Therapeutic potential of low-intensity ultrasound (part 1): thermal and sonomechanical effects

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Abstract In this first part of the review, we will focus on and discuss various aspects of low-intensity ultrasound (US), with emphasis on mild thermal effects, apoptosis induction, and sonomechanical effects. Mild thermal effects of US have been commonly applied to physical therapy. Though US has clear beneficial effects, the advantage of using US over other heating modalities remains unclear. US has also been used in vivo and clinically in the treatment of wounds and fractures, with promising results. On the biomolecular level, studies have shown that US can induce apoptosis and that certain conditions can provide optimal apoptosis induction. As to potential therapeutic applications, in addition to the thermal and other physical effects, apoptosis induction by US may offer direct and rapid treatment of tumors or cancer tissues. Technological advances and rapidly accelerating research in this field are providing an ever-increasing array of therapeutic options for low-intensity US.

Keywords low-intensity ultrasound · physical therapy · sonomechanical effects

Introduction

Very low average intensity ultrasound (US) has been used in medical imaging (sonography) with a high level of safety. However, recent advances and new applications of this technology have also required higher intensities and longer imaging times. This has triggered research to verify the effects of the US intensities used in imaging, including higher intensities, not only to investigate the potential risks of modern sonography but also to harness its potential for therapeutic application.

Good US imaging has provided an “eye” in diagnosing and localizing treatment targets deep in the body, while therapeutic US provides a noninvasive method to treat or cure deep-tissue targets. The use of high-intensity focused US (HIFU) is now seeing great progress in its clinical applications, with sonography or magnetic resonance imaging (MRI) aiding treatment procedures. Although the use of low-intensity US in therapy has remained a subject of basic research, it also offers a broader spectrum of potential clinical applications because of its nonthermal effects and versatility when combined with other therapeutic methods.

Whereas high-intensity US generally utilizes thermal effects, low-intensity US mainly utilizes nonthermal effects. The nonthermal effects of US can be classified into cavitation and noncavitational effects. Cavitation effects are due to the ultrasonically induced cavitation known to be the primary cause of sonoluminescence and sonochemical reactions producing reactive oxygen species. Acoustic cavitation is the process in which small bubbles in a liquid are forced to oscillate (stable cavitation) or collapse (inertial cavitation) in the presence of an acoustic field. This principle of mechanical disturbance brought about by cavitation is similar to that caused by shock waves. Together with cavitation, other ultrasonic effects that are considered to be nonthermal, and perhaps even noncavitational, offer greater potential for cancer therapy, especially in combination with other therapeutic agents. Promise for such combinations is evident in the outcome of some of the studies previously reviewed, which showed potentiation of anticancer effects when US and anticancer drugs were combined. Noncavitational effects of US also exhibited some therapeutic potential, particularly in wound and fracture healing. The mechanism might be related to mild heating, mechanical stimulation of cells (sonostimulation), or sonoporation.

The expanding use of US in medicine has led to increased demand for more research on the mechanisms by which US
interacts with living cells and tissues. Studies on the biological, chemical, and physical effects of US have revealed promising results. In this review, we will focus on and discuss various aspects of low-intensity US, generally less than 1.0 W/cm² spatial-average temporal-average intensity (I<sub>STTA</sub>), although some may be as high as 5 W/cm², with emphasis on mild thermal effects and sonomechanical effects. Part 2 of this article will also focus on biomolecular effects, US-mediated permeabilization (sonopermeabilization), and US-mediated gene transfection (sonotransfection).

### Thermal effects of low-intensity US

#### Physical therapy

The use of US in physical therapy started in the early 1940s, following a series of developments in ultrasonic technology. US modalities used in physical rehabilitation utilize the same physical principle of its predecessor devices, which is the production of ultrasonic waves using piezoelectric transducers that convert electrical currents into mechanical vibrations.

The transducer head is then put in direct contact with the skin of the body part to be treated. US gel is applied on the US head or over the local area to minimize friction and facilitate transmission of the waves. For treatment of the hands and the feet, however, which have smaller and more uneven surface areas, submersion in degassed water is also recommended. Depending on the part to be treated, the sound waves pass through the local soft tissues such as connective tissue and muscles.

The biophysical effects of ultrasonic energy on living tissues are divided into thermal and nonthermal effects. Knowledge of the effectiveness of US was traditionally based on studies on tissue repair in animals, and to a large extent, on in vitro studies. Moreover, a look at the information currently available online on the supposed benefits of US therapy for musculoskeletal disorders cites stimulation of blood flow to promote healing, relieve pain and inflammation, reduce muscle spasms, and increase the range of motion. However, a good number of studies on the clinical effectiveness of US in physical therapy revealed contrasting results. This lack of consistency in the effect of US therapy indicates that a definitive conclusion on the rationale for the use of US therapy has not been reached.

On the effect of US therapy, Baker et al. conducted a review of 76 journal articles and noted that results of in vitro studies are different from those of in vivo studies due to the presence of the extracellular environment that tends to protect the cells, tissues, and organs by maintaining homeostasis. In addition, cavitation, which has been said to be responsible for the beneficial effects of US rather than thermal heating, proved difficult to recreate in vivo using the intensities generally used in clinical practice.

A systematic review conducted by Van der Windt et al. of three trials indicated that US is ineffective in treating soft tissue shoulder problems. However, due to the small and limited number of trials reviewed in their study, further studies on higher-quality trials are necessary. Similarly, a meta-analysis by Gam and Johanssen of 293 articles on the effects of US published since 1950 resulted in only 13 reviewable cases. The researchers concluded that the use of US in therapy needs firm evidence to support its use through well-designed studies.

In another study, on the other hand, application of low-wave US (LWUS) on the noninjured Achilles tendon of human subjects significantly increased functional ankle mobility after treatment. However, results of the application of a hot water bottle (HWB) revealed that it was as effective as treatment with LWUS. This indicates that LWUS is no more effective than a HWB, and that subjects with proper guidance may get the same benefits as those from US therapy, but in the patient’s own time, thus allowing the patient more independence. Other studies also indicate negative effects observed on application of US to osteoarthritis of the knee, the range of motion and pain management in burn patients, and in management of soft tissue disorders of the shoulder.

In conclusion, the use of various modalities is common as part of the physical therapy plan in addressing the long- and short-term goals of patients. Physical therapists do not have to rely on these modalities for treatment, but depending on the needs of the patient, the need for such modalities may arise. One of the most commonly used modalities is indeed US. Based on studies, US is frequently used by physical therapists. In Canada, about 94% of physical therapists use US. In the northeastern United States, 64% of therapists use this modality at least once per day. In Brisbane, Australia, 93% of physical therapists use US. In the United Kingdom, in physical therapy clinics of the National Health Science hospitals, 20% employ US, and this percentage is 54% in private physical therapy practices.

However, whether US is therapeutically effective or not still requires further investigation. In the process of seeking evidence to support the empirical inclusion of US in a treatment plan, therapists need to stay abreast of current data, and they have to rely on their experience and clinical decision-making skills to make the best decision in creating the most beneficial treatment plan for the patient, particularly if they deem that US is necessary.

#### Wound healing

US has been used both therapeutically and diagnostically in medicine. US has been reported to stimulate growth of cells in tissues that require growth or repair, such as in the healing of fractures and wounds. US has been shown to accelerate wound healing (especially chronic leg ulcers), and several mechanisms have been suggested. Ulcerations occur easily when chronic skin alterations are present and are typically located on the inner side of the lower leg and may eventually lead to extensive ulceration of the complete circumference of the lower leg. Topical application of thera-