LUND UNIVERSITY

Effects of high intensity focused ultrasound on the intervertebral disc

Persson, Johan K

2006

From the Department of Orthopaedics
Lund University Hospital
Lund, Sweden

Effects of high intensity focused ultrasound on the intervertebral disc

Johan Persson

Thesis 2006

Contact address

Johan Persson
Biomechanical Laboratory
Department of Orthopaedics
Lund University Hospital
SE-221 85 Lund, Sweden
Tel. +46 (0)46 222 07 39
E-mail: johan_k.persson@med.lu.se

I don't care much about music. What I like is sounds.
Dizzy Gillespie

List of Papers

This thesis is based on the following papers:

I. **Ultrasound nucleolysis: An in vitro study**
    Persson J, Strömqvist B, Zanoli G, McCarthy I, Lidgren L.
    Ultrasound in Medicine and Biology 2002; (28): 1189-1197.

II. **Modeling of the heat distribution in the intervertebral disk**
    Persson J, Hansen E, Lidgren L, McCarthy I.
    Ultrasound in Medicine and Biology 2005; (31): 709-717.

III. **Effects of high intensity focused ultrasound on the intervertebral disc: A potential therapy for disc herniations**
    Forslund C, Persson J, Strömqvist B, Lidgren L, McCarthy I.
    Journal of Clinical Ultrasound 2006; (34):330-338.

IV. **Ultrasound attenuation and absorption in the intervertebral disc**
    Persson J, Lidgren L, McCarthy I.
    Submitted

V. **Heating of the intervertebral disc by high intensity focused ultrasound, evaluated with MRI. A technical note**
    Persson J, Olsrud J, Forslund C, Strömqvist B, McCarthy I.
    Submitted

Contents

Introduction

Ultrasound in medicine, a short history

Sounds are the result of the transmission of mechanical vibrations through a medium. Ultrasound is sound at too high a pitch for the human ear to detect. The lowest ultrasound frequencies are therefore around 20 kHz, but typically frequencies used in medical ultrasound are in the range 1–10 MHz. Ultrasound is widely used in medical imaging, as it is non-invasive, and there are no known harmful effects at the power levels used for diagnostic imaging. Ultrasound imaging depends on echoes produced by interfaces within tissues. Karl Dussik and co-workers performed the first experiments using ultrasound as a diagnostical tool in the early 1940's (Dussik, 1942). Inge Edler and Helmut Hertz were pioneers in the work on echocardiography (Edler and Hertz, 1954).

Therapeutic ultrasound preceded diagnostic ultrasound by two decades when Robert Wood and Alfred Loomis in the 1920's showed that ultrasound can produce heat and destroy tissue (Wood and Loomis, 1927). Twenty years later ultrasound was used as a magic "cure everything" treatment on conditions such as arthritic pain, gastric ulcer, eczema, asthma, haemorrhoids, urinary incontinence, and elephantiasis. In the 1950's the brothers William and Francis Fry used ultrasound as a neurosurgical tool on patients with Parkinson's disease (Fry and Fry, 1960).

Interactions of ultrasound with tissue

Transmission of mechanical vibrations through a viscous medium such as soft tissue attenuates energy from the ultrasound beam. For a plane wave with initial intensity I_0, the intensity decreases with distance, x, according to

$$I(x) = I_0 e^{-2\alpha x} \quad (1)$$

where α is the amplitude attenuation coefficient of tissue. The intensity in the acoustical wave is proportional to the amplitude squared which means that the intensity attenuation coefficient, μ, is 2α. The total attenuation in the tissue is due to the combined losses from absorption and scattering of the ultrasound beam.

Transmission of sound through tissue results in a loss of energy from the ultrasound beam, and it is the absorption of the ultrasound energy that produces heating in tissue. The rate of temperature increase is proportional to the absorption coefficient. In many tissues, the absorption coefficient is close in magnitude to the attenuation coefficient.

