use, perceived importance of ultrasound in treatment plans, and parameter selections for specific impairments. The survey had a 44.9% (207 participants) return rate from the 457 physical therapists surveyed. Responses identified that 49.3% of practitioners used ultrasound for pain management compared to 83.6% to treat soft tissue inflammation. Additionally, 70.9% of practitioners used ultrasound to address tissue extensibility, and 68.8% incorporated ultrasound into the treatment of soft tissue and scar tissue injuries. Furthermore, practitioners consistently used 3 MHz when treating superficial tissues and 1 MHz for deep tissues, regardless of the

therapeutic goals. Intensities selected for treatments ranged from 0.10 W/cm^2 to 3.30 W/cm^2 for superficial tissues and from 0.40 W/cm^2 to 4.00 W/cm^2 for deep tissues. However, over 60% selected an intensity between 1.0 and 2.0 W/cm^2 for superficial tissues, and 80% selected that same range for deep tissues for the six treatment goals. The duty cycle, however did show a selection change between the treatment goals. The continuous duty cycle had a higher incidence when the treatment goal was to increase tissue extensibility (93.6%), decrease pain (75%), and remodel scar tissue (81.8%). Only soft tissue inflammation and swelling indicated a higher use of pulsed duty cycle (52.8%). However, Wong et al[14] did not address the treatment time; therefore, temperature outcome of the selected parameters could not be assessed.

To examine clinical importance and practitioners' fundamental understanding of ultrasound, de Brito Vieira et al[29] conducted a brief 19 question interview with 55 physical therapists. Results indicated that 85.4% of participants used ultrasound to treat acute conditions, and a higher percentage of practitioners used ultrasound to treat chronic conditions (91.7%) than seen in prior studies. Participants indicated they saw the highest improvement clinically with soft tissue inflammation (85.4%), acute pain (83.3%), and chronic pain (64.6%). Additionally, tissue type influenced the likelihood of ultrasound application. Results indicated ultrasound was used 87.5% in musculature injuries, 62.5% in the treatment of tendinous conditions, and 39.6% when ligaments were involved. The continuous duty cycle was primarily used for chronic conditions. However, 12.2% indicated the use of continuous duty cycle when treating acute pain in musculoskeletal tissue. One MHz was the preferred frequency for the treatment of deep tissues. However, both 1 and 3 MHz frequencies were indicated to be used for superficial tissue injuries. Intensities varied from 0.1 to 1.0 W/cm^2 regardless of the condition or tissue depth. The treatment time was between 2 and 4 minutes. Based on the given parameters, the maximal

temperature increase expected would be 2.4°C (3 MHz, 1.0 W/cm^2, 100% duty cycle, 4 minutes).[3,26-27]

To further explore patterns in ultrasound usage, Armijo-Olivo et al[15] developed a 4-part survey focused on the use of ultrasound as a part of a physical therapy practice, used with different impairments, the practitioners' beliefs related to ultrasound, and demographics of the participants. A total of 438 (19%) out of the 2,269 physical therapists contacted participated in the survey. Based on the demographics, ultrasound was used in greater regularity in private practice clinics (58%). It was significantly higher (61%) than those working in other settings when asked if ultrasound was used daily. Furthermore, practitioners who indicated that ultrasound was not incorporated into treatment plans mainly worked in a hospital setting (37%). Of the total participants, 18% reported that they had never used an ultrasound unit before. Of those that reported the use of ultrasound, 74% incorporate ultrasound into treating soft tissue and scar tissue injuries. Furthermore, 65% of participants reported using ultrasound to increase the extensibility of soft tissue, 37% indicated use for acute pain relief, and 24% stated ultrasound was used for chronic pain relief. However, Armijo-Olivo et al[15] did not address the specific parameters related to the impairments. Therefore, limited inferences could be made about the potential effectiveness of the treatment plans.

There are limited inferences regarding treatment goals in relation to biophysical effects caused by an increase in tissue temperature. De Brito Vieira et al[29] was the only survey that included adequate detail to estimate the temperature increase. Furthermore, the dose-response was not able to be calculated because no detail was evaluated about the ultrasound units used by the participants. Additionally, Roebroeck et al[82] was the only survey to explore treatment durations and the possible implications of a cumulative dose-response. Future surveys should

include treatment parameters (frequency, intensity, duty cycle), application parameters (treatment time, treatment area, treatment duration, and movement of the transducer), and ultrasound manufacture standards (ERA and BNR) to allow for the calculation of predicted temperature increase and energy dose.

Influences on Clinical Decision Making

The variation in ultrasound perceived effectiveness by practitioners could stem from the practitioner's parameter selections relative to the treatment goals. For example, practitioners who use the heating rate model to design ultrasound treatment plans rely on selecting parameters (frequency, intensity, duty cycle, time) based off a desired biophysical effect correlated to a specific tissue temperature increase. However, each parameter can influence different aspects of the treatment and the tissue temperature change. To explore the clinical decision-making process in parameter selection several previously discussed studies also included questions that addressed treatment decision-making and general knowledge about ultrasound.

Robinson and Snyder-Mackler[80] indicated that participants relied on information learned since graduation from an entry-level physical therapy program. Respondents indicated their clinical decision-making was based on professional colleagues (43%), academic publications (25%), continuing education seminars (20%), and manufacturers' sales representatives (25%). Fourteen years later, Warden and McMeeken[83] found that physiotherapists relied on formal undergraduate training (83%) and clinical experience (76%). The difference in participants' responses indicates an increase in ultrasound education in the entry-level programs from 1988 to 2002. Additionally, Warden and McMeeken[83] reported evidence-based research (35%), continuing education (26%), and textbooks (19%) were used when determining ultrasound parameters. However, in a later study, Armijo-Olivo et al[15] found the clinical decision to apply

ultrasound relied primarily on a physiotherapist's clinical experience (40%) followed by undergraduate training (19%), with only 13% reported evidence-based research affected their clinical decision.

When determining the proper ultrasound parameter selection, Warden and McMeeken[83] found that 97% of participants focused on the nature of the problem (acute or chronic), 87% considered the specific pathology being treated, and 75% considered tissue depth. Additionally, 80% considered the type of tissue being treated, and 72% identified the body region as an essential factor. However, limited inquiries were made into practitioners' understanding of the differences in heating rate between muscle and tendon which was identified by Chan et al[44] to be significantly greater (tendons heated 3.45 faster than muscle tissue).

Clinical decision-making has been shown to rely on experience or entry-level professional education. Thus, practitioners may not be influenced by recent literature. In addition, understanding relevant literature regarding treatment goals may be time-consuming for individual practitioners. Several considerations must be factored: year of the ultrasound manufactured, the unit's manufacturer, the tissue being treated, human versus animal subjects, and parameter selections evaluated. Regular literature reviews should be conducted to summarize relevant information and regular surveys conducted to ensure adequate information has reached the practitioners to improve the use of evidence based clinical decision-making.

Systematic Review, Approach, and Methodology

It is critical to understand the methodology process of systematic reviews to further understand the current body of systematic reviews and the need for further systematic evaluation of therapeutic ultrasound. A systematic approach to a review allows for a transparent and well-defined process to critically evaluate the available evidence.[84] A systematic review and analysis

incorporates five steps: (a) clarification of the problem, (b) identification of studies within the scope, (c) mapping and the creation of the conceptual framework, (d) synthesis or implantation of conceptual framework, (e) apprising the relevance and quality of the evidence.[84]

Clarification of the Problem

The goal of undertaking a systematic review is to deliver a generalizable answer to a basic question to influence policy, simplify large amounts of empirical data into practical application, or identify flaws in the existing evidence that effect replicability. The first step is to identify existing assumptions about the intervention, assumptions about the intervention's application, priorities for intervention, and outcomes for judging effectiveness. The next step is to identify the stakeholders needs and develop a review question that addresses the appropriate scope and depth of existing literature.

Integrative Non-systematic Review

To determine the value of undertaking a full systematic review and assist in identifying of gaps or assumptions within the empirical evidence, an integrative non-systematic review can be helpful.[85] This approach identifies relevant literature regardless of study design, subject type, or publication date. Therefore, there is no predetermined search terms, identification process for relevant studies, or study selection process at the outset.[85] The non-linear strategy might appear less efficient than protocol-driven search strategies. However, the strategy has been shown to yield more relevant studies per hour spent searching and is more likely to identify important sources that would otherwise be missed.[87] The approach has been described to find detailed and a wide range of research in a particular area of study, thereby providing a mechanism for summarizing and distributing research findings to practitioners who might otherwise lack time or

resources to undertake such work themselves.[86] Through the integrative non-systematic review, inconsistencies were identified, and focused research questions were developed.

Review Question

A systematic review aims to gather relevant existing data and bring it together to allow insight into an idea or concept. However, a formal systematic review may fail to consider the complexity associated with an intervention. There are several methodological challenges to consider when evaluating or performing a systematic review with a meta-analysis. Noyes et al[88] outline the concern with the current review methodology, which is insufficient in both synthesis and interpretation of evidence due to limited control or exploration of the complexity underlining moderators within the primary research.

Complex interventions and intervention complexity describe interventions with outcomes dependent on variable characteristics or moderators within the intervention.[89-90] In the case of therapeutic ultrasound, the thermal increase of the tissue is dependent on several parameter variables which impact the tissue in different ways in addition to causing a thermal temperature increase. Intervention complexity in this case relates to situations in which the intervention's expected effect could be modified by variant properties or characteristics of the intervention itself. Furthermore, complexity in implementation refers to situations in which an intervention's expected effect is modified by variant characteristics of implementation processes. Within ultrasound studies, this can be seen in the velocity of the transducer during the application, the size of the treatment area, or the coupling method. There could be complexity in context in which there are expected effect of an intervention modified by variant properties or characteristics of the settings or in the case of ultrasound research the tissue type and area on the body being treated. Finally, complexity in participant responses, the expected effects of an

intervention to be modified by variant characteristics of participants receiving an intervention. Therefore, clear procedural details for the ultrasound implementation are needed to be further identified and evaluated due to the complexity of the intervention.[89-90]

The fundamental starting point of a systematic review is developing a review question or a series of questions that explains the effect and controls for the complexity. A review question needs to address the relations within intervention, the context, and outcomes to enhance the applicability of the review findings. Noyes et al[88] recommended designing the review questions to provide evidence of predictor variation which would later allow practitioners to achieve the desired intervention effect. Sutcliffe et al[89] suggest approaching the standard Population, Intervention, Comparator, and Outcome (PICO) framework differently than when developing a research question for primary research. A review question needs to be based on the stakeholder's outcomes of interest and seeks to identify a range of approaches that might improve the outcomes. However, to answer the questions, what works, for whom it consistently works, and in what situation does it work. A diverse population must be both in subject matter and intervention approaches, which may be useful situationally or with population subgroups. Although randomized controlled trials (RCTs) are the gold standard within medical research, review questions addressing effectiveness may require different types of research methodology to answer the questions related to intervention complexity.

Identification of Studies within the Scope

Following the identification of the review questions, the PICO framework can assist in identifying the search inclusion and exclusion criteria. Identifying the population is multi-prong.[84] First, identify the ideal subject population that appears in the research. Within ultrasound, the target population may be acute or chronic conditions that resulted in unhealthy

tissue. However, studies that included subjects with chronic autoimmune conditions (systemic rheumatic, multiple sclerosis, fibromyalgia, rheumatoid arthritis) may lead to a skew in the summary effect estimator that does not represent the target population of the analysis. Therefore, both inclusion and exclusion criteria must be clearly defined. Depending on the review questions, the population could include study methodology or intervention of interest. The remainder of the PICO framework may not appear consistent with the primary research framework due to how the review question is constructed.[84]

Mapping and the Creation of Conceptual Framework

The procedural framework of a systematic review aims to test a hypothesis by identifying sufficient studies for an unbiased sample size based on quality empirical evidence. Different methods exist regarding effectively executing a systematic review, but there are several common themes.[84] The identification criteria provide transparent details for a studies inclusion or the reason for elimination. Optimally, the search, elimination, and documentation are established priori. A hierarchical approach for implementing the criteria for study exclusion allows reviewers additional information for potential future use. Any additions or changes to the process must be clearly outlined to ensure transparency and replicability.

The procedural framework depends on whether the review question aims to configure characteristics across and between studies or if the review questions aim to aggregate findings with the same covariates. The framework focused on configuring across different research methodology adopt an exhaustive search approach. An exhaustive search aims to identify all relevant studies with the available resources to avoid systematic bias or publication bias.[84] Deciding on the appropriate search databases should be based on availability and where the most relevant source material is likely to be with different perspectives to avoid excessive overlap but

ensure relevant studies are identified. Kastner et al[90] estimated the number of total studies captured during a systematic search is about 68% of known articles when using four databases.

Constructing a linear search framework involves predetermined specific search concepts, terms, and resources to locate the literature. Boolean operators (AND/OR) and controlled vocabulary are recommended to create search patterns to accurately identify relevant studies between different databases to maintain sensitivity and precision in the identification process.[84] The iterative search approach is appropriate when the review aims to identify literature that supports studies found with the linear search or to explore the available literature prior to constructing a linear search.

The screening and record-keeping process should be outlined prior to a linear search or a search that combines linear with iterative to maintain transparency and consistency. A strategy should be in place that allows for a sizable quantity of literature and information to be summarized in an assessable manner to facilitate management and analyzation. In most cases, a coding system should be implemented that assist in identifying relevant studies for specific review question or statistical processes.[84]

There are no systematic or empirical guidelines as to when to stop the exhaustive search. Therefore, systematic searches should be restricted for practical application with methodology that recognizes the time and personal constraints, availability of resources, and the nature of the academic publications.[84]

Synthesis or Implantation of Conceptual Framework

In general, a meta-analysis based on a pooled effect size uses a series of calculations from the results of multiple studies to answer the review question. The basic series of calculations include: a) selecting and calculating the desired descriptive statistic for each study, b) calculating

the average of the descriptive statistic across studies, c) calculating and controlling variance across the studies.[91] The systematic review with an intervention component analysis (ICA) involved two distinct analysis components or two serial review questions, the identification of the effectiveness of an intervention, and the identification of variables in the intervention that seem to influence the outcome. Therefore, based on the ICA research questions, a traditional meta-analysis approach may not address the research question.

Relevance and Quality of the Evidence

Following a systematic review, an appraisal and reflection are necessary to determine if the information identified and the results calculated quality. First, the methodology should be examined to ensure appropriate standards are met, and the process is relevant to the review question. Second, identify the methods of the included studies that also met appropriate standards with a suitable methodology in relation to the research question. Finally, the statistical results and subsequent conclusions should be evaluated by the nature of the studies included and to the extent of the available evidence.[84]

Existing Systematic Reviews

Systematic reviews focused on thermal therapeutic ultrasound have been conducted with different methodology. The existing systematic reviews addressing ultrasound dose-response are limited and have already been discussed.[17,79] The remainder of the available systematic review focused on ultrasounds effectiveness on specific diagnosed conditions with limited evidence evaluating the type of treatment tissue or the variation within the intervention.

Cochrane Review

Cochrane reviews aim to prepare, maintain, and promote systematic reviews to inform health and social care decisions. The Cochrane Handbook for Systematic Reviews of

Interventions provides methodological guidance for the preparation and maintenance of Cochrane Reviews on the effects of interventions.[92] However, several of the existing Cochrane reviews that address therapeutic ultrasound as an intervention do not address the underlining complexity, creating misleading or unclear results.

Ebadi et al[93] conducted a systematic review to evaluate if therapeutic ultrasound was safe and effective in treating non-specific chronic low back pain. Of the 868 studies identified in the initial electronic search, which included five databases (CENTRAL, MEDLINE, EMBASE, PEDro, and PsycLIT), only seven met the criteria. No significant improvement in the ultrasound group in the three studies used in the meta-analysis to address pain intensity compared to placebo (mean difference [95%CI] -7.12 [-17.99 to 3.75]). Additionally, no statistical improvement in flexion (standardized mean difference (SMD) [95%CI] 0.18 [-0.62 to 0.98]) or extension range of motion (SMD [95%CI] -0.33 [-0.85 to 0.19]). However, moderate improvements were noted for low back function compared to placebo (standardized mean difference [95%CI] -0.45 [-0.84 to -0.05]). From a systematic and meta-analysis perspective, the study was executed transparently to limit bias. However, limitations exist in the methodology and documentation process that may affect future statistical analysis if the study was reproduced. A major variable not considered was the complexity of ultrasound application and treatment protocol in the seven studies included in the review. Ebadi et al[93] noted the only indication that the ultrasound application parameters and dose were inconsistent. The lack of information limits the clinical application and the ability to explain why the range of motion was unaffected but overall function was moderately improved.

Page et al[94] evaluated the effectiveness of therapeutic ultrasound in treating individuals with carpal tunnel. The initial search included five databases (CENTRAL, MEDLINE,

EMBASE, CINAHL Plus, and AMED), with date ranges from as early as 1937 to 2012. Eleven studies were included in the review from the 414 total studies identified. One of the eleven studies addressed the primary review question about ultrasounds. Short-term effect on overall improvement of carpal tunnel. One included study indicated overall significant short-term improvement following a 7-week treatment protocol (RR 2.36; 95% CI 1.40 to 3.98). Another indicated after 3-months a significant increase in overall improvement was reported when ultrasound was combined with splinting compared to splinting alone (RR 3.02; 95% CI 1.36 to 6.72). Page et al[94] explored the effect of different frequencies and intensities of ultrasound within studies. However, no meta-analysis was able to be conducted between studies.

Cochrane reviews may be considered the gold standard for healthcare related systematic review methodology. However, the meta-analysis could be expanded to account for the complexity of the intervention by the addition of examining the parameter variables.

Sequential Meta-analysis

Sequential meta-analysis is a technique that reveals the date by which enough research has become available to show a treatment is identified as effective. Once established, the meta-analysis is updated regularly, which allows the information provided to be current. This idea was first noted by Thomas Chalmers, who was the driving force behind establishing the Cochrane Collaboration and review methodology.[92] To highlight how to review methodology may impact the results when complexity is not accounted for, it is necessary to look at sequential systematic reviews published within and outside the Cochrane Library. For example, three systematic reviews have been published in succession on ultrasounds effectiveness as an intervention for individuals with knee osteoarthritis.

Rutjes et al[95] conducted a Cochrane review that compared therapeutic ultrasound to sham or non-specific intervention in patients with knee or hip osteoarthritis. The primary outcome measures for inclusion were pain and function. Out of the 2,156 potentially relevant references, five studies were identified with the inclusion criteria. Two studies evaluated pulsed ultrasound, two continuous, and one evaluated both pulsed and continuous ultrasound. The methodological and reporting quality for the five studies was poor with a high degree of heterogeneity among the trials. Outcome measures for pain included change in pain scores between ultrasound and control of -1.2 cm on a 10-cm VAS (95% CI -1.9 to -0.6 cm). A difference in function scores of -1.3 units with the standardized disability scale ranging from 0 to 10 (95% CI -3.0 to 0.3). Rutjes et al[95] concluded that therapeutic ultrasound might be beneficial for patients with osteoarthritis of the knee. However, what makes the treatment effective is not addressed in the review.

