Review

Therapeutic ultrasound

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Abstract

Therapeutic ultrasound has been in use for many years. Early applications were those for which tissue heating was the goal, and so it was used for soft tissue injuries such as may be incurred during sport. More recently, attention has been drawn both to high intensity focused beams that may be used for thermal ablation of selected regions, and also to low intensity fields that appear to be able to stimulate physiological processes, such as tissue repair, without biologically significant temperature rises. Ultrasonic tools are used for therapeutic effect in dentistry and are being investigated for use in thrombolysis. This paper reviews the various therapeutic applications of ultrasound. © 1999 Elsevier Science Ireland Ltd. All rights reserved.

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1. Introduction

The ability of ultrasound to interact with tissue to produce biological changes has been known for a long time (Wood and Loomis, 1927). Much of the early drive to understand these interactions came from an interest in harnessing ultrasonically induced changes for therapeutic benefit. More recently, the concern has been to understand any possible hazard that may arise from diagnostic ultrasound imaging.

It is convenient to divide therapeutic ultrasound into two classes, applications that use ‘low’ intensity (0.125–3 W cm\(^{-2}\)) and those using ‘high’ intensities (\(\geq 5\) W cm\(^{-2}\)). The intention of the lower intensity treatments is to stimulate normal physiological responses to injury, or to accelerate some processes such as the transport of drugs across the skin. The purpose of the high intensity treatments is rather to selectively destroy tissue in a controlled fashion. An alternative classification scheme would be in terms of applications for which the sound is directly coupled to the tissue via a coupling medium, and those for which the ultrasound transducer is coupled to a waveguide terminated with a tool specifically designed for the task required.
2. Physiological basis for therapeutic ultrasound

Two types of mechanism are commonly invoked to explain the effects produced by therapeutic ultrasound. These are classed as thermal and non-thermal effects. It is, however, often extremely difficult to identify positively the mechanisms involved in producing biological change, and indeed to isolate non-thermal effects from thermal ones.

2.1. Heat

The energy transported by an ultrasonic beam is attenuated as it passes through tissue. If the intensity in the beam is $I_0$ at a point in the tissue, it will be reduced to $I(x)$ at a distance $x$ from this point, where

$$I(x) = I_0 e^{-\mu x}.$$  

Here, $\mu$ is the intensity attenuation coefficient. The energy loss is due to scattering out of the beam, and to absorption. Energy scattered out of the beam may be absorbed elsewhere in the tissue. Acoustic absorption results in tissue heating. If it is assumed that all the energy attenuation is due to absorption, the rate at which heat is deposited is given by the product of the intensity attenuation coefficient and intensity, $\mu I$. The rate at which the temperature rises is given by $\mu I/\rho C$, where $\rho$ is the density of the tissue and $C$ is its heat capacity. This gives, for example, a rate of temperature rise in liver subjected to 3 MHz ultrasound at an intensity of 1 W cm$^{-2}$ of 0.14°C s$^{-1}$ (8.64°C min$^{-1}$) or to 1 MHz ultrasound at the same intensity of 0.048°C s$^{-1}$ (2.88°C min$^{-1}$). In reality, absorption accounts for 60–80% of total attenuation.

In general, reports of the therapeutic benefits obtained from thermal effects of ultrasound have not been accompanied by accurately measured temperature distributions, nor by rigorous dosimetry. Reports have, in the main, been based only on qualitative evidence. However, the high absorption coefficients of large protein molecules mean that collagenous tissues may be heated preferentially, and it is often these tissues that a physiotherapist is treating. Highly collagenous regions that may be exposed include superficial cortical bone, periosteum, menisci, synovium and capsules of joints, myofascial interfaces, intermuscular scars, fibrotic muscle, tendon sheaths and major nerve trunks. The extent of physiological response to heating may depend on a number of factors, including maximum temperature achieved, rate of temperature rise, time of heating and heated volume.

Beneficial effects thought to arise from ultrasonically induced heating include an increase in extensibility of collagenous structures such as tendons and scar tissue, a decrease in joint stiffness, pain relief, changes in blood flow, decrease in muscle spasm and, at high intensities, selective tissue ablation as achieved in focused ultrasound surgery (ter Haar, 1986).

2.2. Non-thermal effects

Non-thermal mechanisms that can produce beneficial (therapeutic) changes in tissue may be cyclic or non-cyclic in nature. The early literature refers to ‘micro-massage’ (Summer and Patrick, 1964). This is presumably thought to be an effect due to the periodic nature of the sound pressure field. The main non-cyclic effect thought to be involved in ultrasound therapy is acoustic streaming. This may be due to stable, oscillating cavities, or to radiation forces in intra- or extracellular fluids. Streaming may act to modify the local environment of a cell, leading, for example, to altered concentration gradients in the vicinity of an extracellular membrane. The concentration gradient affects the diffusion of ions and molecules across a membrane, and thus streaming may account for the reported changes in the potassium and calcium content of cells following ultrasonic exposure (Chapman et al., 1979; Mortimer and Dyson, 1988).