Specular reflection of ultrasound occurs when the interface is smooth over an area which is several times as great as the ultrasound wavelength. The magnitude of the reflection depends on the angle of incidence and the acoustic impedance mismatch (the acoustic impedance being the sound velocity times the density of the tissue). If irregularities in the surface are about the same size as the wavelength, diffuse reflection will occur. Rayleigh scattering occurs when the particles are much smaller than the wavelength. Reflection between different types of tissues is the base of diagnostic ultrasound but in therapeutic ultrasound makes for a potential problem. Most soft tissues have similar acoustic impedances but bone and air-filled cavities (as the respiratory system and the gastrointestinal tract) are the exception. Therefore the angle of insonation needs to be carefully chosen in order to avoid gaseous or bony passages.

High intensity focused ultrasound

High intensity focused ultrasound (HIFU) is used therapeutically with the specific aim of increasing tissue temperatures. HIFU can be compared with the optical equivalent of focusing the sun's rays by the use of a magnifying glass. In the acoustical case the ultrasound may be focused to targets deep into tissues which result in heating of well defined volumes without affecting the intermediate tissue (Figure 1).
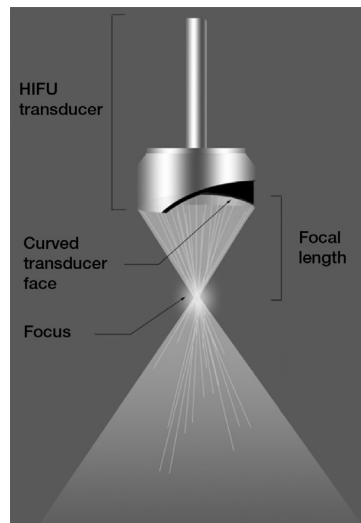
Figure 1. Principal sketch of the ultrasound field from a spherical focused ultrasound transducer. The high ultrasound energy in the focus can raise the temperature locally without affecting the intermediate tissue.

Therapeutic ultrasound can be divided into two categories: low and high intensity ultrasound. Low intensity ultrasound is used in physiotherapy to treat soft tissue injuries (Dyson et al., 1968) and bone injuries (Heckman et al., 1994) by stimulating normal physiological processes. An intensity above 5 W cm^{-2} is defined as high intensity ultrasound (ter Haar G., 1999). The intention with high intensity ultrasound is to destroy or change tissue in a controlled fashion within small volumes. This is achieved by a combination of thermal effects leading to cell death or protein denaturation in the treated tissue, or by non-thermal effects such as cavitation. Research on HIFU has been performed on treatment in areas such as oncology (Wu et al., 2004, Kohrmann et al., 2002), various eye conditions (Thijssen, 1993), heart (Lee et al., 2000), and brain disorders (Hynynen et al., 2001a). Today several clinical treatments and trials for tumour ablation are performed at different HIFU centres, and two commercial HIFU devices exists for tumour treatment (Hynynen et al., 2001b, Hindley et al., 2004, Wu et al., 2004).

The shape and position of the heated region is determined by the ultrasound intensity distribution around the focus, the ultrasound attenuation and absorption in the tissue, and the effect of thermal diffusion. The choice of size, focal length, and acoustic power of the ultrasound transducer affects the intensity field. The size of the "cigar shaped" heated volume is usually 1-3 mm in the transverse plane. To increase the treated volume, it is possible to place the lesions side by side by repositioning the non-invasive ultrasound probe (Visioli et al., 1999, Kohrmann et al., 2002). When using interstitial ultrasound transducers the transducer can be rotated in order to increase the treatment volume (Lafon et al., 2002).

The frequency of the ultrasound affects the size of the focus and the attenuation. An increased frequency leads to an increased ultrasound attenuation but produces a more distinct focus. Therefore the frequency needs to be optimised with respect to the required focal depth and the size of the focus. Using a large aperture ultrasound transducer yields smaller focal regions. It also leads to a smaller temperature increase in the area in front of the focus because the ultrasound energy is distributed over a larger area.