Zhang et al[96] and Wu et al[97] conducted a similar systematic review to Rutjes et al[95] but only included randomized control studies that compared therapeutic ultrasound with a sham or no intervention in patients with osteoarthritis of the knee. Zhang et al[96] identified 2,496 potentially relevant references, ten studies met the inclusion criteria. Following a meta-analysis, therapeutic ultrasound showed a positive effect on pain (SMD = -0.93, 95%, CI = -1.22 to -0.64, $P < 0.01$, p for heterogeneity = 0.12, $I^2 = 42\%$). The Western Ontario and McMaster Universities physical function score was used as an outcome measure for physical function, therapeutic ultrasound appeared to positively reduce the score resulting in improved physical function (SMD = -0.37, 95% CI = -0.73 to -0.01, P = 0.04, p for heterogeneity = 0.94, $I^2 = 0\%$). No adverse safety events were caused by therapeutic ultrasound in any trial. Therapeutic ultrasound reduces knee pain and improves physical functions in patients with knee osteoarthritis and could be a safe treatment. Wu et al[97] assessed the effectiveness and safety of therapeutic ultrasound with

sham ultrasound on pain relief and functional improvement in knee osteoarthritis. A total of 2,493 potentially relevant references were identified, with only fifteen studies included. Meta-analyses demonstrated that therapeutic ultrasound significantly relieved pain ($P < 0.00001$) and reduced the Western Ontario and McMaster Universities (WOMAC) physical function score ($P = 0.03$). In addition, therapeutic ultrasound increased the active range of motion ($P < 0.00001$) and reduced the Lequesne index ($P < 0.00001$). There was no evidence to suggest that ultrasound was an unsafe treatment.

Rutjes et al,[95] Zhang et al,[96] and Wu et al[97] included tables, which outlined the parameter of each study reviewed. However, there was no inquiry into if a change in frequency, intensity, duty cycle, or treatment time affected the success of a study. Furthermore, there is no examination of the cumulative effect or dose-response of the intervention, nor was there acknowledgment of the possible effect of variation in between ultrasound models/manufacturers. Due to the replication of similar methodology, all three studies provided limited clinical application.

Conclusion

After decades of clinical use and research, therapeutic ultrasound is still not fully understood due to primary and secondary literature limitations. Based on the literature discussed, there are biological effects during any ultrasound treatment. However, there are inconsistencies in results due to the lack of systematic evaluation of parameters and total energy delivered to the tissue during the ultrasound intervention.

Suppose the end goal is to establish a dose-response relationship for given treatment goal. In that case, a traditional meta-analysis may not be appropriate until manufacture and practitioner selected parameters are understood. An ICA may be expanded to include the effectiveness and

examine the intervention's complexity. Furthermore, clinical practitioners would have evidence-base recommendations on which parameter has a greater influence on treatment goals or potentially how to control for variation in manufacturer standards. Additionally, it is difficult to advocate or object to policy change in manufacture standards or federal regulation without a clear dose-response.

CHAPTER III. METHODOLOGY AND PROCEDURES

Phase 1 included the systematic review with an intervention component analysis (ICA) which involved two distinct analysis components. First, the identification of how interventions differ. Then identify which of these differences in intervention characteristics seem to influence outcome.[89] To understand differences between interventions, an analysis was used to identify any clinically significant differences between the predicted and actual outcomes reported. The outcomes reported and the parameter variables were then combined in the final phase of the ICA, which sought to understand variation in outcomes through mapping effectiveness against the intervention characteristics.[84, 89]

Phase 2 included a four-part survey to investigate trends within parameter selection in the clinical setting and influences on clinical decision making. The treatment parameters evaluated were frequency, duty cycle, intensity, and treatment time. Identification of ultrasound units was investigated, and participants were asked about known manufacture parameter standards (ERA and BNR). Additionally, basic knowledge of ultrasound was assessed as well as where the practitioner's knowledge came from.

Phase 1: Systematic Approach

The systematic approach to a review allowed for a transparent and well-defined process to critically evaluate the available evidence. The systematic review and analysis process incorporated five steps: (a) clarification of the problem, (b) identification of studies within the scope, (c) mapping and the creation of the conceptual framework, (d) synthesis or implantation of conceptual framework, (e) apprising the relevance and quality of the evidence.[84]

Clarification of the Problem

Systematic Review and Analysis

The primary research question identified from the integrative non-systematic review was, "What parameter or component makes therapeutic ultrasound effective?" The purpose of the ICA was to establish a dose-response recommendation that can be adapted to accommodate different ultrasound manufacturers. A systematic review with an ICA assisted in distinguishing between ultrasound interventions that were successful, inherently faulty (failure of intervention or ultrasound as an intervention), and those that were incorrectly delivered (implementation failure). In addition, the review examined which intervention components had a common impact that produced a beneficial intervention for unhealthy muscle or connective tissue in human subjects. For this study, beneficial or effectiveness was determined by the outcomes of the original studies' reported significance ($P < 0.05$). Combined, the narrative analysis and ICA aim to answer the following questions:

1. To what extent can the predicted tissue temperature increase based off the selected parameters (intensity, frequency and time) accurately predict a significant treatment outcome.
    a. H_0: $r = r_0$ The null hypothesis is the predicted tissue temperature increase, regardless tissue pathology, are equally effective.

    H_A: $r \neq r_0$ The alternate hypothesis is the predicted tissue temperature increase, regardless tissue pathology, is different for at least one range of BNR.
2. To what extent can parameters components predict the effectiveness of an ultrasound intervention success. Components include: (a) BNR (b) ERA (c) total energy delivered?

a. H_0: $r = r_0$ The null hypothesis is that the reported or manufacture cited BNR, regardless tissue pathology, are equally effective.

H_A: $r \neq r_0$ The alternate hypothesis is that the reported or manufacture cited BNR, regardless tissue pathology, is different for at least one range of BNR.

b. H_0: $r = r_0$ The null hypothesis is that the reported or manufacture cited ERA, regardless tissue pathology, are equally effective.

H_A: $r \neq r_0$ The alternate hypothesis is that the reported or manufacture cited ERA, regardless tissue pathology, is different for at least one range of ERA.

c. H_0: $r = r_0$ The null hypothesis is that the predicted total energy delivered for "successes" treatments for each condition groups will be equal.

H_A: $r \neq r_0$ The alternate hypothesis is that the predicted total energy delivered for "successes" treatments for each condition groups will be different.

Identification of Studies within the Scope

Search Strategy

The process of study identification for the systematic review and analysis occurred in phases. Potential studies were identified through three databases PubMed, Web of Science, and EBSCO; however, the EBSCO database includes academic search premier, Medline, SPORTDiscus & CINAHL. Due to the type and number of databases included, the expected capture of relevant studies would be > 68% and two viewpoints (medical and educational).[86] The database searches were restricted based on the date of publication (1995 to date of search), access to full text (including interlibrary loan), and language (English or prior translation into English).[84]

The search strategy used a combination of controlled vocabulary and free text terms in a predetermined pattern to identify relevant studies, which included terms for therapeutic ultrasound and generalized terms for outcome measures linked to unhealthy tissue. The following search was completed with no alterations for the three databases: (therapeutic ultrasound OR thermal ultrasound) AND (pain OR Pain Management OR pain threshold OR Muscle Spasms OR Spasms OR Generalized Spasm OR Range of Motion OR Joint Range of Motion OR Joint Flexibility OR Scar OR cicatrix OR scarring).

Inclusion and Exclusion Criteria

Inclusion criteria, which followed the Population, Intervention, Comparator, and Outcome (PICO) framework was created to identify relevant studies. Studies that met the following inclusion criteria were included in the analysis and ICA: (a) the population of the studies included human adult subjects $\geq$ 18-years-age that had a diagnosed acute or chronic conditions which resulted in unhealthy tissue, (b) the study included therapeutic ultrasound as an independent assessment with all necessary parameter variables, (c) randomized control trial design, (d) in order to ensure comparable, outcome measures were limited to pain scale, force-generating testing, range of motion, and patient-reported outcome measures (PROMs), (e) literature collected from the databases were included from 1995 to date of search, free full text, English text.

Studies that met the following exclusion criteria were eliminated from the further investigation: (a) studies evaluating non-soft tissues or autoimmune conditions (bone injuries or conditions, internal organ injuries, systemic rheumatic, multiple sclerosis, fibromyalgia, rheumatoid arthritis, osteoarthritis), (b) studies were eliminated due to incomplete treatment parameters (frequency, mode/duty cycle, intensity, and treatment time, transducer ERA and

BNR, tissue type, the total treatment duration), (c) non-therapeutic ultrasound treatments were excluded (diagnostic ultrasound, phonophoresis, or bone stimulators), (d) studies were excluded due to design (review, meta-analysis, case study, or non-randomized control), (e) studies were excluded if outcome measure excluded examiners impression of change instead of a measurable outcome, (f) studies published prior to 1995, full text requiring purchase from an outside source, non-English text, abstract only text.

Mapping and the Creation of Conceptual Framework

Screening Process

The primary screening process was completed by only one researcher and involved several steps (Figure 1). Steps were taken to allow for transparency during the screening process. Detailed records were maintained regarding the search and screening process, including dates and critical aspects of the decision-making process.

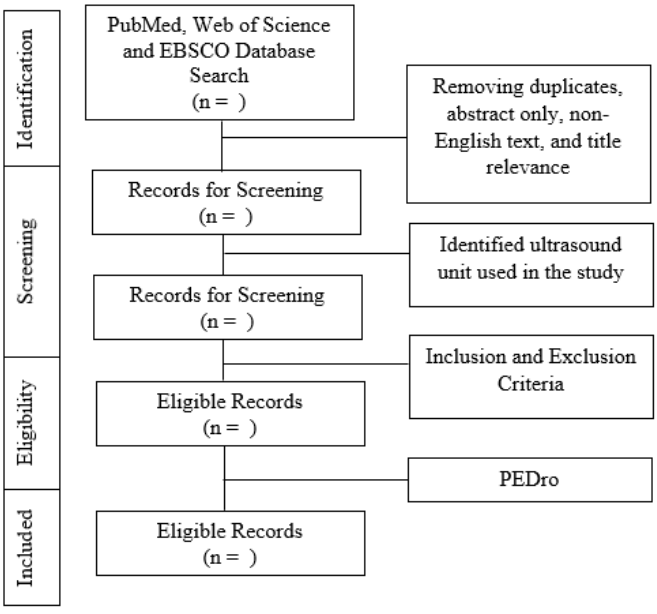

Figure 1. Mapping used during the screening process.

Data Extraction

Data extraction and management used a standardized data extraction process which one reviewer completed. The data extraction included raw and coded information on the study design, intervention, control, participants, inclusion/exclusion criteria, outcome measures, and intervention and control group raw scores. Relevant intervention characteristics extracted for the ICA included authors' reported outcome, type of outcome measure, tissue type, treatment goal, brand of ultrasound, frequency, intensity, duty cycle, treatment time, ERA, BNR, and total number of treatments (Table 13).

The inclusion and exclusion criteria limited the acceptable missing data. However, two exceptions were made to compensate for expected incomplete reporting by primary researchers. The manufacturer's reported BNR and ERA were identified with the operation or service manual if the brand and model of the ultrasound were stated. If the operation or service manual could not be found, the ultrasound manufacturers were contacted directly to request the information. Clear documentation was kept for all cases where the BNR or ERA was found through the operation manual.

Table 13. Raw Studies Parameters

Author	Frequency	Intensity	DC	Tx Time	BNR	ERA	Total Tx	Tissue
Study 1								
Study 2								
Study 3								
.								
Study K								

Note. DC = duty cycle; Tx = treatment

Synthesis or Implantation of Conceptual Framework

Several phases of calculations occurred as a part of the data analysis. A set of calculations were completed to: (a) establish the energy dosage for all studies, (b) calculate the predicted temperature change based on the outlined parameters and determine if the predicted temperature

should result in success or failure, (c) identify the p-value within each study for a given outcome result and code significant results as success or insignificant as failure (Table 14, Table 15, and Table 16).

Energy Dosage

Calculations were completed from the extracted information to determine the spatial average–temporal average (SATA, W/cm^2), the energy density per treatment (J/cm^2), total energy delivered during a single treatment (J), and total exposure to ultrasound over the entire duration of the study (hours). In addition, the standardized mean and standard deviation for each outcome group was calculated.

The following equations were used to determine the calculated variables.[17, 79]

1. SATA (W/cm^2) = average intensity (W/ cm^2) X duty cycle (%)
2. Energy density per treatment (J/cm^2) = SATA (W/cm^2) X time per treatment (seconds)
3. Total energy per treatment (J) = SATA (W/cm^2) X transducer head size or effective radiating area (cm^2) X time per treatment (seconds)
4. Total exposure (hours) = number of treatments X time per treatment (seconds)
5. Total energy delivered over entire study duration (J) = total energy per treatment (J) X number of treatments

Table 14. Raw Studies Energy Dose

Author	SATA (W/cm2)	Energy density per treatment (J/cm2)	Total energy per treatment (J)	Total exposure (hours)	Total energy delivered over entire study duration (J)
Study 1					
Study 2					
Study 3					
.					
Study K					

Predicted Temperature Change

Calculations were completed from the extracted information to determine the predicted tissue temperature increase. Two formulas were used based on the primary target tissue in each study. Based on Chan et al[44] results, all studies focused on treating unhealthy connective tissue had the treatment time multiplied by 3.45 due to the increased heating rate. Note Chan et al[44] and Draper et al[3] share identical ultrasound manufacturers, BNR and ERA.

1. Predicted thermal change (C) in muscle tissue = temperature increased per minute (Table 1) X time per treatment in minutes X duty cycle.
2. Predicted thermal change (C) in connective tissue = temperature increased per minute (Table 1) X (time per treatment in minutes X 3.45) X duty cycle.

Table 15. Raw Studies Predicted Temperature Increase with Expected Outcome and Actual Outcome for Tendon Tissue

			Pain			ROM		
Author	Tissue	Thermal change	Expected	Outcome	Code	Expected	Outcome	Code
Study 1								
Study 2								
Study 3								
.								
Study K								

Intervention Parameters for Predicted Outcome Verses Significant Outcome

A probability matrix was employed to address the accuracy of the existing predictive model (predicted tissue temperature increase that corresponds to a specific biophysical outcome) against a study's ability to produce a significant effect on an outcome measure. Further statistical analysis was completed from the probability matrix to evaluate the prevalence and accuracy. Two predetermined groups were established, muscle and connective tissue, due to the need for different predictive formulas. Exceptions were made for studies that involved the joints, due to muscle and tendon both being present in the targeted tissue, the studies were included in both

groups. Subgroups were identified for pain management and range of motion; additional subgroups were identified for future evaluation but not considered for evaluation due to potential low statistical power due to the sample size.

The matrix was defined based on the following criteria:

- True Positives (TP): all cases with a predicted yes and the actual result yes
- True Negatives (TN): all cases with a predicted no and the actual result no
- False Positives (FP): all cases with a predicted yes and the actual result no ('Type I error')
- False Negatives (FN): all cases with a predicted no and the actual result yes ('Type II error')

Table 16. Probability Matrixes Layout

	Outcome	
Predicted	TP	FP
	FN	TN

Probability statistics were completed based on the probability matrix results to evaluate ultrasound effectiveness or accuracy within the literature. Sensitivity values are calculated only from those with a significant outcome measure ($p < 0.05$) with the condition of interest. In contrast, specificity values are calculated from those without a significant outcome measure. A 100% sensitivity or specificity implies that the ultrasound treatment parameters will be effective 100% of the time. The ultrasound treatment parameters will be non-effective in 100% of cases in patients with the condition of interest.

Likelihood ratios and probability metrics are calculated from the sensitivity and specificity values. The positive likelihood ratio is derived from treatment interventions with significant outcome and without significant outcome of interest. A strong positive likelihood

ratio is notable as > 1.0. However, when evaluating the negative likelihood ratio, a smaller value closer to 0 is preferred as it reflects a non-effective intervention finding.

Intervention Parameters for Ultrasound Manufacturer Standards

Inconsistencies between ultrasound manufacturers and models have been established in the literature.[3-5,11-12,76] To evaluate the extent BNR and ERA have on the significance of an outcome measure, the mean BNR for a significant outcome ($p < 0.05$) was identified and the mean BNR for a non-significant outcome. In addition, a t-test was used to determine if there was a significant difference between the means of two groups (effective vs non-effective and true positives vs false positives). The exact process was used for ERA and total energy delivered in a single treatment.

Relevance and Quality of the Evidence

Calculating the probability matrix allowed for a statistical evaluation of the current method for determining a predicted outcome based on a predicted temperature increase. Furthermore, an explanation of the frequency of type I error or type II error occurring. Finally, the t-test compared the means of two groups to determine whether an ultrasound treatment influenced the outcome or whether two groups differed.

Phase 2: Ultrasound Usage and Trends in Clinical Practice

Purpose of the Study

The primary goal was to ascertain trends within parameter selection by clinical athletic trainers to evaluate if thermal effects occurred in clinical practice in treating specific impairments. Primary treatment parameters were evaluated (frequency, duty cycle, intensity, and treatment time) and manufacture parameters (ERA and BNR) to calculate the total energy delivered during a single treatment and predicted thermal outcome. Conditions examined

evaluated underlining pathologies associated with tissue extensibility, pain management, muscle restriction, and scar tissue remodeling.

Research Questions

The primary research questions were “What parameter or component makes therapeutic ultrasound effective within unhealthy tissue?” and “To what extent do ultrasound manufacture standards (transducer effective radiating area and beam non-uniformity) affect the outcome or acoustical dose?”

Research Question 1

To what extent do the selected parameters (intensity, frequency, duty cycle, and time) match the results of the non-systematic review and systematic review from phase one.

H_0: $r = r_0$ The null hypothesis is the selected parameters are equal to the parameters selected in the research.

H_A: $r \neq r_0$ The alternate hypothesis is the selected parameters are different to the parameters selected in the research.

Research Question 2

To what extent do the selected parameters (intensity, frequency, duty cycle, and time) match the predicted tissue temperature for the practitioner’s treatment goal.

H_0: $r = r_0$ The null hypothesis is the predicted tissue temperature increase, regardless of the tissue pathology, are equal.

H_A: $r \neq r_0$ The alternate hypothesis is the predicted tissue temperature increase, regardless of the tissue pathology, is different.

Research Question 3

To what extent do practitioners understand differences in ultrasound manufacture standards (transducer effective radiating area and beam non-uniformity) that may affect the desired thermal outcome.

(a) H_0: $r \geq r_0$ The null hypothesis is 75% or more of the participants understand the concept of BNR.

H_A: $r < r_0$ The alternate hypothesis is less than 75% of the participants understand the concept of BNR.

(b) H_0: $r \geq r_0$ The null hypothesis is 75% or more of the participants understand the concept of ERA.

H_A: $r < r_0$ The alternate hypothesis is less than 75% of the participants understand the concept of ERA.