3. Physiotherapy

Ultrasound was originally introduced into physiotherapy as an alternative diathermy technique, to compete with hot pack, microwave and radiofrequency heating. Its main use has been in
the treatment of soft tissue injuries, but it has also been applied to bone and joint conditions and to accelerate wound healing. Over the years, there has been a move toward reducing the average intensities used, either by reducing the power to the transducer, or by the use of pulsing regimes. This reflects an effort to make use of any non-thermal effects that may exist.

There is a dearth of published, scientifically designed clinical trials for ultrasound physiotherapy, and so the exposures used are largely empirically determined. Most physiotherapy units offer spatial average intensities up to 3 W cm$^{-2}$ and offer one or more transducers operating at discrete frequencies in the range 0.75–5 MHz. The choice of transducer depends on the depth of the target to be treated, deeper targets requiring lower frequencies because of the frequency dependence of ultrasonic attenuation. Devices offer either discrete intensity settings or continuously variable controls. The output may be continuous or pulsed. Pulsed exposures are often chosen when thermal effects are to be kept to a minimum. Commonly available pulsing regimes are 2:2 and 2:8 ms (Pye and Milford, 1992).

Therapy transducers are usually made of low loss lead zirconate titanate (PZT4). They are mounted in a light-weight, hand-held waterproof housing, and are air-backed. For physiotherapy applications, the sound is usually coupled directly into the patient through a thin layer of coupling medium (e.g. aqueous gel or mineral oil), although for awkward geometries the limb to be treated may be immersed in a small waterbath.

3.1. Applications

3.1.1. Soft tissue injuries

It has been demonstrated both in the laboratory, and in clinical trials that ultrasound can stimulate tissue repair and wound healing if correctly applied (Dyson et al., 1968; Dyson, 1990). It appears that exposure to ultrasound during the initial ‘inflammatory’ phase of tissue repair can lead to an acceleration of this phase, although ultrasound is not in itself an anti-inflammatory agent. The second phase of healing is the ‘proliferative’ stage. This is the stage at which cells migrate to the site of injury and start to divide, granulation tissue is formed, and fibroblasts begin to synthesise collagen. Ultrasound has been shown to enhance collagen synthesis by fibroblasts. The final phase of tissue repair is one of ‘remodelling’. There is also evidence that scar tissue treated with ultrasound may be stronger and more elastic than ‘normal’ scar tissue.

There are few published clinical trials of the effect of ultrasound on wound healing, although Dyson et al. (1976) and Callam et al. (1987) have demonstrated that ultrasound can accelerate the healing of varicose ulcers, Galitsky and Levina (1964) showed that ultrasound improved the ‘take’ of skin grafts at trophic ulcer sites, and McDiarmid et al. (1988) were able to demonstrate an improvement in healing rate of infected pressure sores.

3.1.2. Bone injuries

Repair of bone injuries follows the same inflammatory, proliferative and remodelling phases seen for soft tissue repair. Experimental studies using fractures in rat fibulae have found that ultrasound treatment during the inflammatory and early proliferative phases of repair enhanced healing, but that exposure during the late proliferative phase proved disadvantageous, leading to a delay in boney union (Dyson and Brookes, 1983; Pilla et al., 1990). Heckman et al. (1994) demonstrated similar acceleration of healing in human tibial fractures. For bone healing, it appears that while low intensities (0.03–0.5 W cm$^{-2}$ spatial average, temporal average intensity) can produce beneficial effects, too high an intensity (≤0.5 W cm$^{-2}$ spatial average, temporal average intensity) can be deleterious (Tsai et al., 1992; Reher et al., 1997).

4. Ultrasound for cancer therapy

The potential use of ultrasound for the treatment of cancer was first mentioned in the literature in 1933 when it was reported that it had no specific effect on Ehrlich’s carcinoma (Szent-Györgi, 1933). After this, enthusiasm for this approach has come in waves with, for example, the first report of successful application in human
skin metastases in 1944 (Horvath, 1944), while a conference in Erlangen in 1944 concluded that enthusiasm for its potential was not backed up by clinical results and that its use “should be discontinued” (Kremkau, 1979).

Ultrasound has been used as a heating source for hyperthermic cancer treatments (Field and Bleehen, 1979) either on its own, or in conjunction with radio- or chemotherapy. The aim of these treatments is to maintain a uniform temperature distribution of 43–45°C in the tumour for times of the order of 60 min while keeping surrounding normal tissues at physiologically acceptable levels (ter Haar and Hand, 1981). A variety of sources have been designed to achieve this type of large area heating pattern. These include the use of lens systems, curved transducers, mirror systems and crossed beams of phased arrays (ter Haar and Hand, 1981; Hunt, 1982). The biophysics of ultrasonic cell killing at these temperatures is poorly understood, and it seems likely that non-thermal effects also play a part (Morton et al., 1983).