The active part of an ultrasound transducer consists of a disc made of piezo crystal, usually the material lead zirconium titanate (PZT). When an electrical pulse is applied to the piezo crystal, the thickness of the crystal is changed. Applying a sine wave to the transducer will lead to a vibration in the crystal and therefore an acoustical field in the medium in front of the crystal (coupling medium) with the same frequency as the applied electrical signal. The acoustic pressure creates movements in the tissue with an amplitude related to the pressure level. Depending on the acoustical medium, different amounts of energy are lost and converted into heat. This energy loss is negligible in water, which therefore is an excellent coupling medium between the ultrasound transducer and the tissue. The PZT material can be formed into spherical shapes which will result in focused ultrasound fields. The disadvantage with mechanically focused ultrasound probes is that they have fixed focal lengths. This can be overcome by using the ultrasound phased-array technique. The phased-array transducer consists of several individual piezo elements. By exciting the piezo elements in a certain time-sequence it is possible to focus and to steer the beam both longitudinally and transversally. As an example, Hynynen et al. developed a 500-element ultrasound phased-
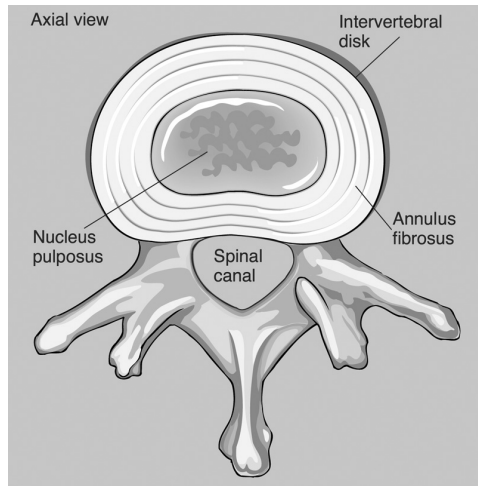
Figure 2. An image of the intervertebral disc and the spinous processes of the vertebra. The disc consists of an inner gel-like material of proteoglycans and collagens called the nucleus pulposus. The outer part of the disc is the ring structured collagen tissue, annulus fibrosus.
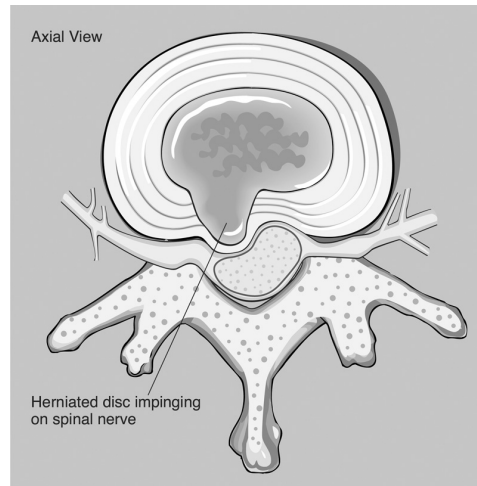

Figure 3. A cross section of an intervertebral disc with contained disc herniation. The annulus fibrosus bulges onto the nerve root which might cause sciatica.

array system for non-invasive HIFU treatment of the brain (Hynynen et al., 2004).

Disc herniation, background

The intervertebral discs permit mobility between the vertebrae and work as vertical shock absorbers. Each disc consists of a central part called the *nucleus pulposus* consisting of a gel-like material of proteoglycans and collagens, which is surrounded by a denser collagen ring structured layer called the *annulus fibrosus*, which has a greater tensile strength (Figure 2). The *nucleus pulposus* of a healthy disc exerts a high osmotic pressure. Except from proteoglycans and collagens the disc consists of water (90% of the young *nucleus pulposus*), which is mainly extracellular because of the disc's low cell content. The healthy disc is the largest avascular structure in the body. Between the disc and the vertebrae a quarter of a millimetre thick cartilaginous tissue is found, the vertebral end-plate.