Participants

A sample population of 2,000 athletic trainers were recruited through email obtained from the National Athletic Trainers Association (NATA). Baruch[114] identified that the average response rate for studies that utilized data collected from organizations is 35.7%, therefore based on the sample population, the expected response rate would be about 357 responses. The inclusion criteria included participants currently practicing as certified athletic trainers. The exclusion criteria included incomplete surveys, retired athletic trainers, or non-certified athletic trainers. Participants will be randomly assigned an identification (ID) number.

Procedures

Participants were contacted by email through the NATA Qualtrics platform in conjunction with the NATA data collection service program. Before beginning the survey,

participants were presented with information about the study and the consent form, by proceeding to the survey, participants consent to participate. Once the consent was completed, the estimated time for completing the survey was 10 to 15-minutes.

Participants accessed the survey through Qualtrics (Qualtrics LLC, Provo, UT), a GDPR (General Data Protection Regulation) compliant web-based survey software. The study was conducted in a six-week data collection window with reminders sent bi-weekly following the initial participation invitation. Before distributing the survey, the study proposal and survey were submitted for Institutional Review Board (IRB) approval through NDSU to ensure participant protection.

The survey was composed of four parts: demographic, ultrasound availability and manufacture standards, uses of ultrasound specific to thermal biophysical effects, and influences on clinical decision-making (Appendix A). The survey was developed based on prior published surveys and anecdotal clinical experience. However, modifications were made to make the survey applicable to isolate parameter selections for specific biophysical effects. Additionally, because BNR and ERA had not previously been evaluated, questions were added specifically to address participants' understanding of the concepts and possible clinical implications on treatment goals. The survey was comprised of closed and opened ended questions. The closed-ended questions primarily addressed demographics, uses of ultrasound specific to thermal biophysical effects, and influences on clinical decision-making. However, due to the different ultrasound manufacturers and available models within manufacturers, open-ended questions were used to gather information about ultrasounds availability and specific brands/models in clinical use.

The survey was pilot-tested with a small cohort of three athletic trainers before distribution for validity purposes. Additionally, the survey was evaluated by content experts to improve content validity.

Data Analysis

Several phases of calculations occurred as a part of the data analysis. A set of calculations were completed to: (a) calculate means, standard deviations, and frequencies. (b) establish the energy dosage for the four physiological categories for each reported ERA, (c) calculate the predicted temperature change based off the outlined parameters and determine if the predicted temperature that should result in success or failure, (d) calculate means and standard deviations for the designated BNR and ERA questions to determine if 75% or more of the participants understand the concepts.

Parameter Selection

Calculations were completed from the data to determine means, standard deviations, and frequencies for each parameter separately.

Energy Dosage

Calculations were completed from the extracted information to determine the spatial average–temporal average (SATA, W/cm^2), the energy density per treatment (J/cm^2), and total energy delivered during a single treatment (J). In addition, the standardized mean and standard deviation for each outcome group was calculated.

The following equations were used to determine the calculated variables.[17, 79]

1. SATA (W/cm^2) = average intensity (W/ cm^2) X duty cycle (%)
2. Energy density per treatment (J/cm^2) = SATA (W/cm^2) X time per treatment (seconds)

3. Total energy per treatment (J) = SATA (W/cm^2) X transducer head size or effective radiating area (cm^2) X time per treatment (seconds)

Predicted Temperature Change

Calculations were completed from the data to determine the predicted tissue temperature increase. Two formulas were used based on the primary target tissue based on the inquired impairment. Based on Chan et al[44] results, all studies focused on treating unhealthy connective tissue had the treatment time multiplied by 3.45 due to the increased heating rate. Note Chan et al[44] and Draper et al[3] share identical ultrasound manufacturers, BNR and ERA.

1. Predicted thermal change (C) in muscle tissue = temperature increased per minute (Table 1) X time per treatment in minutes X duty cycle.
2. Predicted thermal change (C) in connective tissue = temperature increased per minute (Table 1) X (time per treatment in minutes X 3.45) X duty cycle.

Conceptual Understanding of BNR and ERA

The survey included specific questions related to the conceptual understanding of BNR and ERA. The mean and standard deviation were calculated for participants that selected the relevant facts related to the conceptual question. Based on the sample size a percent was calculated of the participants selected all the appropriate facts related to the conceptual question were calculated.

CHAPTER IV: MANUSCRIPT AND RESULTS

Dose-Response for Therapeutic Ultrasound: A Systematic Review and Intervention Component Analysis

Introduction

Therapeutic ultrasound is a dynamic and complex modality that has been documented to affect tissue extensibility,[9-10,44,55] scar tissue,[59] pain management,[62-66] blood flow,[67-71] and trigger points.[73-75] Alteration to one or more of an ultrasound's treatment parameters will affect the total dose of acoustical energy delivered to the tissue resulting in a specific tissue temperature increase or biophysical effect. The main parameters used to adjust ultrasound acoustical wave production include frequency,[3-4] intensity,[3, 5] and duty cycle.[6] However, how the ultrasound is applied (treatment time,[3] treatment area,[7, 31, 44] and movement of the transducer[8, 45-46]) and the ultrasound manufacture standards (transducer effective radiating area[43] and beam non-uniformity) can influence the total dose of acoustical energy delivered.

The literature often reports the thermal outcome to estimate the total amount of acoustical energy delivered. The total predicted thermal change during treatment is based on the relative change from an individual's baseline. Therefore, mild heating can be considered an increase of 1°C, moderate heating is an increase of 2°C to 3°C, and an increase of $\geq$ 4°C is considered vigorous heating.[26-27] One method used to calculate a predicted tissue temperature increase is based on research by Draper et al.[3] The process uses a known frequency and intensity to determine the heating rates per minute, which are the results from Draper et al[3] study, the heating rates per minute is multiplied by the total minutes the treatment is delivered. However, based on the literature,[3-13] this method of calculating predicted thermal change may not be uniformly applied due to different ultrasound devices producing different rates of heating.

There is another method to calculate the total amount of acoustical energy delivered during a single treatment.[17, 79] First, the spatial average–temporal average (SATA) is calculated by taking the average intensity multiplied by the duty cycle. Then, the SATA is multiplied by the treatment time in seconds and multiplied by the transducer head size or effective radiating area (ERA) to equal the total energy per treatment. This approach incorporates one variable (ERA) to control for manufacturer differences. Variations have been found when comparing the rate per minute heating model to the acoustical energy model (Table 17). Hayes et al[4] and Miller et al[7], used the same treatment parameters, evaluated at the same depth, and had the same acoustical energy delivered during a single treatment. However, the reported heating rate was lower in Hayes et al[4] by 0.132°C/min. This difference may indicate that an error occurred, or another variable should be controlled, like beam non-uniformity (BNR).

Table 17. At 2.5 cm the Energy Density, Total Energy, and Rate Per Minute Heating for 1 MHz Frequency, 1.5 W/cm^2 Intensity, 100% Duty Cycle in Muscle Tissue.

Study	Brand	BNR	ERA (cm^2)	SATA (W/cm^2)	Energy density (J/cm^2)	Total energy (J)	Rate per min heating (°C/min)
Draper et al,[3] 1995	Omnisound 3000	1.8:1	4.1	150	90000	369000	0.40
Rose et al,[10] 1995	Omnisound 3000	1.8:1	4.1	150	90000	369000	0.364
Miller et al,[7] 2008	Omnisound 3000	2.0:1	5	150	90000	450000	0.262
Hayes et al,[4] 2004	Theratouch 7.7	5.5:1	5	150	90000	450000	0.13

Although ultrasound has been documented to affect biological tissue, there has been a lack of uniform application for specific biophysical outcomes. This inconsistency may stem from the fundamental variation between ultrasound devices or the broader range of biological effects than proposed initially. Therefore, the purpose of this systematic review is to identify trends and differences in the literature between ultrasound interventions during the treatment of unhealthy tissue and to evaluate the effectiveness of the intervention parameters and manufacturer

standards. The goal is to provide clinicians with evidence-based insight to improve patient outcomes when targeting specific biophysical effects.

Methodology

A systematic review was undertaken to assist in distinguishing between ultrasound interventions that were successful, inherently faulty (failure of intervention or ultrasound as an intervention), and those that were incorrectly delivered (implementation failure). In addition, the review examined which intervention components had a collective impact that produced a beneficial intervention for unhealthy muscle or connective tissue in human subjects. For this study, beneficial or effectiveness was determined by the outcomes of the original studies' reported significance ($P < 0.05$).

Search Strategy

The search was performed in August of 2021. Potential studies were identified through three databases PubMed, Web of Science, and EBSCO; however, the EBSCO database includes academic search premier, Medline, SPORTDiscus & CINAHL. The following search terms were used with no alterations between the three databases: (therapeutic ultrasound OR thermal ultrasound) AND (pain OR Pain Management OR pain threshold OR Muscle Spasms OR Spasms OR Generalized Spasm OR Range of Motion OR Joint Range of Motion OR Joint Flexibility OR Scar OR Cicatrix OR Scarring).

Inclusion and Exclusion Criteria

The following inclusion criteria were used: (a) the population of the studies included human adult subjects ($\geq$ 18) that had acute or chronic conditions which resulted in unhealthy tissue, (b) ultrasound as an independent assessment with all necessary parameter variables, (c) randomized control trial design, (d) outcome measures were limited to pain scale, force-

generating testing, range of motion, and patient-reported outcome measures (PROMs), (e) literature was limited to publications between 1995 to date of search, free full text, and English text.

Studies that met the following exclusion criteria were eliminated from further investigation: (a) populations with non-soft tissue or autoimmune conditions (bone conditions, internal organ injuries, systemic rheumatic, multiple sclerosis, fibromyalgia, rheumatoid arthritis, osteoarthritis), (b) incomplete treatment parameters (frequency, duty cycle, intensity, and treatment time, tissue type, transducer ERA and BNR), (c) non-therapeutic ultrasound treatments (diagnostic ultrasound, phonophoresis, or bone stimulators), (d) review, meta-analysis, or case studies, (e) no objective outcomes measures, (f) publications prior to 1995, full text requiring purchase from an outside source, non-English text, or abstract only text.

Primary Search Process

The primary screening process was completed by one researcher and involved several steps (Figure 2). Steps were taken to allow for transparency during the screening process. Detailed records were maintained regarding the search and screening process, including dates and critical aspects of the decision-making process.

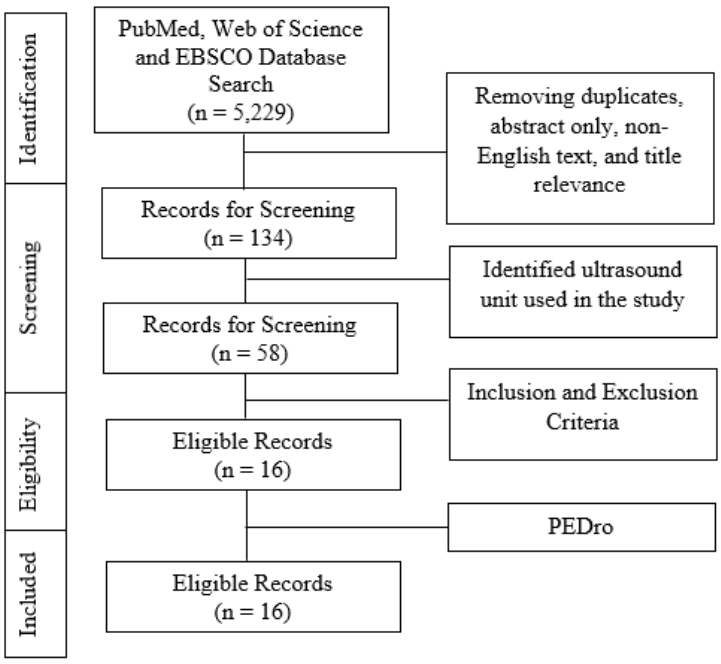

Figure 2. Mapping and results from systematic search.

The initial database search identified a total of 5,229 documents. Only 2.56% of the documents passed the initial screening process. The process included screening the title and abstract for apparent exclusion content. All remaining 134 eligible full documents were reviewed: 76 were eliminated because no ultrasound unit was identified, 13 were removed due to multiple parameters missing, and 21 were removed for missing only one parameter. Additionally, 4 studies were eliminated due to accessibility and another 4 were eliminated due to the inability to identify the BNR and ERA through a service manual or by contacting the manufacturer. The 16 remaining studies were eligible for further evaluation.

Data Extraction and Outcome Measures

Data extraction and management used a standardized data extraction process. The data extraction included raw and coded information on the study design, intervention, control, participants, inclusion/exclusion criteria, and outcome measures. Relevant intervention characteristics extracted for the ICA included authors' reported outcome, type of outcome

measure, tissue type, treatment goal, brand of ultrasound, frequency, intensity, duty cycle, treatment time, ERA, and BNR (Table 18).

Table 18. Raw Studies Parameters

Author	Frequency	Intensity	DC	Tx Time	BNR	ERA	Total Tx	Tissue
Ebadia et al,[98] 2013	1	1.5	100	8	5:1	5	10	Muscle
Gursel et al,[99] 2004	1	1.5	100	10	6:1	5	15	Tendon
Akinoglu et al,[100] 2017	3	1	20	8	5.2:1	1.9	7	Tendon
Yalvac et al,[101] 2018	1	1.5	100	5	5:1	1	10	Tendon
Yildiz et al,[102] 2011	1	1	20	15	5:1	5	10	Tendon
Reda & Ema,[103] 2016	1	1	100	5	3.2:1	6	8	Muscle
Johansson et al,[104] 2005	1	1	100	10	5:1	4	10	Tendon
Armagan et al,[105] 2014	1	1	100	10	5:1	5	15	Tendon
Armagan et al,[105] 2014	1	1	25	10	5:1	5	15	Tendon
Analan et al,[106] 2015	1.1	1.5	100	5	4.5:1	4.1	NA	Joint
Tantawy et al,[107] 2013	1	1	100	10	5:1	5	16	Muscle
Licciardone et al,[108] 2013	1	1.2	100	10	5:1	10	6	Muscle
Santamato et al,[109] 2009	1	2	100	10	6:1	4.6	10	Joint
Otadi et al,[110] 2012	1	1	25	5	5:1	5	10	Joint
Draper et al,[111] 2010	3	1.4	100	5	2.7:1	4.2	2	Muscle
Çatalbas et al,[112] 2018	1	1	100	10	5:1	5	10	Tendon
Çatalbas et al,[112] 2018	1	1	25	10	5:1	5	10	Tendon
Manca et al,[113] 2014	3	1.5	100	12	6:1	5	10	Muscle

Note. DC = duty cycle; Tx = treatment

Two exceptions were made to compensate for expected incomplete reporting by the primary researchers. The manufacturer's reported BNR and ERA were identified through the operation or service manual if the brand and model of the ultrasound were stated in the primary literature. If the operation or service manual could not be found, the ultrasound manufacturers were contacted directly to request the information. Clear documentation was kept for all cases where the BNR or ERA was found through sources outside of the primary research. Of the 16 studies included, only 3 reported a BNR. The remaining were identified through service manual specific to the manufacture and model.

Statistical Analysis

Several phases of calculations occurred as a part of the data analysis. Calculations were completed to determine the following: (a) energy dosage, (b) predicted temperature change based on the outlined parameters. Additionally, for each study the p-value for specific outcome measures were coded based on significant (success) or insignificant (failure). The studies were then organized into a probability matrix and the conditional probability was calculated based on the studies pooled sample sizes.

Energy Dosage

Calculations were completed from the extracted information to determine the spatial average–temporal average (SATA, W/cm^2), the energy density per treatment (J/cm^2), total energy delivered during a single treatment (J), and total exposure to ultrasound over the entire duration of the study (hours). In addition, the standardized mean and standard deviation for each outcome group was calculated.

The following equations were used to determine the calculated variables seen in Table 19.[17, 79]

1. SATA (W/cm^2) = average intensity (W/ cm^2) X duty cycle (%)
2. Energy density per treatment (J/cm^2) = SATA (W/cm^2) X time per treatment (seconds)
3. Total energy per treatment (J) = SATA (W/cm^2) X transducer head size or effective radiating area (cm^2) X time per treatment (seconds)
4. Total exposure (hours) = number of treatments X time per treatment (seconds)
5. Total energy delivered over entire study duration (J) = total energy per treatment (J) X number of treatments

Table 19. Raw Studies Energy Dose

Author	SATA (W/cm^2)	Energy density per treatment (J/cm^2)	Total energy per treatment (J)	Total exposure (hours)	Total energy delivered over entire study duration (J)
Ebadia et al,[98] 2013	150	72000	360000	1.33	720000
Gursel et al,[99] 2004	150	90000	450000	2.5	1350000
Akinoglu et al,[100] 2017	20	9600	18240	0.93	67200
Yalvac et al,[101] 2018	150	45000	45000	0.83	450000
Yildiz et al,[102] 2011	20	18000	90000	2.5	180000
Reda & Ema,[103] 2016	100	30000	180000	0.67	240000
Johansson et al,[104] 2005	100	60000	240000	1.67	600000
Armagan et al,[105] 2014	100	60000	300000	2.5	900000
Armagan et al,[105] 2014	25	15000	75000	2.5	225000
Analan et al,[106] 2015	150	45000	184500	NA	NA
Tantawy et al,[107] 2013	100	60000	300000	2.67	960000
Licciardone et al,[108] 2013	120	72000	720000	1	432000
Santamato et al,[109] 2009	200	120000	552000	1.67	1200000
Otadi et al,[110] 2012	25	7500	37500	0.83	75000
Draper et al,[111] 2010	140	42000	176400	0.17	84000
Çatalbas et al,[112] 2018	100	60000	300000	1.67	600000
Çatalbas et al,[112] 2018	25	15000	75000	1.67	150000
Manca et al,[113] 2014	150	108000	540000	2	1080000

Predicted Temperature Change

Calculations were completed from the extracted information to determine the predicted tissue temperature increase. Two formulas were used based on the primary target tissue in each study. Based on Chan et al[44] results, all studies focused on treating unhealthy connective tissue had the treatment time multiplied by 3.45 due to the increased heating rate. Note Chan et al[44] and Draper et al[3] shared identical ultrasound manufacturers, BNR and ERA.

1. Predicted thermal change (C) in muscle tissue = temperature increased per minute (Table 1) X time per treatment in minutes X duty cycle.
6. Predicted thermal change (C) in connective tissue = temperature increased per minute (Table 1) X (time per treatment in minutes X 3.45) X duty cycle.

Intervention Parameters

A probability matrix was employed to address the accuracy of the existing predictive model (predicted tissue temperature increase that corresponds to a specific biophysical outcome)

against a study's ability to produce a significant effect on an outcome measure (Tables 20, 21, and 22). A conditional probability analysis was completed to evaluate the prevalence and accuracy of the studies. Two predetermined subgroups were established, muscle tissue and connective tissue, due to the need for different predictive formulas for tissue temperature increase. An exception was made to studies that involved joints, due to muscle and tendon both being present in the targeted tissue the studies were included in both groups. Subgroups were identified for pain management and range of motion. Additional subgroups were identified for future evaluation but not considered in this analyzation because of potential low statistical power due to sample size or due to limited understanding of the temperature increase necessary to illicit the biophysical outcome.