A problem that is common to all hyperthermia treatments, whatever the energy source for heating, is the necessity to know the temperature distribution within tissue, as there is a very narrow dividing line between temperatures that are toxic to cells (> 42°C) and those that are not (< 41.8°C). A solution to this technically complex problem is to subject tissues to temperatures well above this threshold, and to use exposure times that are sufficiently short that the vascular perfusion to the heated volume can have no effect on the resultant temperature rise. This is the principle of focused ultrasound surgery which is discussed in Section 5 and for which one application lies in cancer treatment.

5. Focused ultrasound surgery

A surgical technique that is to replace a conventional surgical knife or scalpel should be reproducible and controllable in its ability to destroy tissue, it should be able to affect a sharply defined region only, and should preferably be quick. High intensity focused ultrasound beams have most of these qualities. The tissue ablation technique that makes use of such beams is known interchangeably as high intensity focused ultrasound (HIFU) or focused ultrasound surgery (FUS).

The principle behind FUS is that a high intensity ultrasound beam brought to a tight focus may kill cells lying within the focal volume while all other tissue in the ultrasound beam path are spared. This gives a method of selective tissue ablation at depth within tissue. Spatial peak intensities in the focus of ~ 1 kW cm⁻² are used. Temperatures in excess of 60°C are reached during the 1–2 s exposure times. This is sufficient to kill cells. Typically, ellipsoidal focal volumes of length 1–2 cm and diameters 1–2 mm are achieved.

FUS was initially investigated for its potential to destroy tissue volumes in the brain selectively, for neuro-anatomical studies. Early clinical research centred on the use of FUS for the treatment of Parkinson’s disease (Ballantine et al., 1960; Fry and Fry, 1960). However, despite promising results, the introduction of L-dopa drug treatment at that time meant that FUS did not gain popular acceptance. Despite promising results from ophthalmological applications for the treatment of glaucoma and retinal detachment and for sealing traumatic capsular tears (Coleman et al., 1985; Rosecan et al., 1985; Silverman et al., 1991), it was not until the 1990s that FUS gained much clinical acceptance. Widespread use of ophthalmological FUS applications was hindered by the parallel development of laser techniques.

Recent interest in FUS has been in urology, for treatment of benign prostatic hyperplasia (BPH), and in oncology, for the treatment of soft tissue tumours in, for example, the liver, the kidney, prostate and bladder. FUS is a non-invasive technique that can be used on an outpatient basis. Early clinical trials in which selected volumes of the enlarged prostate have been ablated to alleviate the symptoms of BPH have shown encouraging results with increased flow rate and decreased post-void residual volume (Gelet et al., 1993; Madersbacher et al., 1994; Uchida et al., 1998).

ter Haar et al. (1998) have published encouraging early results of a phase I clinical trial for the treatment of soft tissue tumours of the liver,
kidney and prostate in fully conscious patients. Regions of tumours lying up to 12 cm below the skin surface were ablated, while all normal tissue lying in the beam path was unharmed. Prostate cancer has also been treated with some early success in a number of patients (Bihrle et al., 1994; Madersbacher et al., 1995; Gelet et al., 1996; Chapelon et al., 1998).

5.1. Vascular occlusion

FUS can also be used to interrupt blood flow (Delon-Martin et al., 1995; Hynynen et al., 1996; Rowland et al., 1997). Hynynen et al. (1996) demonstrated occlusion of the flow in rabbit renal arteries and Rivens et al. (1998) have shown interruption of flow in rat femoral vessels. Possible applications of the finding lie in the treatment of varicose veins and of feto–fetal transfusion syndrome (FFTS). Vaey et al. (1997) have described the potential application of FUS to stop bleeding in hepatic trauma.

5.2. Menière’s disease

Ultrasound may be used in place of more conventional surgery to treat Menière’s disease, the disease of the inner ear which leads to attacks of vertigo. A fine, high intensity ultrasound beam is directed into the lateral semi-circular canal of the ear, and used to destroy the sensory neuro-epithelium of the crista and maculae in the labyrinth (Angell James, 1967). A number of different techniques have been devised to achieve this and good success rates have been reported (Sorensen and Andersen, 1979).

6. Tool surgery

It is not the remit of this review to provide in-depth consideration of the therapeutic uses of ultrasonically driven tools. Tools have been designed for tissue debulking and aspiration, and for tissue cutting. The use of intravascular ultrasonically driven wire tips have been investigated, both for the acceleration of dissolution of blood clots and for the acceleration of dissolution of clots by thrombolytic drugs (Siegel, 1996; Tachibana and Tachibana, 1996). Specialised tips have been designed for use in dentistry. Ultrasonic scaling is becoming a widespread technique and ultrasonic tools are also used for curettage (Walmsley, 1988).

7. Conclusions

It is often forgotten that the first uses for ultrasound in the medical field were for therapeutic applications. Despite considerable early interest in its potential to produce beneficial effects, enthusiasm for many of the techniques proposed was not sustained. An increased understanding of the way in which ultrasound interacts with tissue has led to a resurgence of interest in ultrasound therapy, and to a better understanding of the appropriate exposure regimes for the generation of specific beneficial effects.

References


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