The disc starts ageing in the late adolescence and gradually loses its fluid content. This might lead to cracks and fissures in the *annulus fibrosus*, and the *nucleus pulposus* might protrude through these

cracks. Three different stages of disc herniation can be defined. In the first stage a bulge occurs posterior of the disc which might compress the spinal nerve (Figure 3). In the second stage the *nucleus pulposus* bursts through the *annulus fibrosus* and in the last stage parts of the *nucleus pulposus* leak out from the disc and are located in the spinal canal. The first two stages represent contained and the third stage non-contained disc herniations. The compression of the spinal nerves might lead to sciatica (causing radiating pain through the thigh and calf and occasionally into the foot) but also chemical inflammatory reactions, which are a source of pain symptoms (Olmarker et al., 1995). Disc herniations are most common (90%) at the L4–5 and L5–S1 level, due to anatomical and mechanical reasons.

30% of healthy young adults have disc herniation without any symptoms (Boden et al., 1990). For patients with symptomatic contained disc herniation (not having perforated the posterior ligament) the main problem is sciatica and the second problem is low back pain. As much as 75% of the disc herniations are estimated to be resolved spontaneously. The remaining patients often require surgery. In Sweden approximately 2000 lumbar discectomies are performed each year (Nationellt Kompetenscentrum för Ortopedi, 2005). Before

invasive procedures are considered the patients are treated with analgesia, rest and physiotherapy for at least 2 months.

The history of surgical treatment of disc herniation started in the 1930's, demonstrating favourable effects of open surgery (Mixter and Barr, 1934). Today lumbar discectomy is usually performed either as an open or microscope-assisted procedure. Results are satisfactory in around 80% of the cases but a significant complication rate of 2–5% has to be anticipated (Spangfort, 1972, Strömqvist et al., 2001). This combined with the need for costly hospital care, surgery and rehabilitation after conventional surgery has created an interest for minimally invasive approaches to lumbar disc herniation.

In the 1960's a new treatment method was developed using the enzymatic substance chymopapain to depolymerise the proteoglycan and glycoprotein molecules in the *nucleus pulposus*. The chymopapain was injected into the *nucleus pulposus*, and the chemical process led to a decrease in the water binding capacity in the disc resulting in a reduced volume. The major disadvantage with this method is anaphylactic reactions occurring in 1% of the patients.

Thermal treatment has also been used in lumbar disc herniation with some promising results. Percutaneous laser discectomy (Mayer et al., 1992) and percutaneous radiofrequency coagulation by means of a cauterising instrument (Sluijter, 1988) are established techniques. The more recently developed intradiscal electrothermal anuloplasty (IDET) method (Saal and Saal, 2002, Pauza et al., 2004) is intended for treatment of discogenic low back pain.

In laser discectomy, a needle with a laser-fibre is introduced through the disc into the *nucleus pulposus*. As the affected tissues absorb the laser, light is converted to heat. At 100ºC, tissue vaporises and ablation takes place. As a small amount of *nucleus pulposus* is vaporised, intradiscal pressure decreases, allowing the disc to return to its normal state (Schenk et al., 2006).

In the IDET method heat is distributed from a navigable catheter with a thermal resistive coil, via a trocar inserted into the disc under local anaesthesia and fluoroscopic control. The heating starts at a coil temperature of 65°C and increases incrementally to 90°C, lasting for about 60 minutes. However, all of these thermal techniques are invasive with respect to the disc, and complicated deep infections are known to occur. The observed clinical improvement has been shown not to only depend on thermal denervation (deprivation of a nerve supply) of the disc. The patophysiological mechanism probably involves shortening of the collagen as well but it is not yet fully understood. Hayashi et al. have shown that the temperature at which protein degradation starts to occur in collagen is 65ºC (Hayashi and Markel, 2001). Saal and Saal suggested that when the conducted heat from the temperature increase reaches the *annulus fibrosus*, posterior annular fissures might be welded together (Saal and Saal, 2002, Pauza et al., 2004, Freeman et al., 2005).

The use of electrothermal energy for therapeutic modification of connective tissue is today an established method. HIFU treatment of the disc is a step towards a less invasive treatment. With HIFU treatment, the disc does not have to be perforated during the therapeutic procedure.

Aim of the thesis

General aim

The purpose of this study was to study and try to optimise high intensity focused ultrasound treatment of the intervertebral disc, from a physical point of view.