The matrix was defined based on the following criteria (Tables 23 and 24):

- True Positives (TP): all cases with a predicted temperature was indicated for the targeted biophysical effect and the actual result was significantly effective for that biophysical effect based on the outcome measure.
- True Negatives (TN): all cases with a predicted temperature was not indicated for the targeted biophysical effect and the actual result was insignificantly effective for that biophysical effect based on the outcome measure.
- False Positives (FP): all cases with a predicted temperature was indicated for the targeted biophysical effect but the actual result was insignificantly effective for that biophysical effect based on the outcome measure ('Type I error').
- False Negatives (FN): all cases with a predicted temperature was not indicated for the targeted biophysical effect but the actual result was significantly effective for that biophysical effect based on the outcome measure ('Type II error').

Table 20. Raw Studies Predicted Temperature Increase with Expected Outcome and Actual Outcome for All Tissue Types

Author	Tissue	Thermal change	Pain			ROM		
			Expected	Outcome	Code	Expected	Outcome	Code
Ebadia et al,[98] 2013	Muscle	2.4℃	Yes			No		
Gursel et al,[99] 2004	Tendon	3℃	Yes	Yes	TP	No	Yes	FN
Akinoglu et al,[100] 2017	Tendon	0.96℃	No	Yes	FN	No		
Yalvac et al,[101] 2018	Tendon	1.5℃	No	Yes	FN	No		
Yildiz et al,[102] 2011	Tendon	0.6℃	No	No	TN	No		
Reda & Ema,[103] 2016	Muscle	1℃	No	No	TN	No	Yes	FN
Johansson et al,[104] 2005	Tendon	2℃	Yes	Yes	TP	No		
Armagan et al,[105] 2014	Tendon	2℃	Yes	Yes	TP	No		
Armagan et al,[105] 2014	Tendon	0.5℃	No	Yes	FN	No		
Analan et al,[106] 2015	Joint	1.5℃	Yes	No	FP	No	No	FN
Tantawy et al,[107] 2013	Muscle	2℃	Yes	Yes	TP	No		
Licciardone et al,[108] 2013	Muscle		No	No	TN	No		
Santamato et al,[109] 2009	Joint	4℃	No	Yes	FN	Yes	Yes	TP
Otadi et al,[110] 2012	Joint	0.25℃	No	Yes	FN	No		
Draper et al,[111] 2010	Muscle		No			No	Yes	FN
Çatalbas et al,[112] 2018	Tendon	1℃	No	Yes	FN	No		
Çatalbas et al,[112] 2018	Tendon	0.5℃	No	Yes	FN	No		
Manca et al,[113] 2014	Muscle	10.8℃	No	Yes	FN	No	Yes	FN

TP: all cases with a predicted temperature was indicated for the targeted biophysical effect and the actual result was significantly effective for that biophysical effect based on the outcome measure.
TN: all cases with a predicted temperature was not indicated for the targeted biophysical effect and the actual result was insignificantly effective for that biophysical effect based on the outcome measure.
FP: all cases with a predicted temperature was indicated for the targeted biophysical effect but the actual result was insignificantly effective for that biophysical effect based on the outcome measure ('Type I error').
FN: all cases with a predicted temperature was not indicated for the targeted biophysical effect but the actual result was significantly effective for that biophysical effect based on the outcome measure ('Type II error').

Table 21. Raw Studies Predicted Temperature Increase with Expected Outcome and Actual Outcome for Muscle Tissue Types

Author	Tissue	Thermal change	Pain			ROM		
			Expected	Outcome	Code	Expected	Outcome	Code
Ebadia et al,[98] 2013	Muscle	2.4℃	Yes			No		
Reda & Ema,[103] 2016	Muscle	1℃	No	No	TN	No	Yes	FN
Tantawy et al,[107] 2013	Muscle	2℃	Yes	Yes	TP	No		
Licciardone et al,[108] 2013	Muscle		No	No	TN	No		
Draper et al,[111] 2010	Muscle		No			No	Yes	FN
Manca et al,[113] 2014	Muscle	10.8℃	No	Yes	FN	No	Yes	FN

TP: all cases with a predicted temperature was indicated for the targeted biophysical effect and the actual result was significantly effective for that biophysical effect based on the outcome measure.
TN: all cases with a predicted temperature was not indicated for the targeted biophysical effect and the actual result was insignificantly effective for that biophysical effect based on the outcome measure.
FP: all cases with a predicted temperature was indicated for the targeted biophysical effect but the actual result was insignificantly effective for that biophysical effect based on the outcome measure ('Type I error').
FN: all cases with a predicted temperature was not indicated for the targeted biophysical effect but the actual result was significantly effective for that biophysical effect based on the outcome measure ('Type II error').

Table 22. Raw Studies Predicted Temperature Increase with Expected Outcome and Actual Outcome for Tendon Tissue

Author	Tissue	Thermal change	Pain			ROM		
			Expected	Outcome	Code	Expected	Outcome	Code
Gursel et al,[99] 2004	Tendon	10.35℃	No	Yes	FN	Yes	Yes	TP
Akinoglu et al,[100] 2017	Tendon	3.31℃	Yes	Yes	TP	No		
Yalvac et al,[101] 2018	Tendon	5.18℃	Yes	Yes	TP	Yes		
Yildiz et al,[102] 2011	Tendon	2.07℃	Yes	No	FP	No		
Johansson et al,[104] 2005	Tendon	6.9℃	No	Yes	FN	Yes		
Armagan et al,[105] 2014	Tendon	6.9℃	No	Yes	FN	Yes		
Armagan et al,[105] 2014	Tendon	1.73℃	Yes	Yes	TP	No		
Analan et al,[106] 2015	Joint	5.18℃	No	No	TN	Yes	No	FP
Santamato et al,[109] 2009	Joint	13.8℃	No	Yes	FN	Yes	Yes	TP
Otadi et al,[110] 2012	Joint	0.86℃	No	Yes	FN	No		
Çatalbas et al,[112] 2018	Tendon	3.45℃	Yes	Yes	TP	No		
Çatalbas et al,[112] 2018	Tendon	0.5℃	No	Yes	FN	No		

TP: all cases with a predicted temperature was indicated for the targeted biophysical effect and the actual result was significantly effective for that biophysical effect based on the outcome measure.
TN: all cases with a predicted temperature was not indicated for the targeted biophysical effect and the actual result was insignificantly effective for that biophysical effect based on the outcome measure.
FP: all cases with a predicted temperature was indicated for the targeted biophysical effect but the actual result was insignificantly effective for that biophysical effect based on the outcome measure ('Type I error').
FN: all cases with a predicted temperature was not indicated for the targeted biophysical effect but the actual result was significantly effective for that biophysical effect based on the outcome measure ('Type II error').

Table 23. Probability Matrixes Layout

	Outcome	
Predicted	True Positive (TP)	False Positive (FP)
	False Negative (FN)	True Negative (TN)

Table 24. Probability Matrixes for Expected and Actual Outcomes Based on the Number of Studies

		Pain			Range of Motion	
Muscle and Tendon		Positive	Negative		Positive	Negative
	Positive	4	1	Positive	1	0
	Negative	8	3	Negative	5	0
Muscle		Positive	Negative		Positive	Negative
	Positive	1	0	Positive	0	0
	Negative	1	1	Negative	3	0
Tendon		Positive	Negative		Positive	Negative
	Positive	4	1	Positive	1	0
	Negative	6	1	Negative	2	0

Intervention Parameters for Ultrasound Manufacturer Standards

Inconsistencies between ultrasound manufacturers and models have been established in the literature.[3-5,11-12,76] To evaluate the extent BNR and ERA have on the significance of an outcome measure, the mean BNR for a significant outcome ($P < 0.05$) was identified as well as the mean BNR for a non-significant outcome. A two-tailed t-test was used to determine if there was a significant difference between the means of two groups (effective vs. non-effective and true positives vs. false negative). The same process was used for ERA and total energy delivered in a single treatment.

Results

The initial database search identified a total of 5,229 documents. However, only 2.56% of the documents passed the initial screening process, 0.01% of the documents remained after

screening for the type of ultrasound unit used, and after screening for the remaining parameter criteria only 0.003% of the documents were able to be included for evaluation.

The sample size in the included studies ranged from 11 to 233 participants with 6 different pathologies (Table 25). Four studies evaluated ultrasound as an isolated intervention, 3 studies evaluated ultrasound paired with a splinting protocol, and the remainder of the studies paired the ultrasound treatment with an additional intervention that was consistent for all groups.

Data was collected for two tissue types (muscle and tendon) and two subgroups (pain management and range of motion) (Tables 26 and 27). When all tissue types were evaluated for pain using the predicted thermal change in muscle tissue formula (n = 545), the sensitivity of the intervention being effective was low (34%) but specificity which implies the ultrasound treatment parameters that were predicted to be ineffective and were ineffective was high (96%). Therefore, it can be assumed that an ultrasound treatment that does not meet the appropriate temperature increase to match the biophysical effect would result in an ineffective treatment. Furthermore, this grouping had a strong positive likelihood of 8.83, which indicates the treatment intervention would have a moderate increase in the likelihood of a positive outcome regardless of the predicted thermal increase matching the biophysical effects. However, there was also a small negative likelihood of 0.69, which reflects all the non-effective intervention findings. Results indicate that regardless of tissue type, the selected parameters and application method used in the literature have a strong chance of success based on the predicted temperature as expected outcome.

Table 25. Study Demographics

Author	N	N	Condition	Additional Intervention
Ebadia et al,[98] 2015	22	22	Chronic non-specific low back pain	Exercise
Gursel et al,[99] 2004	40	17	Shoulder pathology	US and physical therapy interventions / exercise
Akinoglu et al,[100] 2017	54	26	Plantar fasciitis	US and a home exercise program
Yalvac et al,[101] 2018	48	24	Lateral epicondyle	Stand alone
Yildiz et al,[102] 2011	51	17	Carpal tunnel	Splinting
Reda & Ema,[103] 2016	50	25	Neck pain	US and Static stretching
Johansson et al,[104] 2005	85	41	Impingement syndrome	US and a home exercise program
Armagan et al,[105] 2014	46	15	Carpal tunnel	Splinting
Analan et al,[106] 2015	46	16	Rotator cuff disease	Standard physiotherapy program (HP, TENS, exercises)
Tantawy et al,[107] 2013	22	11	Non-specific back pain	Exercise program
Licciardone et al,[108] 2013	45	15	Low back pain	Stand alone; independently receive additional interventions
Santamato et al,[109] 2009	455	233	Subacromial impingement syndrome	Stand alone
Otadi et al,[110] 2012	70	35	Supraspinatus tendon	Home exercise program
Draper et al,[111] 2010	42	21	Upper trapezius trigger point	Stand alone
Çatalbas et al,[112] 2018	26	13	Carpal tunnel syndrome	Night splints
Manca et al,[113] 2014	54	18	Upper trapezius trigger point	Stand alone

Table 26. Probability Matrixes for Expected and Actual Outcomes Based on Study's Sample Size

		Pain			Range of Motion	
Muscle and Tendon		Positive	Negative		Positive	Negative
	Positive	88	11	Positive	35	0
	Negative	171	275	Negative	78	0
Muscle		Positive	Negative		Positive	Negative
	Positive	15	25	Positive	0	0
	Negative	12	0	Negative	50	0
Tendon		Positive	Negative		Positive	Negative
	Positive	73	149	Positive	35	0
	Negative	11	17	Negative	28	0

The modified predicted thermal change formula was used to further examine pain but limit the tissue type to tendon/joint (n = 250). The sensitivity was high (87%), specificity was low (10%), the positive likelihood ratio was low (0.97), and the negative likelihood ratio was

high (1.28). This indicates that the selected parameters or application method was not consistently appropriate for managing pain in connective tissue.

Table 27. Probability Matrixes Probabilities for Expected Outcome and Actual Outcome

		All		Muscle		Tendon	
		Pain	ROM	Pain	ROM	Pain	ROM
Accuracy	(TP+TN)/N	0.67	0.31	0.29	0	0.36	0.56
Misclassification	(FP+FN)/N	0.33	0.69	0.71	1	0.64	0.44
Sensitivity (TPR)	TP/(TP+FN)	0.34	0.31	0.56	0	0.87	0.56
Specificity (TNR)	TN/(TN+FP)	0.96	0	0	0	0.10	0
False Positive Rate (FPR)	FP/(TN+FP)	0.04	0	1		0.90	0
False Negative Rate (FNR)	FN/(TP+FN)	0.66	0.69	1		0.13	0
Positive Predictive Value (PPV)	TP/(TP+FP)	0.89	1	0.38		0.33	1
Negative Predictive Value (NPV)	TN/(TN+FN)	0.62	0	0		0.61	0
Positive Likelihood Ratio	TPR/FPR	8.83	0	0.56		0.97	0
Negative Likelihood Ratio	FNR/TNR	0.69	0	0		1.28	0

When examining all tissue types (n = 16), there was no significant difference that was found between effective and non-effective treatments when examining the BNR ($P = 0.2$; $t = 4.3$; $df = 2$), ERA ($P = 0.33$; $t = 2.78$; $df = 4$), and total energy delivered ($P = 0.18$; $t = 2.18$; $df = 12$). Additionally, no significant difference was found between true positive and false negative when examining the BNR ($P = 0.43$; $t = 12.7$; $df = 1$), ERA ($P = 0.3$; $t = 2.26$; $df = 9$), and total energy delivered ($P = 0.23$; $t = 2.23$; $df = 10$). No significant difference was found between true positive and true negative when examining the BNR ($P = 0.43$; $t = 12.71$; $df = 1$), ERA ($P = 0.31$; $t = 4.3$; $df = 2$), and total energy delivered ($P = 0.06$; $t = 3.18$; $df = 3$).

Table 28. Mean (Standard Deviation) for all Tissue Types for Pain Management

		Positive	Negative
BNR	Positive	5.25 (0.25)	4.5 (0)
	Negative	5.28 (0.16)	4.1 (0.66)
		Positive	Negative
ERA	Positive	4.75 (0.25)	4.1 (0)
	Negative	4.06 (0.58)	5.5 (0.5)
		Positive	Negative
Total energy per treatment	Positive	322500 (44791.18)	184500(0)
	Negative	205342.5 (80621.87)	135000 (45000)

Results specific to tendon showed no significant difference between effective and non-effective treatments when examining the BNR (P = 0.24; t = 4.3; df = 2), ERA (P = 0.57; t = 2.78; df = 4), and total energy delivered (P = 0.42; t = 3.18; df = 3).

The mean and standard deviation were explored to evaluate different trends in parameter selection for pain in all types of tissue: 1.3±0.2 MHz frequency, 1.2±0.1 W/cm^2 intensity, 76±9.2 duty cycle, 9.06±0.7 minutes for treatment time, 5.06:1 ± 0.16:1 BNR, 4.8±0.47 and ERA 256702.5±53229.82 J delivered per treatment, 10.8±0.79 total treatment were administered, and with the total energy delivered over entire study duration 565120±112203.26 J. Additionally, no significant difference between effective and non-effective treatments when examining the frequency (P = 0.21; t = 2.2; df = 11), intensity (P = 0.84; t = 3.18; df = 3), duty cycle (P = 0.97; t = 3.18; df = 3), or treatment time (P = 0.83; t = 4.30; df = 2).

Table 29. All Tissue Types Pain Innervation Mean (Standard Deviation)

		Positive	Negative
Frequency	Positive	1 (0)	1.1 (0)
	Negative	1.5 (0.42)	1 (0)
		Positive	Negative
Intensity	Positive	1.13 (0.13)	1.5 (0)
	Negative	1.25 (0.13)	1 (0)
		Positive	Negative
Duty Cycle	Positive	100 (0)	100 (0)
	Negative	61.88 (14.42)	60 (40)
		Positive	Negative
Treatment Time	Positive	10 (0)	5 (0)
	Negative	8.75 (0.9)	10 (2.5)

Discussion

The purpose of this study was to evaluate the predicted tissue temperature and the total energy delivered during a treatment. Also, to evaluate if there was a trend in dose-response to assist clinicians in reaching effective ultrasound treatments for specific biophysical effects (pain reduction and increase range of motion). Additionally, a systematic intervention component

analysis (ICA) was used to determine if any single parameter influenced the ultrasounds effectiveness when treating unhealthy tissue.

Pain

A moderate increase in tissue temperature (2-3℃) has been recommended to help reduce pain.[26-27] However, the literature supports a wider temperature range. Mardiman et al[65] noted a significant increase in subject's pain threshold with a treatment protocol that resulted in a 1℃ predicted tissue increase or 150,000 J delivered during a treatment. The literature[64] also supported a higher tissue increase (4.8°C) which inhibits sympathetic activity by affecting the rate at which messages are transmitted by sensory and motor nerves. However, due to a smaller transducer with an ERA of 1.5 W/cm^2 there was a smaller amount of energy delivered to the tissue (72,000 J).[64]

Including all tissue types, the mean parameters for a true positive effect would be 1 MHz frequency, 1.13 W/cm² intensity, 100% duty cycle for 10-minutes which equaled a 2℃ increase. Additionally, the mean false negatives would be 1.5 MHz frequency, 1.25 W/cm² intensity, 61% duty cycle for 8.75-minute treatment time. The predicted temperature could not be calculated as the predictive formula does not allow for 1.5 MHz or a 2 MHz frequency. However, the mean parameters for a false positive effect would be 1 MHz frequency, 1.5 W/cm² intensity, 100% duty cycle for 5-minutes which equaled a 1.5℃ increase. Additionally, based on the true negative parameters (1 MHz, 1 W/cm^2, 60%, 6.25-minutes), heating below 0.75℃ would yield an insignificant reduction in pain 96% of the time.

Analan et al[106] was the only study identified as false positive, there are possible explanations for the treatment protocol (1 MHz, 1.5 W/cm^2, 100%, 5-minutes) to fail to elicit the expected pain reduction. Although the treatment area was within the recommended 2-3 times the

ERA, the treatment area may have been too small to effectively treat the rotator cuff injury. The next possible explanation could be a difference in the ultrasound units. Analan et al[106] used the Gymna Combi 200 with a reported 4.5:1 BNR and 4.1 ERA, however in the literature[65] the Therasonic Mark 3a was used with a 5 cm^2 transducer but an unknown BNR. Additionally, it is possible that the ERA or BNR was affected by the increase in intensity. Gange et al[12] noted an unexplained tissue temperature decrease as the intensity increased, 1 W/cm^2 increased tissue temperature by 0.7℃/per minute but 1.75 W/cm^2 increased by 0.39℃/per minute when using the Dynatron Solaris 708 (6:1 BNR and 5 cm^2 ERA). Therefore, it is possible that due to the higher intensity the BNR or ERA was affected causing a lower than predicted tissue temperature increase. Further research is needed to evaluate if a change in BNR or ERA is related to intensity and a corresponding change in tissue temperature heating.