Specific aims

The specific aims were:
- To investigate the feasibility of heating the intervertebral disc using HIFU in an *in vitro* bovine disc model.

- To model the heat distribution for HIFU heating in an intervertebral disc model using finite element analysis.
- To elucidate the effects of ultrasound heating on the intervertebral disc on an *in vivo* and *in vitro* animal model.
- To measure the ultrasound attenuation and absorption coefficients in the bovine *annulus fibrosus*.
- To study if magnetic resonance imaging (MRI) could be used for measuring the temperature distribution in a bovine disc during HIFU treatment.

Methods

Ultrasound equipment

Several different ultrasound transducers with different characteristics were used in the experiments (Figure 4). Frequencies in the range of 1 to 7.6 MHz were used and the sizes of the ultrasound probes were 5 to 50 mm in diameter. Except for the plane piezo transducers used in paper IV, the ultrasound transducers were focused with focal lengths in the order of 10 to 100 mm. The piezo crystal in the ultrasound transducers were of the material Pz26 manufactured by Ferroperm A/S (Kvistgård, Denmark). The 5 mm diameter ultrasound probe with a central hole for water cooling and the flat 18 mm diameter probe were mounted by SonoMed Ltd (Warszawa, Poland). The other ultrasound transducers were mounted in-house.

The 5 mm diameter transducer used in paper III and V had a small hole in the centre of the transducer allowing for a flow of water. This provided cooling of the piezo crystal and acoustic coupling between the probe and the tissue.

The equipment for operating and monitoring the ultrasound consisted of function generator (model PM 5134, Philips, Eindhoven, Netherlands or model TG1404, TTi, Cambridgeshire, UK), power amplifier (model ENI 2100L, ENI Inc., Rochester, NY, US or model 75A250 Amplifier Research, Souderton, UK), and oscilloscope (model 2230 or model TDS 210, Tektronix, Beaverton, OR, US). The equipment was connected according to Figure 5.

Temperature measurement equipment

At the contact point between two dissimilar metals, a small voltage is produced. This electric voltage is dependent of the types of metal used and the surrounding temperature. In our experiments thermocouples of the materials nickel-chromium and nickel-aluminium alloys (K-type, Omega engineering, CT, US) with a diameter of 0.8 mm with exposed junctions were used. The thermocouples

were connected to a PC via an A/D converter (National Instruments), and LabVIEW (National Instruments) was used to record the data.

Acoustic pressure and intensity measurements

The acoustic pressure in water was measured using a 0.5 mm needle hydrophone coupled to a pre-amplifier (Precision Acoustics, Dorchester, UK), Figure 6. The output signal from the preamplifier was measured with an oscilloscope (model TDS 210, Tektronix, Beaverton, OR). In paper II a 0.4 mm coplanar hydrophone was used to measure the acoustic output.

Figure 4. Three of the ultrasound transducers used in the experiments. From left: 50 mm diameter transducer with 100 mm geometrical focal length, 18 mm diameter plane transducer, and finally a 5 mm diameter ultrasound probe with a focal length of 1.5 mm and a central hole for water cooling.
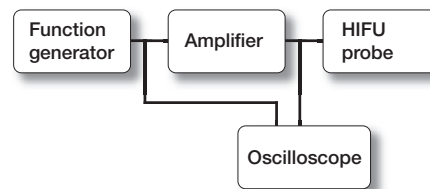

Figure 5. Connection diagram of the ultrasound operating and monitoring equipment.

Figure 6. The needle hydrophone used for acoustic pressure measurements. The active tip of the hydrophone is 0.5 mm in diameter and the scale in the picture is in cm.

The ultrasound output from the transducers was calibrated using an ultrasound balance (Model UPM-DT-1, Ohmic Instruments Co., Easton, MD, US) for a range of applied voltages.

Finite element analysis

The influence of the thermal and acoustic constants on the temperature distribution in the disc was studied. Effects of non-linear propagation were not taken into account in the model. The heat transfer equation (2) was used to model the temperature distribution in the disc during HIFU heating.

$$\frac{\partial T}{\partial t} = \frac{\lambda}{\rho C_s} \left(\frac{\partial^2}{\partial x^2} + \frac{\partial^2}{\partial y^2} + \frac{\partial^2}{\partial z^2} \right) T + \frac{Q}{\rho C_s} \qquad (2)$$

The equation (2) describes the heat transfer in the system, where the temperature (T) is a function of the position and time, $\partial T / \partial t$ is the rate of temperature change, λ the thermal conductivity, ρ and C_s is the density and heat capacity. Q is the heat source given by

$$Q = 2\alpha I(x, y, z) \qquad (3)$$

where α is the ultrasound amplitude (or pressure) absorption constant.

The ultrasound intensity, I, was approximated to a circularly symmetrical Gaussian beam (Filipczynski et al., 1993, Hill et al., 1994). Linear wave propagation was assumed and plane-wave attenuation in the tissue was included in the model. This approximation produces a symmetric field without any side-lobe effects.

The solutions to the heat equations were solved using finite element analysis with the program FEMLAB v. 3 (Comsol AB, Stockholm, Sweden). Finite element analysis is a numerical analysis technique used for solving differential equations. The method subdivides a domain into a series of smaller elements in which the differential equations are approximately solved. Finally the solutions are put together and a numerical solution for the whole domain is received.

Magnetic resonance imaging

The MRI measurements were performed using a Siemens Magnetom Allegra 3T head scanner with the standard quadrature head coil. Temperature monitoring based on the proton resonance frequency shift method was used (Ishihara et al., 1995, de Poorter et al., 1994). A gradient echo pulse sequence was used with the settings: repetition time (TR) = 100 ms, echo time (TE) = 10 ms and flip angle (FA) = 30º. The slice thickness was 2 mm and the matrix size was 192×192 with a field of view of 130 mm, resulting in an in-plane resolution of 0.7 mm. The dynamic resolution (scan time) was 15 s. During two thermal experiments five imaging slices were positioned parallel and orthogonal to the HIFU probe. In each experiment a reference magnetic resonance (MR) scan was obtained with the entire disc at the same temperature as the surrounding water. The ultrasound was then activated and MR phase images were acquired every 15 seconds during the six minutes of heating. After the ultrasound was switched off, a few more MR images were acquired to monitor the cooling process.

Temperature changes were calculated off-line using the MR phase images as input to a computer program written in IDL (RSI, Boulder, CO, USA), applying a temperature coefficient of 0.01 ppm ºC^{-1}. The protein degradation temperature in collagen is 65ºC (Hayashi and Markel, 2001), which corresponds to a temperature increase of 28ºC relative to the normal body temperature. Treated volumes were therefore estimated from all five image slices, using Matlab (Mathworks Inc., Natick, MA, USA) to calculate the volume sum of voxels with a temperature change greater or equal to 28ºC. This
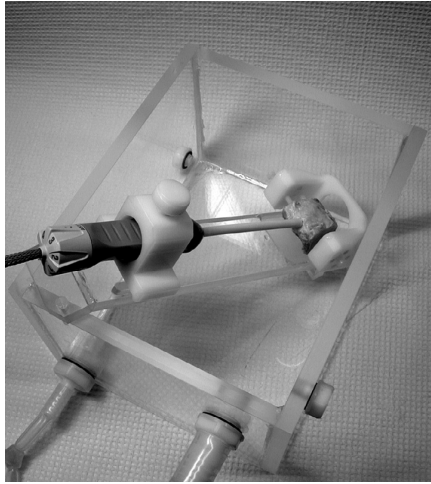
Figure 7. The experimental set-up used in the MR experiment. A bovine motion segment is mounted in the water bath with an ultrasound transducer placed to the disc.

was done for each time-point in the thermal experiment where the image slices were parallel to the HIFU probe, and thus covered the entire intervertebral disc.

The entire setup, consisting of a water bath with a holder to keep the disc and the probe immersed in water (Figure 7), was placed at the isocenter of the MR scanner.