Calculating the total energy delivered to the tissue used 5 variables: intensity, duty cycle, treatment time, and ERA. However, in this study there was no statistically significant difference between the effective and ineffective treatment for any of the individual parameter variables. There was no statistically significant difference between the total energy delivered. However, this study showed that the total energy delivered to the tissue is higher in the effective treatments (true positive mean of 322,500 J; false negative mean of 205,342.5 J) then in the ineffective treatments (false positive mean of 184,500 J; true negative mean of 135,000 J). Therefore, further research is necessary to identify a minimum dose of acoustical energy in which a response occurred for a given treatment area.

Range of Motion

Three laboratory studies were conducted to establish the recommendation of 4℃ with a 3.3-minute stretching window to increase tissue extensibility in both muscle and tendons.[9-10,44]

However, there is limited literature to support this recommendation in unhealthy tissue. Knight et al[55] showed no significant effect following 18 ultrasound treatments with a predicted increase of 2.1℃.

Within this study, all studies that evaluated range of motion showed a positive effect even when the parameters did not match the predicted 4℃ tissue temperature increase. Based on the given parameters of each study the predicted tissue temperature increased ranged from 1℃ to 10.8℃. The mean parameters for a successful intervention were 1.7 MHz, 1.5 W/cm^2, 100%, for 7.8 minutes. The mean tissue temperature increase was 3.4℃. Additionally, the mean number of treatments was 7.5 with a median number of 10. Therefore, ultrasound appears to be affective at a lower than 4℃ tissue temperature change for range of motion.

Parameter Selection

The goal of this study was to evaluate the different components of the ultrasound treatment including the effect BNR and ERA may have on the outcome. This study did not yield significant results related to BNR and ERA. This could be linked to the assumption that all ultrasound units were calibrated to the manufacture standards. Only Armagan et al[105] and Manca et al[113] reported a BNR, the rest of the BNR were identified through service manuals. However, based on the Food and Drug Administration Department of Health and Human Services[30] there is a possible error of 50% between two ultrasound transducers of the same make and model. John et al[43] confirmed the intra-manufacturer variability in the ERA due to the spatial average intensity ranging from 16% to 35% between transducers.[43] Therefore, further research is needed to evaluate to what extent ERA and BNR changes could influence a tissues dose-response.

Predicted Temperature

This study is built around the assumption that calculating the predictive thermal outcome is accurate. Although the process used has been a recommended method for designing treatment plans. The assumption of uniform heating across all properly calibrated ultrasound units has been shown to be faulty. The literature has shown a difference in the rate per minute of heating between different manufacturer brands with different reported ERA and BNR (Tables 30 and 31). [4-5,11-13,76-77] Therefore, studies identified as false negative or false positive could have been misidentified.

The top three manufactures that appeared in this study were Enraf Nonius (Sonoplus 434, 492), Chattonooga (2778, 2738, 27335), and Gymna (Combi 200, Pulson 200, Pbyaction 190). Other manufacturer used were: 1 EU-940, BTL-58205, Petsan 250, Eme-Medical Ultrasonic 1300, Omnisound 3000P, and Mettler (Sonicator 730). Although, the ultrasound models included in this study have similar manufacturer, the models do not match those reported in the literature. [4-5,11-13,76-77] Therefore, a comparison between ultrasound model could not be completed based on alternative predictive formulas for specific ultrasound models. Due to the wide range of ultrasound manufacturers and models, it is critical to explore methods for controlling for variability between units.

Table 30. 3 MHz Rate Per Minute Heating for 100% Duty Cycle in Muscle Tissue

Study	Manufacturer	BNR	ERA (cm^2)	Depth (cm)	Intensity (W/cm^2) [a]			
					0.5	1.0	1.5	2.0
Draper et al,[3] 1995	Omnisound 3000	1.8:1	4.1	0.8	0.3	0.58	0.82	1.5
				1.6	0.31	0.58	0.96	1.3
Hayes et al,[4] 2004	Theratouch 7.7	5.5:1	5	2.5			1.19	
Gallo et al,[6] 2004	Omnisound 3000	3.6:1	3.8	2	0.28			
Miller et al,[7] 2008	Omnisound 3000	3.6:1	5	2.5		0.59		
Draper and Ricard,[9] 1995	Omnisound 3000	1.8:1	4.5	1.2			0.88	
Holcomb and Joyce,[11] 2003	Omnisound 3000	3.7:1	4.9	1.2		0.58		
	Forte 400	2.3:1	4.6	1.2		0.39		
Gange et al,[12] 2018	Dynatron Solaris 708	6:1	5	1		0.7		
				1.75		0.39		
				2.5		NA		
Smith,[13] 2019	Chattanooga Intelect Legend XT	5.0:1	3.0-5	1		0.68		
				1.75		0.52		
				2.5		0.21		

[a]Mean values (given or calculated with available data) expressed in °C/min

Table 31. 1 MHz Rate Per Minute Heating for 100% Duty Cycle in Muscle Tissue

Study	Manufacturer	BNR	ERA (cm^2)	Depth (cm)	Intensity (W/cm^2) [a]			
					0.5	1.0	1.5	2.0
Draper et al,[3] 1995	Omnisound 3000	1.8:1	4.1	2.5	0.04	0.16	0.40	0.4
				5	0.06	0.16	0.31	0.34
Hayes et al,[4] 2004	Theratouch 7.7	5.5:1	5	2.5			0.13	
Leonard et al,[5] 2004	Theratouch 7.7	5.5:1	4.5	4		0.16		0.07
Miller et al,[7] 2008	Omnisound 300	3.6:1	5	2.5			0.26	
Weaver et al,[8] 2006	Omnisound 3000	2.1:1	5	5.08			0.51	
Rose et al,[10] 1995	Omnisound 3000	1.8:1	4.5	2.5			0.36	
				5			0.32	

[a]Mean values (given or calculated with available data) expressed in °C/min

Limitation

A limitation of this study occurred within the primary literature. Due to incomplete reporting of parameters and ultrasound models the sample size was reduced considerably to only 0.003% of the possible studies. Another limitation was the evaluation of the biophysical effect with the corresponding literature. Data was collected for strength (5/6 studies showed significant results) and disability related to activities of daily life (10/12 studies showed significant results),

however there is no biophysical heating recommendation available to use in this ICA. Additionally, the outcome measures for the biophysical effect did not have complete reporting of outcome measures or primary statistics for calculating a pooled effect size.

Conclusion

The intervention component analysis (ICA), in this study involved two distinct analysis components, the identification of the effectiveness of an intervention and the identification of variables in the intervention that seem to influence the outcome. Based on this study, no single parameter appeared to significantly influenced the overall effectiveness of a treatment protocol. Additionally, there does appear to be a threshold for a dose-response related to pain reduction (205,342.5 J). Although there is limited use of total energy per treatment in the literature, further evaluation into minimum and maximal dose could assist in prescription accuracy by including ERA into the predictive outcome.

CHAPTER V: MANUSCRIPT AND RESULTS

Ultrasound Usage and Trends in Clinical Practice

Introduction

Therapeutic ultrasound is a dynamic and complex modality that has been documented to affect tissue extensibility,[9-10,44,55] scar tissue,[59] pain management,[62-66] blood flow,[67-71] and trigger points.[73-75] Theoretically, these different biophysical effects can be achieved by raising the tissue temperature. A 4℃ increase will affect tissue extensibility and scar tissue. Furthermore, a 2-3℃ increase will affect pain threshold and muscle spasm.[26-27] Alteration to one or more of the treatment parameters will affect the total dose of acoustical energy delivered to the tissue resulting in a tissue temperature increase or biophysical effect. In order to calculate the predicted tissue temperature increase, the following parameters are needed: frequency,[3-4] intensity,[3, 5] duty cycle,[6] and treatment time.[3] Furthermore, how the ultrasound is applied (treatment area,[7, 31, 44] or movement of the transducer[8, 45-46]) and the ultrasound manufacture standards (transducer effective radiating area[43] and beam non-uniformity) can influence the total dose of acoustical energy delivered.

Early surveys (1953-1995) did not address parameter selection but rather access and frequency of therapeutic ultrasound usage in a clinical setting.[80-82] However, modern surveys (1995 – 2022) have explored patterns in ultrasound usage, parameter selection, and clinical decision making.[14-15,29,80,83] Although, due to missing or incomplete treatment parameters by the survey, limited analysis could be completed to estimate the targeted tissue temperature increase from the participants' responses. De Brito Vieira et al,[29] included the necessary parameters (3 MHz, 1.0 W/cm^2, 100% duty cycle, 4 minutes) to calculate the maximal expected temperature increase of 2.4°C based on participants' responses from the survey.

Transducer effective radiating area (ERA) and beam non-uniformity (BNR) are additional parameters that can affect the total dose of acoustical energy delivered to the tissue. However, the ERA and BNR have been shown to be different between ultrasound manufacturers.[3-4,7,10] Although, the literature has demonstrated that not all ultrasound units heat at the same rate, [3-5,11-13,76] limited literature has explored the type of ultrasound units used in clinical practice, ERA, or BNR.

Therefore, the primary goal of this survey was to ascertain trends within parameter selection to evaluate the predicted tissue temperature increase of the treatment protocols to assist in the development of specific treatment protocols for biophysical outcomes. The secondary goal was to evaluate the acoustical energy delivered to the tissue to explore the possibility of using energy dose-response instead of tissue temperature increase for developing treatment protocols.

Methods

The North Dakota State University Institutional Review Board approved this population-based cross-section survey (Appendix B).

Target Participants

A sample population of 2,000 certified athletic trainers were recruited through email obtained from the National Athletic Trainers Association (NATA). The inclusion criteria included participants currently practicing as certified athletic trainers, are 18 years or older, and fluent in English. The exclusion criteria included any survey that did not complete the section which addressed the uses of ultrasound specific to thermal biophysical effects, retired athletic trainers, or non-certified athletic trainers.

Sampling Procedure

Participants were contacted by email through NATA Qualtrics platform in conjunction with the NATA data collection service program. Participants accessed the survey through Qualtrics (Qualtrics LLC, Provo, UT), a GDPR (General Data Protection Regulation) compliant web-based survey software. The study was conducted in a six-week data collection window with reminders sent bi-weekly following the initial invitation to participate for those contacted through the NATA data collection service program.

Survey Instrument

The 27-question survey was composed of four parts: demographic, ultrasound availability and manufacturer standards, uses of ultrasound specific to thermal biophysical effects, and influences on clinical decision-making. The survey was comprised of closed and opened ended questions. The closed-ended questions primarily addressed demographics, uses of ultrasound specific to thermal biophysical effects, and influences on clinical decision-making. However, due to the different ultrasound manufacturers and available models within manufacturers, open ended questions were used to gather information about ultrasounds availability and specific brands/models in clinical use.

Literature[14-15,29,80,83] was used during the development of the survey as well as anecdotal clinical experience. However, questions were tailored to isolate parameter selections for specific biophysical effects. Additionally, because BNR and ERA have not previously been evaluated, questions were added that had not appeared in prior literature to specifically address participants' understanding of the concepts and possible clinical implications on treatment outcomes.

Section one included seven demographic questions, four-questions were formatted as single answer multiple choice and three-questions were select all that apply multiple choice.

These questions addressed level of certification, gender identity, years of experience, and recent continuing education about ultrasound. The remaining three-questions allowed participants to select all relevant professional and post professional education received and outline the current clinical setting. Section two included two-single-answer-questions about the number of ultrasound units and calibration schedule for the ultrasound units. Additionally, one select all that apply question addressed the brands of ultrasound available and three-open-ended-questions addressed the ultrasound model, ERA, and BNR. Section three was set up with four initial questions to gage participants use of ultrasound, reasons for not using ultrasound, and the thermal treatment goals for specific conditions. The next four-questions addressed the treatment parameters: frequency, intensity, duty cycle, and treatment time. All of the questions in section three were setup in a single answer multiple choice matrix. Therefore, the participants would respond to each question for all five conditions (pain management, tissue extensibility, scar tissue remodeling, chronic tendinopathy, and muscle spasm) before moving to the next question. Section four included two select all that apply questions and four single answer questions. Participants were able to select all of the sources that impacted their knowledge acquisition and decision making in regards to ultrasound. The remaining four-questions addressed concepts of BNR and ERA. The final question was optional for participants interested in entering to win a gift card at the conclusion of the study.

The survey was pilot tested with a small cohort of three athletic trainers before distribution for validity purposes. Additionally, the survey was evaluated by 4 certified athletic trainers to improve content. Feedback from all stakeholders were reviewed and the survey was modified accordingly.

Methods

Participants accessed the survey through a link in a recruitment email. Before beginning the survey, participants were presented with information about the study and the consent form, by proceeding to the survey, participants consented to the study. Once the consent was completed, the estimated time for completing the survey was 10 to 15-minutes.

Data Analysis

Several phases of calculations occurred as a part of the data analysis for the closed ended questions. A set of calculations were completed to: (a) calculate means/medians, standard deviations, and frequencies for the different parameters, (b) calculate the predicted temperature change based off the outlined parameters and determine if the predicted temperature should result in success or failure, (c) establish the energy dosage for the physiological categories for each reported ERA, (d) calculate means and standard deviations for the designated BNR and ERA questions to determine if 75% or more of the participants understood basic concepts related to BNR and ERA. The following formulas were used in the calculations:

1. Predicted thermal change (C) in muscle tissue = temperature increased per minute (Table 1) X time per treatment in minutes X duty cycle.
7. Predicted thermal change (C) in connective tissue = temperature increased per minute (Table 1) X (time per treatment in minutes X 3.45) X duty cycle.
8. Total energy per treatment (J) = SATA (W/cm^2) X transducer head size or effective radiating area (cm^2) X time per treatment (seconds)

All analyses were completed in STATA and were completed by the primary investigator. No data was replaced or inserted if the data was missing. Therefore, the conditions and parameters have different sample sizes.

The three open-ended questions were used to establish the ERA necessary for calculating the total energy. If the participant did not know the ERA or BRN but were able to identify the ultrasound manufacturer model, the ERA for the ultrasound unit was identified through service and operational manuals.

Results

Participants

Of the 2,000 surveys distributed, 79 were returned with a response rate of 3.95%. All survey responses were reviewed by the primary investigator. A total of 46 participants were removed, 45 participants for no response to section three and 1 participant identified as a non-certified athletic trainer. Participants identified as 12 males and 21 females, no data was collected pertaining to participants age. Regarding demographic responses, participants were able to select multiple responses to best reflect their clinical environment or educational experience. Demographic data including education, years of experience, and clinical setting can be found in Table 32.

When asked about where participants gained their knowledge of ultrasound, 91% indicated formal education which consisted primarily of undergraduate entry level programs (94%) with some post-professional athletic training masters or doctorates (33%) (Table 33).

When making clinical decisions about incorporating ultrasound into a treatment plan, participants (64%) relied on clinical experience followed by formal professional education (61%), textbooks (57%), peer recommendations (36%), evidence-based research (33%), continuing-education courses (21%), and ultrasound manufacturers (6%) (Table 33).

Table 32. Demographic Information

		Responses
Degrees	Bachelors in another area other than athletic training	3
	Bachelors in Athletic Training (professional)	31
	Masters in Athletic Training (professional)	1
	Masters in Athletic Training (post professional)	5
	Masters in another area other than athletic training	3
	Doctorate in Athletic Training (post professional)	6
	Doctorate in another area other than athletic training	5
Experience	0-5 years	16
	6-10 years	8
	10-15 years	2
	15-20 years	1
	More than 20 years	6
Clinical Setting	Clinic or hospital	5
	College or university	18
	Industrial	0
	High school or secondary school	14
	Armed forces or first responders	1
	Other	4

Table 33. Knowledge Acquisition and Influences

		Responses
Education about ultrasound	Textbooks	22
	Formal Education	30
	Continuing Education	5
	Peer Recommendations	5
	Clinical Experience	18
	Evidence-Based Research	7
	Ultrasound Manufactures	1
	Other	0
Main influence on clinical decision making	Textbooks	19
	Formal Education	20
	Continuing Education	7
	Peer Recommendations	12
	Clinical Experience	21
	Evidence-Based Research	11
	Ultrasound Manufactures	2
	Other	0
CEU's related to ultrasound in the last 5 years	0 Continuing Education	16
	1-2 Continuing Education	13
	3-4 Continuing Education	2
	5 or More Continuing Education	5

Modality Selection

Table 34 shows how participants reported ultrasound use for 5 conditions, while Table 35 shows the participants' rational for infrequent or never including ultrasound in a treatment plan.

Additional reasons participants stated for not including ultrasound was time (4), state regulations (1), and access to ultrasound (1). Additional conditions participants reported regularly using ultrasound included: bruising/contusion (3), swelling/edema (2), tendonitis (1), post-surgical (1), and muscle strains (1)

Table 34. Frequency of Including Ultrasounds into a Treatment Plan

	Frequently[a]	Infrequently	Never	No response
Pain management	8	8	15	2
Tissue extendibility	8	14	9	2
Scar tissue remodeling	10	11	10	2
Chronic tendinopathy	9	13	9	2
Muscle Spasm	8	10	13	2

[a] Frequently is defined as including ultrasound in more than 50% of clinical cases which present with the condition. Infrequent is defined as including ultrasound in less than 50% of clinical cases which present with the condition.

Table 35. Reasons for Not Including Ultrasound into a Treatment Plan

	Lack of research	Lack of training	Not effective in clinical experience	Other interventions preferred	Other	No response
Pain management	2	2	3	15	2	9
Tissue extendibility	3	1	3	12	3	11
Scar tissue remodeling	3	1	2	6	11	10
Chronic tendinopathy	2	1	2	12	5	11
Muscle Spasm	2	2	2	16	3	8

Predicted Temperature Change Relative to Parameter Selection

Participants identified the parameter setting they would use to achieve their therapeutic goal for the 5 outlined conditions. For all conditions the predicted temperature increase ranged from 0.05 to 9.8℃ in muscle tissue or 0.86℃ to 33.81℃ for tendons. The individual predicted temperature increase based on the parameters reported by the participants is located in Appendix C. Predicted temperature outcomes were not calculated for groupings that selected 2 MHz frequency, this is due to the lack of formal literature regarding rate of heating using 2 MHz.