Summary of Papers

Paper I: Ultrasound nucleolysis: An *in vitro* study

In this study the concept of heating the intervertebral disc with HIFU was investigated.

Material and methods

Two types of focused ultrasound transducers were designed. One 50 mm diameter ultrasound transducer for non-invasive use (Figure 8) and one smaller transducer (5 mm diameter) intended for invasive use. The optimal frequency for transducers with different sizes and focal lengths were calculated using Kossoff's model for central axis intensity (Kossoff, 1979). These calculations were supplemented with ultrasound intensity simulations performed with the program Ultrasim98 (Holm, 2001).

As a measure of the intensity distribution in front of the 50 mm diameter ultrasound transducer the temperature at the beam axis and perpendicular to this was measured. A thermocouple with a 1×1×1 mm rubber on the tip was used.

Temperatures in discs in bovine motion segments (vertebra-disc-vertebra) were measured with thermocouples during ultrasound exposure (Figure 9). The temperature increase in the disc from the ultrasound exposure using double 50 mm diameter ultrasound transducers was compared with single transducer use. Secondly the temperature raise in the disc was studied using small 5 mm ultrasound probes.

Results

The intensity calculations based on Kossoff's model showed that a good intensity gain can be reached using a 1.1 MHz, 50 mm transducer with 100-mm focal distance.

The experiments showed that it was possible to increase the temperature by more than 10ºC in bovine *nucleus pulposus* using a 1.1 MHz, 50 mm diameter ultrasound transducer with an ultrasound output of 5 W. The use of a single ultrasound transducer increased the heating in the *annulus fibrosus*, compared to using two orthogonal transducers.

The smaller ultrasound transducers, aimed for percutaneous treatment, reached extremely high temperatures at the surface during treatment. This caused temperature rises in the disc due to heat conduction from the contact point of the piezo crystal.

Conclusions

It was shown that it is possible to heat intervertebral discs with HIFU delivered by 50 mm diameter ultrasound transducers. The smaller (5 mm diameter) invasive ultrasound transducers reached high temperatures at the surface during treatment. It was concluded that a chilling irrigation system in this transducer was necessary.

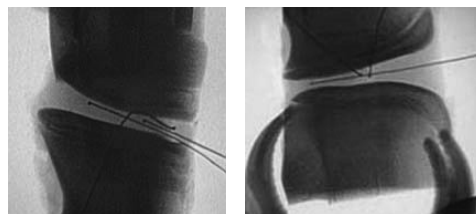**Figure 8.** Dimensions used to design the non-invasive ultrasound transducer used in paper I.

Figure 9. Radiograph of the thermocouple placements in the bovine motion segment.
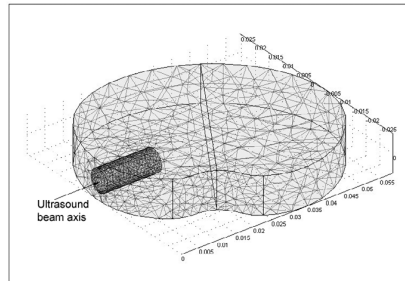
Figure 10. The geometry and mesh used in the FE model in paper II. The disc height used was 10 mm. The mesh is finer in the region where the ultrasound intensity field is applied. The scale on the axis is in meters.
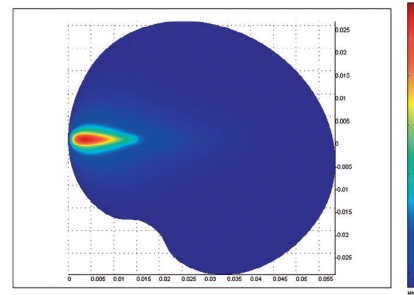

Figure 11. The temperature distribution produced by the applied Gaussian acoustic field after 120 s of ultrasound exposure. The units are in meters and the temperature scale in °C. Treated volume had a length of 12 mm and a width of 4 mm.
See paper II, page 712, for a colour version of this figure.