Table 36. Sample Size, Median, Mean, and Standard Deviation

		Pain management	Tissue extendibility	Scar tissue remodeling	Chronic tendinopathy	Muscle Spasm
Treatment Goal	n	24	25	2f6	25	25
	Median	2℃	2℃	2℃	2℃	2℃
	Mean	1.96℃	2.56℃	1.85℃	2.32℃	2.28℃
	SD	0.69	0.87	0.83	0.9	0.89
Duty Cycle	n	29	31	31	31	28
	Median	0.5	1	0.5	0.75	0.88
	Mean	0.67	0.8	0.65	0.72	0.73
	SD	0.3	0.28	0.29	0.29	0.30
Frequency	n	29	31	31	31	29
	Median	1 MHz	1 MHz	2 MHz	2 MHz	1 MHz
	Mean	1.79 MHz	1.65 MHz	2.13 MHz	2.03 MHz	1.31 MHz
	SD	0.90	0.88	0.92	0.95	0.66
Intensity	n	26	29	29	29	27
	Median	1 W/cm^2	1.5 W/cm^2	1 W/cm^2	1 W/cm^2	1.5 W/cm^2
	Mean	1.13 W/cm^2	1.33 W/cm^2	1.24 W/cm^2	1.26 W/cm^2	1.35 W/cm^2
	SD	0.41	0.41	0.41	0.37	0.46
Treatment Time	n	27	29	29	29	27
	Median	5 minutes	7 minutes	7 minutes	5 minutes	7 minutes
	Mean	5.74 minutes	6.31 minutes	6.21 minutes	6.17 minutes	6.22 minutes
	SD	1.51	1.58	1.57	1.51	1.60
Predicted Heating in Muscle	n	20	24	23	24	23
	Median	1.45℃	2.1℃	2.1℃	2.05℃	1.4℃
	Mean	1.81℃	2.44℃	2.61℃	2.59℃	1.72℃
	SD	1.6	1.66	2.22	2.17	1.61
Predicted Heating in Tendon	n	20	24	23	24	
	Median	4.83℃	7.24℃	7.26℃	7.07℃	
	Mean	5.82℃	8.43℃	8.51℃	8.95℃	
	SD	5.36	5.72	7.55	7.48	

The median, mean, and standard deviation for the different parameters is outlined in Table 36. Continuous ultrasound was the chosen duty cycle over pulse ultrasound when the goal was to increase tissue extensibility (61.3%). However, for the other four conditions a pulse duty cycle was preferred. For all conditions the thermal increase desired for the treatment goal had a median of 2℃ and a mean between 1.84℃ and 2.56℃. Although, the predicted thermal increase for all conditions appears close to the treatment goals indicated in textbooks[26-27] there is a wide range of temperatures potentially reached: pain management (0.05℃ to 7.2℃ in muscle; 0.17℃

to 24.84℃ in tendon), tissue extensibility (0.25℃ to 7.2℃ in muscle; 0.86℃ to 24.84℃ in tendon), chronic tendinopathy (0.35℃ to 9.8℃ in muscle; 1.21℃ to 33.81℃ in tendon) and scar tissue remodeling (0.15℃ to 9℃ in muscle; 0.52℃ to 31.05℃ in tendon), and muscle spasm (0.05℃ to 7.2℃ in muscle).

Calculated Acoustical Dose

In order to estimate the total dose of acoustical energy delivered in a treatment, the ERA of the ultrasound unit was necessary. From the thirty-three responses included for analysis, participants indicated the following ultrasound brands were available at their clinical site: Chattanooga (16), Dynatronics (9), Rich-Mar (6), US Pro 2000® (1), and unknown (6). However, only six participants were aware of the model of ultrasound unit available. Furthermore, only one participant was able to identify the appropriate ERA and BNR for the ultrasound model in their clinical setting. The remaining ERA and BNR were identified through service and operational manuals (Table 37).

Table 37. BNR and ERA Based on Ultrasound Model.

Ultrasound Model	BNR	ERA for a 5 cm^2 transducer
US Pro 2000® 2nd Edition	5.0:1*	4.0 cm^2 ± 20%*
Dynatron 125	1 MHz = 3.4:1	1 MHz = 3.4 cm^2
Dynatron 125	3 MHz = 5.4:1	3 MHz = 3.3 cm^2
Dynatron 925	±10	5 cm^2
Dynatron 950+	±10	5 cm^2
Chattanooga Vectra	6.0:1	4.0cm^2, ±1.0
Chattanooga Intellect transport	5.0:1	5 cm^2
Rich-Mar VI	5.5:1	5 cm^2
Rich-Mar Winner EVO	5.5:1	5 cm^2

*Reported by the participant

Due to the limited ultrasound models reported, the total dose of energy was calculated using each of the three ERAs reported (3.4/3.3 cm^2, 4 cm^2, 5 cm^2) for all of the treatment protocols. The individual energy dose based on the parameters reported by the participants is located in Appendix D. For all conditions the energy dose per treatment ranged from 127.5 J to

4200 J. The median, mean, and standard deviation was determined for the different ERAs (Table 38).

Table 38. Sample Size, Median, Mean, and Standard Deviation

ERA		Pain management	Tissue extendibility	Scar tissue remodeling	Chronic tendinopathy	Muscle Spasm
3.3 cm^2 3.4 cm^2	n	20	24	23	24	21
	Median	990 J	1530 J	990 J	1020 J	1020 J
	Mean	1047.9 J	1608.09 J	1176.98 J	1211.5 J	1247.5 J
	SD	690.61	868.85	791.17	699.09	710.56
4.0cm^2	n	25	27	28	28	25
	Median	1200 J	1680 J	1200 J	1200 J	1680 J
	Mean	1542 J	1861.11 J	1385 J	1466.786 J	1634.4 J
	SD	789.53	989.42	900.96	803.5479	899.17
5.0cm^2	n	25	27	28	27	25
	Median	1500 J	2100 J	1500 J	1500 J	1987.5 J
	Mean	1542 J	2326.39 J	1735.71 J	1833.48 J	2013 J
	SD	986.9	1236.78	1127.44	1004.43	1181.78

Understanding of the BNR and ERA

Four questions were asked regarding the basic theory of ERA and BNR usage as well as to highlight the energy transference and safety of the transducer. Three of the 33 participants (9%) understood the area considered as the ERA has to receive at least 5% of the peak ultrasonic energy. Additionally, 51% understood that the ERA is smaller than the surface area of the soundhead on a transducer. Only 40% were able to identify that the BNR represents the average intensity of the ultrasound beam. Furthermore, 41% of participants correctly responded that a lower BNR was consistent with a more uniform intensity of the soundwave.

Discussion

Adjusting ultrasound parameters affects the delivery of the longitudinal sinusoidal wave and the dose of kinetic energy to the tissue. The four main parameters practitioners are able to influence are frequency, duty cycle, intensity, and treatment time. Although significant literature has been published regarding the biophysical effects related to the rise in tissue temperature,

there continues to be inconsistencies in parameter selection which could influence the overall effect the ultrasound has on the tissue.

Pain

According to textbooks[26-27] increasing the tissue temperature by 2-3℃ can help reduce pain. However, the literature supports a wider temperature range. Mardiman et al[65] noted a significant increase in subject's pain threshold with a treatment protocol that resulted in a 1℃ predicted tissue increase. The literature[64] also supported a higher tissue increase (4.8°C) which inhibits sympathetic activity by affecting the rate at which messages are transmitted by sensory and motor nerves.

The survey responses indicated a median temperature of 2℃ and a mean of 1.96℃ when practitioners outlined their treatment goals for pain management. Neither the median (1.45℃) nor the mean (1.81℃) of the calculated predicted tissue temperature increase reached the 2-3°C.[26-27] Furthermore, an unexplained difference in duty cycle was noted between the parameter selection in the literature[65] (1.1 MHz, 1.0 W/cm^2, 100%, 5-minutes) and the median responses of the participants (1 MHz, 1.0 W/cm^2, 50%, 5-minutes). There is limited literature on the reason to use pulsed versus continuous ultrasound other than limiting thermal response in the tissue. Gallo et al[6] noted that the same tissue treatment increase reached with a continuous ultrasound could be reached for a 50% duty cycle if the intensity was doubled. Therefore, one would expect to see an increase in intensity to compensate for the reduction in duty cycle. Thus, the use of pulsed duty cycle may limit the thermal effect causing ineffective treatments, this ineffectiveness could explain why 45% of participants indicated they never used ultrasound to treat pain.

Tissue Extensibility

Often practitioners will treat muscle and/or connective tissue when trying to treat range of motion restrictions related to tissue extensibility. Chan et al[44] evaluated tendon tissue heating rates and noted the tendon tissue heated at a 3.45 times faster rate than muscle tissue. Although the goal with both tissue types is an increase of 4℃ with a 3.3-minute stretching window, parameter selection must be different to accommodate the difference in tissue vascularization and ability to remove heat from the tissue.[9-10,44] However, participants indicated a median temperature of 2℃ and a mean of 2.56℃ as the treatment goal when the tissue type was unspecified.

Based on parameter selection muscle tissue (2.44℃ ± 1.66) would accomplish the treatment goals but would not reach the recommended 4℃. However, the parameter selection would exceed the recommended 4℃ in tendon tissue (8.43℃ ± 5.72). A limitation of this survey, was that the questions did not specify the type of tissue treated. Another limitation of this survey was there was no inquiry about the size of treatment area. Both the tissue type and treatment area would affect overall tissue heating. For example, if the practitioners treated a tendon but used a treatment area double the recommended (2-3 times the ERA) then the mean heating rate would reduce by half (4.22℃) thus reaching the recommended 4℃.[7,31,44] Further information is necessary to understand how practitioners are using ultrasound to affect tissue extensibility and range of motion.

Scar Tissue Remodeling

There is limited literature available addressing scar tissue and collagen fibers past one-week injury. In an animal model, the literature indicated scar tissue development 4-weeks post injury may be positively influenced by a 6°C change in tissue temperature.[59] In this study, 30%

of participants used ultrasound in at least half of their clinical cases involving scar tissue. The overall mean treatment goal was 2.56℃ temperature increase. This does not match with the non-thermal (below 1℃) noted for early collagen formation nor the later stages of scar tissue remodeling (> 4℃).[27] Additionally, the predicted temperature increase does not match with the recommendations nor the literature; muscle tissue had a mean increase of 2.61℃ ± 2.22 and tendon had a mean increase of 8.51℃ ± 7.55. Therefore, it can be assumed that clinicians are not selecting the correct parameters to address scar tissue and collagen fibers.

Further research is needed on granular tissue and what impact healing tissue has on the heating rate of ultrasound as possible changes in parameter selections could be necessary during the different stages of tissue healing to accommodate for the new vessels.[67-71]

Chronic Tendinopathy

A chronic tendinopathy is characterized by pain, swelling, and impairment. A 1℃ increase has been recommended to reduce mild inflammation. Within the literature,[115] a progressive treatment plan has been shown to be beneficial. Over the course of 2-weeks, ultrasound treatments were delivered to cause a 0.25℃ increase which progressed to 1℃ increase by adjustments to the intensity and treatment time. However, Binder et al[115] was published before Chan et al[44] identified tendons increased rate of heating. Therefore, instead of the 1℃ at the end of the 2-week protocol, there would have been a 3.45℃ increase in tendon tissue.

In this study, participants indicated parameters that would cause a mean increase of 2.59℃ ± 2.17 in muscle tissue but a mean increase of 8.95℃ ± 7.48 in tendon tissue. If the assumption is made that participants are treating tendons, the tissue temperature increase far exceeds the 1℃ for mild inflammation and the 4℃ for tissue extensibility. However, if muscle

tissue was the intended target, participants may have generalized between an early and late stage healing treatment protocol which resulted in a mean (2.59℃ ± 2.17) increase between 1℃ and 4℃. Further research is needed to explore trends within progressive ultrasound treatment protocols.

Muscle Spasms

Although textbooks[26-27] recommend an ultrasound treatment protocol with a 2-3℃ tissue temperature increase as a possible treatment for muscle spasm. There is limited literature that addresses ultrasounds effect on muscle spasms. The literature has shown evidence of ultrasound being effective in the treatment of trigger points and range of motion restriction caused by muscle spasm.[74-75] Participants in this survey selected parameters that would elicit a mean of 2.28℃ ± 0.89 tissue temperature increase similar to the recommendations of 2-3℃.[26-27] Additionally, the median parameters (1 MHz, 1.5 W/cm^2, 88%, 7-minutes) are consistent with those found in the literature (1 MHz, 1.0 W/cm^2 to 1.5 W/cm^2, 5 to 10-minutes). Based on this survey, clinicians are able to accurately select ultrasound parameters to treat a muscle spasm in accordance with the literature.

Effective Radiating Area (ERA) and Beam Nonuniformity Ratio (BNR)

ERA and BNR are critical concepts for the accurate use of ultrasound. The literature has shown a difference in the rate per minute of heating between different manufacturer brands with different reported ERA and BNR.[4-5,11-13,76-77] At 2.5 cm depth in muscle tissue, the Omnisound 3000, 1.8:1 BNR and 4.1 cm^2 ERA, has been shown to produce the heating rate of 0.4°C/minute for the following parameters 1 MHz, 1.5 W/cm^2, 100%.[3] Using the same parameters and muscle tissue depth, the Theratouch 7.7, 5.5:1 BNR and 5 cm^2 ERA, produced a heating rate of 0.13°C/ minute.[4] Based on these heating rates a 5-minute ultrasound treatment given with the Omnisound

3000 would cause a 2°C tissue temperature increase which is notably higher than the 0.65°C temperature increase seen in the Theratouch 7.7. Furthermore, changes to the BNR or ERA has been shown to affect the rate of heating for the same model of ultrasound.[3,7] Miller et al[7] conducted a study using the Omnisound 3000, 2.0:1 BNR and a 5 cm^2 ERA, with the same parameters and muscle tissue depth. Results showed a 0.26°C/min heating rate, which would result in a 1.3°C increase for a 5-minute ultrasound treatment. Based on the literature, a BNR above a 1.8:1 did not reach the correct heating rate thus the ultrasound treatment would likely be ineffective. Therefore, it is not surprising that 34% of certified athletic trainers reported never including ultrasound into a treatment protocol regardless of the condition.

Only 1 of the 33 participants was able to report a known ERA and BNR for the type of ultrasound available in their clinic. Additionally, little more than half the participants were able to identify the difference between ERA and transducer sound plate size. This gap in knowledge maybe due to lack of emphasis placed on BNR and ERA in the literature as often the one or both are not reported. However, federal regulations require manufacturers to print ERA and BNR directly on the transducer. Therefore, it could be possible to adjust the treatment parameters to include ERA and BNR. Further, research is needed to establish how to consistently control for ERA and BNR in a rate of heating predictive model or develop energy-based dose-response ranges for specific biophysical outcomes.

Conclusion

Ultrasound has appeared in the literature since the 1950's, although its use has fluctuated over the years it continues to be used in clinical practice. However, there is limited data regarding the parameters used for specific physiological effects. Additionally, limited data has addressed the modifications necessary in parameter selection for different tissue types. Based on

the survey, 31% of certified athletic trainers indicated ultrasound was incorporated into a patient's treatment plan frequently (more than 50% of clinical cases for patients presented with one of the 5 conditions). Based on this survey, certified athletic trainers were able to accurately select ultrasound parameters to treat a muscle spasm in accordance with the literature. Furthermore, regardless of the five conditions the median treatment goal was 2℃ with a mean between 1.85 and 2.56℃.

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APPENDIX A. IRB

NDSU NORTH DAKOTA STATE UNIVERSITY

02/15/2022

Dr. Shannon Lyn David Misialek
Health, Nutrition & Exercise

Re: IRB Determination of Exempt Human Subjects Research:
Protocol #IRB0004039, "Therapeutic Ultrasound: Usage and Trends"

NDSU Co-investigator(s) and research team:

- Shannon Lyn David Misialek
- Stephanie Jean Hamersky

Approval Date: 02/15/2022
Expiration Date: 02/14/2025
Study site(s): The research will be conducted exclusively through electrical means. Participants were contacted by email through the National Athletic Trainers Association (NATA) Qualtrics platform in conjunction with the NATA data collection service program. Surveys obtained through social media platforms will use Qualtrics (Qualtrics LLC, Provo, UT) without affiliation to the NATA.
Funding Agency:
The above referenced human subjects research project has been determined exempt (category 2) in accordance with federal regulations (Code of Federal Regulations, Title 45, Part 46, *Protection of Human Subjects*).

Please also note the following:

- The study must be conducted as described in the approved protocol.
- Changes to this protocol must be approved prior to initiating, unless the changes are necessary to eliminate an immediate hazard to subjects.
- Promptly report adverse events, unanticipated problems involving risks to subjects or others, or protocol deviations related to this project.

Thank you for your cooperation with NDSU IRB procedures. Best wishes for a successful study.

NDSU has an approved FederalWide Assurance with the Department of Health and Human Services: FWA00002439.

APPENDIX B. SURVEY

NDSU NORTH DAKOTA STATE UNIVERSITY

Consent Form:

We are asking you to participate in a research study titled "Therapeutic Ultrasound: Usage and Trends." We will describe this study to you and answer any of your questions. This study is being led by Stephanie Hamersky, PhD candidate in the Department of Health, Nutrition, and Exercise Science at North Dakota State University. The Faculty Advisor for this study is Professor Shannon David-Misialek, Department of Health, Nutrition, and Exercise Science at North Dakota State University.

What the study is about?

The purpose of this research is to identify trends within parameter selection by clinical athletic trainers to evaluate if thermal effect occurred in clinical practice in the treatment of specific impairments. Primary treatment parameters were evaluated (frequency, duty cycle, intensity, and treatment time) as well as manufacture parameters (ERA and BNR) to calculate the total energy delivered during a single treatment and predicted thermal outcome. Conditions examined evaluated underlining symptoms of pathologies associated to tissue extensibility, pain management, muscle restriction, and scar tissue remodeling.

What we will ask you to do?

We will ask you to complete a questionnaire that includes questions about your demographic information, ultrasound availability and manufacture standards, uses of ultrasound specific to thermal biophysical effects, and influences on clinical decision-making. This questionnaire should take approximately 10-15 minutes. No experimental procedures (ie, watching a video before taking the survey) will be administered to participants.

What are the risks and discomforts?

We do not anticipate any risks from participating in this research. However, we are unable to anticipate negative feelings which may be felt by participants may have.

What are the benefits?

We do not anticipate any direct personal benefits from participation in this survey. We expect that the data obtained from this survey will be publishable in a peer-reviewed scientific journal. Publishing this work or presenting it at academic conferences will benefit in the development of standardized dose response of therapeutic ultrasound in unhealthy tissue.

Will I be compensated?

After submitting the questionnaire, you may enter your email address if you wish to be entered into a drawing to win one of seventeen gift cards worth $20.

Privacy/Confidentiality/Data

Unless you choose to submit your email address at the end of the survey, we will not be collecting any personal information. Demographic questions at the beginning of the questionnaire will not include personal identifiers (ie, social security numbers). If you do choose to enter your email address after the questionnaire is complete, this information will be received separately from your survey responses. Your email address will not be linked to those answers. We anticipate that your participation in this survey presents no greater risk than everyday use of the Internet. The questionnaire will be administered on QualtricsXM. This is a common data management platform that many universities and businesses use to send surveys to students, employees, or customers. Questionnaire responses will be stored on the secure Qualtrics servers. The researcher (Stephanie Hamersky) will download/export these data for analysis. Data will only be stored on secure computers that only the researchers access. Your questionnaire response's will never be shared with anyone outside of the research team and will never be sold.

Taking part is voluntary

Your participation in this survey is completely voluntary. You may refuse to participate before the study begins or discontinue at any time with no penalty to you. You may choose not to participate, quit participating at any time, or skip survey questions. There is no penalty to you in any of those situations. Be aware that if you begin the survey and choose to stop part-way, your answers will not be recorded for use in the final analyses. Only individuals who have completed all survey questions are eligible to enter the drawing to win one of seventeen a $20 gift cards.

If you have questions

If you have questions later, you may contact Stephanie Hamersky at stephanie.hamersky@NDSU.edu. If you have any questions or concerns regarding your rights as a subject in this study, you may contact the Institutional Review Board (IRB) for Human Participants in the Office of Research and Creative Activity at 701-231-8995 or access their website at https://www.ndsu.edu/research/for_researchers/research_integrity_and_compliance/institutional_review_board_irb/.

Statement of Consent

I have read the above information and have received answers to any questions I asked. I consent to take part in the study.

By Clicking the next button, I am consenting to this research study.

Section 1: Demographics – Please answer the following questions to the best of your knowledge. Each question allows you to only choose 1 response unless otherwise specified.

1. Are you currently practicing as a Certified Athletic Trainer?
    a) Yes
    b) No
2. How do you identify?
    a) Male
    b) Female
    c) Other
    d) Prefer not to say
3. Select all the degrees that you have completed?
    a) Bachelors in another area other than athletic training
    b) Bachelors in Athletic Training (professional)
    c) Masters in Athletic Training (professional)
    d) Masters in Athletic Training (post professional)
    e) Masters in another area other than athletic training
    f) Doctorate in Athletic Training (post professional)
    g) Doctorate in another area other than athletic training
4. How often have you participated in continuing education units (CEU) related to therapeutic ultrasound in the last 5 years?
    a) 0 CEU's
    b) 1-2 CEU's
    c) 3-4 CEU's
    d) 5 CEU's or more
5. How many years of clinical experience do you have?
    a) 0-5 years
    b) 6-10 years
    c) 10-15 years
    d) 15-20 years
    e) More than 20 years
6. Check all populations you currently work with on a regular basis (5 or more times per week).
    a) Youth 0-12
    b) Youth 13-17
    c) Young adult 18-25
    d) Adult 24-40
    e) Middle age 41-65
    f) Elderly 66 and older
7. What is your current setting? Select the best fit.
    a) Clinic or hospital
    b) College or university
    c) Industrial

d) High school or secondary school
e) Armed forces or first responders
f) Other

Section 2: Ultrasound Machine – The following sections will ask you questions regarding the therapeutic ultrasound machines that you use in clinical practice.

8. How many Therapeutic ultrasound machines do you have at your current location?
    a) 1
    b) 2
    c) 3
    d) 4
    e) 5 or more
9. How frequently are the therapeutic ultrasound machines calibrated?
    a) More than once a year
    b) Once a year
    c) Every few years
    d) Unknown
10. Select all brands of therapeutic ultrasound units currently in your setting?
    a) Dynatronics
    b) Chattanooga
    c) SoundCare
    d) Mettler
    e) Sonicator
    f) SonoSite
    g) Omnisound
    h) Theratouch
    i) Forte
    j) Other
    k) Unknown
11. List all the ultrasound brands model information currently at your setting. If you do not know the model of the ultrasound unit, please mark unknown.
12. List all the ultrasound brands BNR information currently at your setting. If you do not know the BNR of the ultrasound unit, please mark unknown.
13. List all the ultrasound brands ERA information currently at your setting. If you do not know the ERA of the ultrasound unit, please mark unknown.

Section 3: Parameter Selections – The following sections will ask you questions regarding your treatment goals and application of therapeutic ultrasound.

14. Do you use ultrasound to treat the following conditions? Frequently is defined as including ultrasound in more than 50% of clinical cases which present with the condition. Infrequent is defined as including ultrasound in less than 50% of clinical cases which present with the condition.

	Frequently	Infrequently	Never
Pain management			
Tissue extendibility			
Scar tissue remodeling			
Chronic tendinopathy			
Muscle Spasm			

i. Please list any other conditions you regularly use therapeutic ultrasound for.

15. If you do not use ultrasound for the following conditions, indicate why not:

	Lack of research	Lack of training	Not effective in clinical experience	Other interventions preferred	Other
Pain management					
Tissue extendibility					
Scar tissue remodeling					
Chronic tendinopathy					
Muscle Spasm					

i. Please explain what "other" reason you have for not using therapeutic ultrasound.

16. Select your treatment goal in parameter selection for the following conditions:

	Non-Thermal	Thermal	Other
Pain management			
Tissue extendibility			
Scar tissue remodeling			
Chronic tendinopathy			
Muscle Spasm			

i. Please explain what "other" treatment goal you have for using therapeutic ultrasound other than thermal effects.

ii. Select your treatment goal in parameter selection for the following conditions:

	1°C Increase	2°C Increase	3°C Increase	4°C Increase
Pain management				
Tissue extendibility				
Scar tissue remodeling				
Chronic tendinopathy				
Muscle Spasm				

17. Select your commonly used duty cycle for treating the following conditions:

	25% 1:4	50% 1:2	75% 3:4	100% 1:1
Pain management				
Tissue extendibility				
Scar tissue remodeling				
Chronic tendinopathy				
Muscle Spasm				

18. Select your commonly used frequency for treating the following conditions:

	1 MHz	2 MHz	3 MHz
Pain management			
Tissue extendibility			
Scar tissue remodeling			
Chronic tendinopathy			
Muscle Spasm			

19. Select your commonly used intensity for treating the following conditions:

	0.5 W/cm^2	1 W/cm^2	1.5 W/cm^2	2 W/cm^2	Other
Pain management					
Tissue extendibility					
Scar tissue remodeling					
Chronic tendinopathy					
Muscle Spasm					

i. If you marked "other" for an intensity, please indicate your preferred intensity.

20. Select your commonly used treatment duration for treating the following conditions:

	3 minutes	5 minutes	7 minutes	10 minutes	Other
Pain management					
Tissue extendibility					
Scar tissue remodeling					
Chronic tendinopathy					
Muscle Spasm					

i. If you marked "other" for a treatment time please indicate your preferred treatment time.

Section 4: Clinical Decision Making and Knowledge - The following sections will ask you questions regarding your basic knowledge of ultrasound concepts.

21. Where did you learn about therapeutic ultrasound the most?
    a) Textbooks
    b) Formal education
    c) Continuing education
    d) Peer recommendations
    e) Clinical experience
    f) Evidence-based research
    g) Ultrasound manufactures
    h) Other

    i. Please explain what "other" sources you use to learn about therapeutic ultrasound.

22. When determining ultrasound treatment parameters, what sources impact your decision making?
    a) Textbooks
    b) Formal education
    c) Continuing education
    d) Peer recommendations
    e) Clinical experience
    f) Evidence-based research
    g) Ultrasound manufactures
    h) Other

    i. Please explain what "other" factors may affect your decision making when choosing parameters

23. Which of the following is true about ultrasound's effective radiating area (ERA).
    a) Smaller than the surface area of the sound head
    b) Same size as the surface area of the sound head
    c) Consistent between different manufactures with the same size transducer

24. Which of the following is true about ultrasound's effective radiating area (ERA).
    a) Receives at least 5% of the peak sound energy
    b) Receives at least 25% of the peak sound energy
    c) Receives at least 50% of the peak sound energy
    d) Receives at least 75% of the peak sound energy
    e) Receives at least 95% of the peak sound energy

25. Which of the following is true about ultrasound's beam nonuniformity ratio (BNR).
    a) The average intensity of the ultrasound beam
    b) Lower BNR result in more hot spots
    c) A BNR of 9:1 is considered safe

26. Which of the following is true about ultrasound's beam nonuniformity ratio (BNR).
    a) The lower it is, the more uniform the intensity of the sound wave
    b) The higher it is, the more uniform the intensity of the sound wave
    c) BNR does not affect intensity

Optional:

27. If you are interested in entering to win a $20 gift card, please enter an email address where you can be reached. If you are not interested, please type NA to complete the survey.

APPENDIX C. TEMPERATURE

Table C1. Pain Management

Duty Cycle	Frequency	Intensity	Treatment Time	Predicted Thermal Increase in Muscle[3]	Predicted Thermal Increase in Tendon[3,44]
			8 minutes		
50% 1:2	3 MHz		5 minutes		
25% 1:4	1 MHz	0.5 W/cm^2	5 minutes	0.05℃	0.1725℃
25% 1:4	1 MHz	0.5 W/cm^2	5 minutes	0.05℃	0.1725℃
25% 1:4	1 MHz	0.5 W/cm^2			
50% 1:2	2 MHz	1 W/cm^2	7 minutes		
100% 1:1	2 MHz	1 W/cm^2	5 minutes		
50% 1:2	3 MHz	1 W/cm^2	3 minutes	1.8℃	6.21℃
50% 1:2	2 MHz	1 W/cm^2	7 minutes		
50% 1:2	1 MHz	1 W/cm^2	7 minutes	0.7℃	2.415℃
25% 1:4	1 MHz	1 W/cm^2	7 minutes	0.35℃	1.2075℃
75% 3:4	3 MHz	1 W/cm^2	3 minutes	1.35℃	4.6575℃
100% 1:1	3 MHz	1 W/cm^2	5 minutes	3℃	10.35℃
50% 1:2	2 MHz	1 W/cm^2	5 minutes		
100% 1:1	1 MHz	1 W/cm^2	5 minutes	1℃	3.45℃
50% 1:2	1 MHz	1 W/cm^2	5 minutes	0.5℃	1.725℃
100% 1:1	1 MHz	1 W/cm^2	10 minutes	2℃	6.9℃
100% 1:1	1 MHz	1 W/cm^2	7 minutes	1.4℃	4.83℃
100% 1:1	1 MHz	1 W/cm^2	7 minutes	1.4℃	4.83℃
50% 1:2	3 MHz	1 W/cm^2	7 minutes	2.1℃	7.245℃
100% 1:1	3 MHz	1 W/cm^2	5 minutes	3℃	10.35℃
100% 1:1	3 MHz	1.5 W/cm^2	8 minutes	7.2℃	24.84℃
100% 1:1	1 MHz	1.5 W/cm^2	5 minutes	1.5℃	5.175℃
50% 1:2	3 MHz	1.5 W/cm^2	5 minutes	2.25℃	7.7625℃
100% 1:1	1 MHz	1.5 W/cm^2	7 minutes	2.1℃	7.245℃
50% 1:2	1 MHz	2 W/cm^2	5 minutes	1℃	3.45℃
100% 1:1	3 MHz	2 W/cm^2	5 minutes	3.5℃	3.5℃
100% 1:1	2 MHz	2 W/cm^2	5 minutes		
25% 1:4	1 MHz				
50% 1:2	1 MHz		5 minutes		

Table C2. Tissue Extensibility

Duty Cycle	Frequency	Intensity	Treatment Time	Predicted Thermal Increase in Muscle[3]	Predicted Thermal Increase in Tendon[3,44]
50% 1:2	1 MHz		7 minutes		
100% 1:1	3 MHz	0.5 W/cm^2	5 minutes	1.5℃	5.175℃
25% 1:4	1 MHz	0.5 W/cm^2			
25% 1:4	1 MHz	1 W/cm^2	5 minutes	0.25℃	0.8625℃
50% 1:2	2 MHz	1 W/cm^2	7 minutes		
50% 1:2	1 MHz	1 W/cm^2	7 minutes	0.7℃	2.415℃
100% 1:1	3 MHz	1 W/cm^2	5 minutes	3℃	10.35℃
100% 1:1	3 MHz	1 W/cm^2	5 minutes	3℃	10.35℃
75% 3:4	2 MHz	1 W/cm^2	5 minutes		
100% 1:1	1 MHz	1 W/cm^2	10 minutes	2℃	6.9℃
100% 1:1	3 MHz	1 W/cm^2	5 minutes	3℃	10.35℃
100% 1:1	1 MHz	1 W/cm^2	7 minutes	1.4℃	4.83℃
50% 1:2	1 MHz	1 W/cm^2	7 minutes	0.7℃	2.415℃
100% 1:1	3 MHz	1.5 W/cm^2	8 minutes	7.2℃	24.84℃
100% 1:1	1 MHz	1.5 W/cm^2	7 minutes	2.1℃	7.245℃
100% 1:1	1 MHz	1.5 W/cm^2	5 minutes	1.5℃	5.17℃
50% 1:2	3 MHz	1.5 W/cm^2	5 minutes	2.25℃	7.7625℃
100% 1:1	1 MHz	1.5 W/cm^2	8 minutes	7.2℃	24.84℃
50% 1:2	2 MHz	1.5 W/cm^2	7 minutes		
100% 1:1	1 MHz	1.5 W/cm^2	5 minutes	1.5℃	5.175℃
50% 1:2	3 MHz	1.5 W/cm^2	5 minutes	2.25℃	7.7625℃
100% 1:1	1 MHz	1.5 W/cm^2	7 minutes	2.1℃	7.245℃
75% 3:4	3 MHz	1.5 W/cm^2	3 minutes	2.025℃	6.98625℃
100% 1:1	1 MHz	1.5 W/cm^2	10 minutes	3℃	10.35℃
100% 1:1	1 MHz	1.5 W/cm^2	7 minutes	2.1℃	7.245℃
100% 1:1	1 MHz	1.5 W/cm^2	5 minutes	1.5℃	5.175℃
100% 1:1	1 MHz	2 W/cm^2	7 minutes	2.8℃	9.66℃
100% 1:1	1 MHz	2 W/cm^2	7 minutes	2.8℃	9.66℃
100% 1:1	2 MHz	2 W/cm^2	5 minutes		
100% 1:1	1 MHz	2 W/cm^2	7 minutes	2.8℃	9.66℃
25% 1:4	1 MHz				

Table C3. Scar Tissue Remodeling

Duty Cycle	Frequency	Intensity	Treatment Time	Predicted Thermal Increase in Muscle[3]	Predicted Thermal Increase in Tendon[3,44]
			8 minutes		
50% 1:2	1 MHz		7 minutes		
25% 1:4	1 MHz	0.5 W/cm^2			
25% 1:4	1 MHz	1 W/cm^2	3 minutes	0.15℃	0.5175℃
50% 1:2	3 MHz	1 W/cm^2	5 minutes	1.5℃	5.175℃
50% 1:2	3 MHz	1 W/cm^2	7 minutes	2.1℃	7.245℃
50% 1:2	2 MHz	1 W/cm^2	7 minutes		
25% 1:4	1 MHz	1 W/cm^2	5 minutes	0.25℃	0.8625℃
25% 1:4	1 MHz	1 W/cm^2	7 minutes	0.35℃	1.2075℃
100% 1:1	3 MHz	1 W/cm^2	5 minutes	3℃	10.35℃
100% 1:1	3 MHz	1 W/cm^2	5 minutes	3℃	10.35℃
75% 3:4	2 MHz	1 W/cm^2	5 minutes		
100% 1:1	3 MHz	1 W/cm^2	5 minutes	3℃	10.35℃
100% 1:1	3 MHz	1 W/cm^2	10 minutes	6℃	20.7℃
50% 1:2	1 MHz	1 W/cm^2	7 minutes	0.7℃	2.415℃
100% 1:1	3 MHz	1 W/cm^2	5 minutes	3℃	10.35℃
100% 1:1	1 MHz	1 W/cm^2	7 minutes	1.4℃	4.83℃
50% 1:2	3 MHz	1 W/cm^2	7 minutes	2.1℃	7.245℃
25% 1:4	3 MHz	1 W/cm^2	7 minutes	1.05℃	3.6225℃
50% 1:2	2 MHz	1 W/cm^2	5 minutes		
50% 1:2	3 MHz	1 W/cm^2	5 minutes	1.5℃	5.175℃
100% 1:1	3 MHz	1.5 W/cm^2	8 minutes	7.2℃	24.84℃
100% 1:1	1 MHz	1.5 W/cm^2	5 minutes	1.5℃	5.175℃
50% 1:2	3 MHz	1.5 W/cm^2	5 minutes	2.25℃	7.7625℃
100% 1:1	3 MHz	1.5 W/cm^2	10 minutes	9℃	31.05℃
75% 3:4	3 MHz	1.5 W/cm^2	7 minutes	4.725℃	4.725℃
75% 3:4	1 MHz	2 W/cm^2	7 minutes	2.1℃	7.245℃
100% 1:1	1 MHz	2 W/cm^2	7 minutes	2.8℃	9.66℃
100% 1:1	2 MHz	2 W/cm^2	5 minutes		
50% 1:2	3 MHz	2 W/cm^2	7 minutes	1.4℃	4.83℃
50% 1:2	2 MHz	2 W/cm^2	5 minutes		
25% 1:4	1 MHz				

Table C4. Chronic Tendinopathy

Duty Cycle	Frequency	Intensity	Treatment Time	Predicted Thermal Increase in Muscle[3]	Predicted Thermal Increase in Tendon[3,44]
50% 1:2	1 MHz		5 minutes		
25% 1:4	1 MHz	0.5 W/cm^2			
50% 1:2	3 MHz	1 W/cm^2	5 minutes	1.5℃	5.175℃
75% 3:4	3 MHz	1 W/cm^2	5 minutes	2.25℃	7.7625℃
75% 3:4	1 MHz	1 W/cm^2	7 minutes	1.05℃	3.6225℃
50% 1:2	2 MHz	1 W/cm^2	7 minutes		
25% 1:4	1 MHz	1 W/cm^2	7 minutes	0.35℃	1.2075℃
100% 1:1	3 MHz	1 W/cm^2	5 minutes	3℃	10.35℃
100% 1:1	1 MHz	1 W/cm^2	5 minutes	1℃	3.45℃
50% 1:2	3 MHz	1 W/cm^2	5 minutes	1.5℃	5.175℃
100% 1:1	1 MHz	1 W/cm^2	5 minutes	1℃	3.45℃
100% 1:1	3 MHz	1 W/cm^2	5 minutes	3℃	10.35℃
100% 1:1	1 MHz	1 W/cm^2	10 minutes	2℃	6.9℃
100% 1:1	3 MHz	1 W/cm^2	5 minutes	3℃	10.35℃
50% 1:2	1 MHz	1 W/cm^2	7 minutes	0.7℃	2.415℃
50% 1:2	3 MHz	1 W/cm^2	7 minutes	2.1℃	7.245℃
25% 1:4	3 MHz	1 W/cm^2	7 minutes	1.05℃	3.6225℃
100% 1:1	3 MHz	1.5 W/cm^2	8 minutes	7.2℃	24.84℃
100% 1:1	1 MHz	1.5 W/cm^2	5 minutes	1.5℃	5.175℃
50% 1:2	3 MHz	1.5 W/cm	5 minutes	2.25℃	7.7625℃
50% 1:2	3 MHz	1.5 W/cm^2	8 minutes	3.6℃	12.42℃
50% 1:2	2 MHz	1.5 W/cm^2	7 minutes		
100% 1:1	3 MHz	1.5 W/cm^2	5 minutes	4.5℃	15.525℃
75% 3:4	1 MHz	1.5 W/cm^2	5 minutes	1.125℃	3.88125℃
50% 1:2	1 MHz	1.5 W/cm^2	10 minutes	1.5℃	5.175℃
100% 1:1	2 MHz	1.5 W/cm^2	5 minutes		
100% 1:1	3 MHz	1.5 W/cm^2	5 minutes	4.5℃	15.525℃
100% 1:1	3 MHz	2 W/cm^2	7 minutes	9.8℃	33.81℃
100% 1:1	2 MHz	2 W/cm^2	5 minutes		
100% 1:1	1 MHz	2 W/cm^2	7 minutes	2.8℃	9.66℃
25% 1:4	1 MHz				

Table C5. Muscle Spasm

Duty Cycle	Frequency	Intensity	Treatment Time	Predicted Thermal Increase in Muscle[3]
			8 minutes	
50% 1:2	1 MHz		7 minutes	
25% 1:4	1 MHz	0.5 W/cm^2	5 minutes	0.05℃
25% 1:4	1 MHz	0.5 W/cm^2		
	2 MHz	1 W/cm^2	7 minutes	
25% 1:4	1 MHz	1 W/cm^2	7 minutes	0.35℃
25% 1:4	1 MHz	1 W/cm^2	7 minutes	0.35℃
100% 1:1	1 MHz	1 W/cm^2	5 minutes	1℃
100% 1:1	1 MHz	1 W/cm^2	5 minutes	1℃
75% 3:4	1 MHz	1 W/cm^2	5 minutes	0.75℃
100% 1:1	1 MHz	1 W/cm^2	10 minutes	2℃
100% 1:1	1 MHz	1 W/cm^2	7 minutes	1.4℃
100% 1:1	1 MHz	1 W/cm^2	7 minutes	1.4℃
50% 1:2	1 MHz	1 W/cm^2	7 minutes	0.7℃
100% 1:1	3 MHz	1.5 W/cm^2	8 minutes	7.2℃
100% 1:1	2 MHz	1.5 W/cm^2	10 minutes	
100% 1:1	1 MHz	1.5 W/cm^2	7 minutes	2.1℃
100% 1:1	1 MHz	1.5 W/cm^2	5 minutes	1.5℃
50% 1:2	3 MHz	1.5 W/cm^2	5 minutes	2.25℃
100% 1:1	1 MHz	1.5 W/cm^2	7 minutes	2.1℃
100% 1:1	1 MHz	1.5 W/cm^2	7 minutes	2.1℃
100% 1:1	1 MHz	1.5 W/cm^2	5 minutes	1.5℃
75% 3:4	1 MHz	1.5 W/cm^2	5 minutes	1.125℃
50% 1:2	1 MHz	2 W/cm^2	3 minutes	0.6℃
50% 1:2	1 MHz	2 W/cm^2	5 minutes	1℃
100% 1:1	1 MHz	2 W/cm^2	7 minutes	2.8℃
100% 1:1	2 MHz	2 W/cm^2	5 minutes	
50% 1:2	1 MHz	2 W/cm^2	5 minutes	1℃
75% 3:4	3 MHz	2 W/cm^2	5 minutes	5.25℃
25% 1:4	1 MHz			

APPENDIX D. ENERGY

Table D1. Pain Management

Duty Cycle	Frequency	Intensity	Treatment Time	1 MHz = 3.4 cm^2 3 MHz = 3.3 cm^2	4.0cm^2	5 cm^2
			8 minutes			
50% 1:2	3 MHz		5 minutes			
25% 1:4	1 MHz	0.5 W/cm^2	5 minutes	127.5 J	150 J	187.5 J
25% 1:4	1 MHz	0.5 W/cm^2	5 minutes	127.5 J	150 J	187.5 J
25% 1:4	1 MHz	0.5 W/cm^2				
50% 1:2	2 MHz	1 W/cm^2	7 minutes		840 J	1050 J
100% 1:1	2 MHz	1 W/cm^2	5 minutes		1200 J	1500 J*
50% 1:2	3 MHz	1 W/cm^2	3 minutes	297 J	360 J	450 J
50% 1:2	2 MHz	1 W/cm^2	7 minutes		840 J	1050 J
50% 1:2	1 MHz	1 W/cm^2	7 minutes	714 J*	840 J	1050 J
25% 1:4	1 MHz	1 W/cm^2	7 minutes	357 J	420 J	525 J
75% 3:4	3 MHz	1 W/cm^2	3 minutes	445.5 J	540 J	675 J
100% 1:1	3 MHz	1 W/cm^2	5 minutes	990 J	1200 J	1500 J
50% 1:2	2 MHz	1 W/cm^2	5 minutes		600 J	750 J
100% 1:1	1 MHz	1 W/cm^2	5 minutes	1020 J	1200 J	1500 J*
50% 1:2	1 MHz	1 W/cm^2	5 minutes	510 J	600 J	750 J*
100% 1:1	1 MHz	1 W/cm^2	10 minutes	2040 J	2400 J	3000 J
100% 1:1	1 MHz	1 W/cm^2	7 minutes	1428 J	1680 J	2100 J*
100% 1:1	1 MHz	1 W/cm^2	7 minutes	1428 J	1680 J	2100 J
50% 1:2	3 MHz	1 W/cm^2	7 minutes	693 J	840 J	1050 J
100% 1:1	3 MHz	1 W/cm^2	5 minutes	990 J	1200 J	1500 J
100% 1:1	3 MHz	1.5 W/cm^2	8 minutes	2376 J	2880 J	3600 J
100% 1:1	1 MHz	1.5 W/cm^2	5 minutes	1530 J	1800 J*	2250 J
50% 1:2	3 MHz	1.5 W/cm^2	5 minutes	742.5 J	900 J	1125 J
100% 1:1	1 MHz	1.5 W/cm^2	7 minutes	2142 J	2520 J	3150 J
50% 1:2	1 MHz	2 W/cm^2	5 minutes	1020 J	1200 J	3000 J
100% 1:1	3 MHz	2 W/cm^2	5 minutes	1980 J	2400 J	1500 J
100% 1:1	2 MHz	2 W/cm^2	5 minutes		2400 J	3000 J
25% 1:4	1 MHz		5 minutes			
50% 1:2						

*Reported clinical access to an ultrasound unit with the outlined ERA by the participant

Table D2. Tissue Extensibility

Duty Cycle	Frequency	Intensity	Treatment Time	1 MHz = 3.4 cm^2 3 MHz = 3.3 cm^2	4.0cm^2	5 cm^2
50% 1:2	1 MHz		7 minutes			
100% 1:1	3 MHz	0.5 W/cm^2	5 minutes	495 J	600 J	750 J
25% 1:4	1 MHz	0.5 W/cm^2				
25% 1:4	1 MHz	1 W/cm^2	5 minutes	255 J	300 J	375 J
50% 1:2	2 MHz	1 W/cm^2	7 minutes			
50% 1:2	1 MHz	1 W/cm^2	7 minutes	1428 J*	1680 J	2100 J
100% 1:1	3 MHz	1 W/cm^2	5 minutes	990 J	1200 J	1500 J
100% 1:1	3 MHz	1 W/cm^2	5 minutes	990 J	1200 J	1500 J
75% 3:4	2 MHz	1 W/cm^2	5 minutes		900 J	1125 J*
100% 1:1	1 MHz	1 W/cm^2	10 minutes	2040 J	2400 J	3000 J
100% 1:1	3 MHz	1 W/cm^2	5 minutes	990 J	1200 J	1500 J*
100% 1:1	1 MHz	1 W/cm^2	7 minutes	1428 J	1680 J	2100 J
50% 1:2	1 MHz	1 W/cm^2	7 minutes	357 J	420 J	525 J
100% 1:1	3 MHz	1.5 W/cm^2	8 minutes	2376 J	2880 J	3600 J
100% 1:1	1 MHz	1.5 W/cm^2	7 minutes	2142 J	2520 J	3150 J*
100% 1:1	1 MHz	1.5 W/cm^2	5 minutes	1530 J	1800 J*	2250 J
50% 1:2	3 MHz	1.5 W/cm^2	5 minutes	742.5 J	900 J	1125 J
100% 1:1	1 MHz	1.5 W/cm^2	8 minutes	2448 J	2880 J	3600 J
50% 1:2	2 MHz	1.5 W/cm^2	7 minutes		1260 J	1575 J
100% 1:1	1 MHz	1.5 W/cm^2	5 minutes	1530 J	1800 J	2250 J
50% 1:2	3 MHz	1.5 W/cm^2	5 minutes	742.5 J	900 J	1125 J
100% 1:1	1 MHz	1.5 W/cm^2	7 minutes	2142 J	2520 J	3150 J*
75% 3:4	3 MHz	1.5 W/cm^2	3 minutes	668.25 J	810 J	1012.5 J
100% 1:1	1 MHz	1.5 W/cm^2	10 minutes	3060 J	3600 J	4500 J
100% 1:1	1 MHz	1.5 W/cm^2	7 minutes	2142 J	2520 J	3150 J
100% 1:1	1 MHz	1.5 W/cm^2	5 minutes	1530 J	1800 J	2250 J
100% 1:1	1 MHz	2 W/cm^2	7 minutes	2856 J	3360 J	4200 J
100% 1:1	1 MHz	2 W/cm^2	7 minutes	2856 J	3360 J	4200 J*
100% 1:1	2 MHz	2 W/cm^2	5 minutes		2400 J	3000 J
100% 1:1	1 MHz	2 W/cm^2	7 minutes	2856 J	3360 J	4200 J
25% 1:4	1 MHz					

*Reported clinical access to an ultrasound unit with the outlined ERA by the participant

Table D3. Scar Tissue Remodeling

Duty Cycle	Frequency	Intensity	Treatment Time	1 MHz = 3.4 cm^2 3 MHz = 3.3 cm^2	4.0cm^2	5 cm^2
			8 minutes			
50% 1:2	1 MHz		7 minutes			
25% 1:4	1 MHz	0.5 W/cm^2				
25% 1:4	1 MHz	1 W/cm^2	3 minutes	612 J	720 J	900 J
50% 1:2	3 MHz	1 W/cm^2	5 minutes	495 J	600 J	750 J*
50% 1:2	3 MHz	1 W/cm^2	7 minutes	693 J	840 J	1050 J
50% 1:2	2 MHz	1 W/cm^2	7 minutes		840 J	1050 J
25% 1:4	1 MHz	1 W/cm^2	5 minutes	255 J*	300 J	375 J
25% 1:4	1 MHz	1 W/cm^2	7 minutes	357 J	420 J	525 J
100% 1:1	3 MHz	1 W/cm^2	5 minutes	990 J	1200 J	1500 J
100% 1:1	3 MHz	1 W/cm^2	5 minutes	990 J	1200 J	1500 J
75% 3:4	2 MHz	1 W/cm^2	5 minutes		900 J	1125 J*
100% 1:1	3 MHz	1 W/cm^2	5 minutes	990 J	1200 J*	1500 J*
100% 1:1	3 MHz	1 W/cm^2	10 minutes	1980 J	2400 J	3000 J
50% 1:2	1 MHz	1 W/cm^2	7 minutes	714 J	840 J	1050 J
100% 1:1	3 MHz	1 W/cm^2	5 minutes	990 J	1200 J	1500 J*
100% 1:1	1 MHz	1 W/cm^2	7 minutes	1428 J	1680 J	2100 J
50% 1:2	3 MHz	1 W/cm^2	7 minutes	693 J	840 J	1050 J
25% 1:4	3 MHz	1 W/cm^2	7 minutes	346.5 J	420 J	525 J
50% 1:2	2 MHz	1 W/cm^2	5 minutes		600 J	750 J
50% 1:2	3 MHz	1 W/cm^2	5 minutes	495 J	600 J	750 J
100% 1:1	3 MHz	1.5 W/cm^2	8 minutes	2376 J	2880 J	3600 J
100% 1:1	1 MHz	1.5 W/cm^2	5 minutes	1530 J	1800 J*	2250 J
50% 1:2	3 MHz	1.5 W/cm^2	5 minutes	742.5 J	900 J	1125 J
100% 1:1	3 MHz	1.5 W/cm^2	10 minutes	2970 J	3600 J	4500 J
75% 3:4	3 MHz	1.5 W/cm^2	7 minutes	1039.5 J	1260 J	1575 J*
75% 3:4	1 MHz	2 W/cm^2	7 minutes	2142 J	2520 J	3150 J
100% 1:1	1 MHz	2 W/cm^2	7 minutes	2856 J	3360 J	4200 J
100% 1:1	2 MHz	2 W/cm^2	5 minutes		2400 J	3000 J
50% 1:2	3 MHz	2 W/cm^2	7 minutes	1386 J	1680 J	2100 J
50% 1:2	2 MHz	2 W/cm^2	5 minutes		1680 J	2100 J
25% 1:4	1 MHz					

*Reported clinical access to an ultrasound unit with the outlined ERA by the participant

Table D4. Chronic Tendinopathy

Duty Cycle	Frequency	Intensity	Treatment Time	1 MHz = 3.4 cm^2 3 MHz = 3.3 cm^2	4.0cm^2	5 cm^2
50% 1:2	1 MHz		5 minutes			
25% 1:4	1 MHz	0.5 W/cm^2				
50% 1:2	3 MHz	1 W/cm^2	5 minutes	495 J	600 J	750 J*
75% 3:4	3 MHz	1 W/cm^2	5 minutes	742.5 J	900 J	1125 J
75% 3:4	1 MHz	1 W/cm^2	7 minutes	1071 J	1260 J	1575 J
50% 1:2	2 MHz	1 W/cm^2	7 minutes		840 J	1050 J
25% 1:4	1 MHz	1 W/cm^2	7 minutes	357 J*	420 J	525 J
100% 1:1	3 MHz	1 W/cm^2	5 minutes	990 J	1200 J	1500 J
100% 1:1	1 MHz	1 W/cm^2	5 minutes	1020 J	1200 J	1500 J
50% 1:2	3 MHz	1 W/cm^2	5 minutes	495 J	600 J	750 J
100% 1:1	1 MHz	1 W/cm^2	5 minutes	1020 J	1200 J	1500 J*
100% 1:1	3 MHz	1 W/cm^2	5 minutes	990 J	1200 J*	1500 J*
100% 1:1	1 MHz	1 W/cm^2	10 minutes	2040 J	2400 J	3000 J
100% 1:1	3 MHz	1 W/cm^2	5 minutes	990 J	1200 J	1500 J*
50% 1:2	1 MHz	1 W/cm^2	7 minutes	714 J	840 J	1050 J
50% 1:2	3 MHz	1 W/cm^2	7 minutes	693 J	840 J	1050 J
25% 1:4	3 MHz	1 W/cm^2	7 minutes	346.5 J	420 J	525 J
100% 1:1	3 MHz	1.5W/cm^2	8 minutes	2376 J	2880 J	3600 J
100% 1:1	1 MHz	1.5 W/cm^2	5 minutes	1530 J	1800 J*	2250 J
50% 1:2	3 MHz	1.5 W/cm^2	5 minutes	742.5 J	900 J	1125 J
50% 1:2	3 MHz	1.5 W/cm^2	8 minutes	1188 J	1440 J	1800 J
50% 1:2	2 MHz	1.5 W/cm^2	7 minutes		1260 J	1575 J
100% 1:1	3 MHz	1.5 W/cm^2	5 minutes	1485 J	1800 J	2250 J
75% 3:4	1 MHz	1.5 W/cm^2	5 minutes	1147.5 J	1350 J	1687.5 J
50% 1:2	1 MHz	1.5 W/cm^2	10 minutes	1530 J	1800 J	2250 J
100% 1:1	2 MHz	1.5 W/cm^2	5 minutes		1800 J	2250 J
100% 1:1	3 MHz	1.5 W/cm^2	5 minutes	1485 J	1800 J	2250 J
100% 1:1	3 MHz	2 W/cm^2	7 minutes	2772 J	3360 J	4200 J
100% 1:1	2 MHz	2 W/cm^2	5 minutes		2400 J	3000 J
100% 1:1	1 MHz	2 W/cm^2	7 minutes	2856 J	3360 J	4200 J*
25% 1:4	1 MHz					

*Reported clinical access to an ultrasound unit with the outlined ERA by the participant

Table D5. Muscle Spasm

Duty Cycle	Frequency	Intensity	Treatment Time	1 MHz = 3.4 cm^2 3 MHz = 3.3 cm^2	4.0cm^2	5 cm^2
			8 minutes			
50% 1:2	1 MHz		7 minutes			
25% 1:4	1 MHz	0.5 W/cm^2	5 minutes	127.5 J	150 J	187.5 J
25% 1:4	1 MHz	0.5 W/cm^2				
	2 MHz	1 W/cm^2	7 minutes			
25% 1:4	1 MHz	1 W/cm^2	7 minutes	357 J*	420 J	525 J
25% 1:4	1 MHz	1 W/cm^2	7 minutes	357 J	420 J	525 J
100% 1:1	1 MHz	1 W/cm^2	5 minutes	1020 J	1200 J	1500 J
100% 1:1	1 MHz	1 W/cm^2	5 minutes	1020 J	1200 J	1500 J
75% 3:4	1 MHz	1 W/cm^2	5 minutes	765 J	900 J	1125 J*
100% 1:1	1 MHz	1 W/cm^2	10 minutes	2040 J	2400 J	3000 J
100% 1:1	1 MHz	1 W/cm^2	7 minutes	1428 J	1680 J	2100 J*
100% 1:1	1 MHz	1 W/cm^2	7 minutes	1428 J	1680 J	2100 J
50% 1:2	1 MHz	1 W/cm^2	7 minutes	714 J	840	1050
100% 1:1	3 MHz	1.5 W/cm^2	8 minutes	2376 J	2880 J	3600 J
100% 1:1	2 MHz	1.5 W/cm^2	10 minutes		3600 J	4500 J
100% 1:1	1 MHz	1.5 W/cm^2	7 minutes	2142 J	2520 J	3150 J*
100% 1:1	1 MHz	1.5 W/cm^2	5 minutes	1530 J	1800 J*	2250 J
50% 1:2	3 MHz	1.5 W/cm^2	5 minutes	742.5 J	900 J	1125 J
100% 1:1	1 MHz	1.5 W/cm^2	7 minutes	2142 J	2520 J*	3150 J*
100% 1:1	1 MHz	1.5 W/cm^2	7 minutes	2142 J	2520 J	3150 J
100% 1:1	1 MHz	1.5 W/cm^2	5 minutes	1530 J	1800 J	2250 J
75% 3:4	1 MHz	1.5 W/cm^2	5 minutes	1147.5 J	1350 J	1687.5 J*
50% 1:2	1 MHz	2 W/cm^2	3 minutes	612 J	720 J	1500 J
50% 1:2	1 MHz	2 W/cm^2	5 minutes	1020 J	1200 J	900 J
100% 1:1	1 MHz	2 W/cm^2	7 minutes	2856 J	3360 J	4200 J
100% 1:1	2 MHz	2 W/cm^2	5 minutes		2400 J	3000 J
50% 1:2	1 MHz	2 W/cm^2	5 minutes	1020 J	1200 J	900 J
75% 3:4	3 MHz	2 W/cm^2	5 minutes	1485 J	1800 J	1350 J
25% 1:4	1 MHz					

*Reported clinical access to an ultrasound unit with the outlined ERA by the participant