Volume heated to T > 65 °C (cm^3)
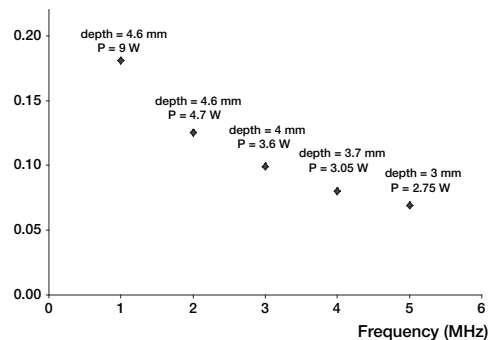
Figure 12. The size of the treated volume after 120 s of 4 MHz ultrasound exposure as a function of the frequency.

Paper II: Modelling of the heat distribution in the intervertebral disk

The heat transfer equation (2) was used to model the heat distribution in the intervertebral disc during HIFU heating. Finite element analysis was used to solve the heat equation. The aim was to optimise the design of a minimally invasive thermal treatment and to study the effects of variation of physical parameters on performance of such a device.

Material and methods

The finite element analysis program FEMLAB v3 (Comsol AB, Stockholm, Sweden) was used to solve the heat transfer equation. The dimensions and shape of the geometry was similar to a human lumbar disc with disc height of 10 mm (Figure 10). The size of the ultrasound transducer was fixed to 5 mm due to surgical limitations and the focal length was set to 15 mm. The ultrasound intensity field was approximated by a circularly symmetrical Gaussian beam (Filipczynski et al., 1993). The initial temperature was chosen to be 37ºC and the temperature on the disc boundaries were kept at 37ºC.

An adaptive approach was used in the simulations, the intensity was chosen so that the peak temperature was limited to 95ºC after 120 s of heating. The size of the treated volume (tissue with temperature 65ºC or above) was studied for, amongst other things: various frequencies, focal lengths, and ultrasound attenuation coefficients.

Results

In Figure 11 the temperature distribution in the disc after 120 s of ultrasound exposure using a 4 MHz, 3.1 W acoustic field is shown. The maximum temperature (95°C) is achieved 3.7 mm from the ultrasound probe. The length of the treatment volume (volume of tissue heated to above 65°C) is 12 mm and the width 4 mm; the total volume is 80 mm^3.

The influence of the frequency on the size of the treated volume was observed when the ultrasound intensity was limited so that the peak temperature after 120 s was 95°C. The simulations show clearly that the size of the treated volume decreases with increasing frequency (Figure 12). Note that the output power needs to be considerably increased to reach a peak temperature of 95°C in the tissue when lower frequencies are used.

The peak temperatures were found to occur well in front of the geometric focus and the effect of increasing focal lengths were found to be the opposite. An increased focal length decreases the depth of the maximum temperature.

Conclusions

It was concluded that it is possible to heat the disc to the target temperature (65ºC) through an extra-discal minimally invasive procedure. However, the depth of the treatment volume is shallow and it is not possible to increase this just by increasing the focal length.

Paper III: Effects of high intensity focused ultrasound on the intervertebral disc: A potential therapy for disc herniations

The paper describes a potential application of HIFU for the minimally invasive treatment of herniated intervertebral discs. The aim was to develop a probe that could produce sufficiently high temperatures locally to shrink collagen fibres in the disc (≥65ºC). Experiments were performed using both an *in vitro* cadaver model and an *in vivo* animal study.

Material and methods

Measurements of acoustic pressure were performed in a water bath using a 0.4 mm coplanar membrane hydrophone. A series of horizontal and vertical scans were performed, at axial positions ranging from 5 to 50 mm from the transducer. From these scans the -6 dB beam width (the width of the ultrasound field where the intensity is a quarter of the maximum intensity) were calculated. A 5 mm diameter ultrasound probe was customised with a geometric focal length of 15 mm. The probe was able to produce 2.5 W acoustic power and was operated at a frequency of 4.1 MHz.

In vitro experiments

Measurements of temperature increase were performed in intervertebral motion segments from bovine tails. The probe was applied perpendicular to the surface of the disc and thermocouples were placed at depths of 2, 3, 4, 6 and 9 mm in the disc as well as in the vertebral body.
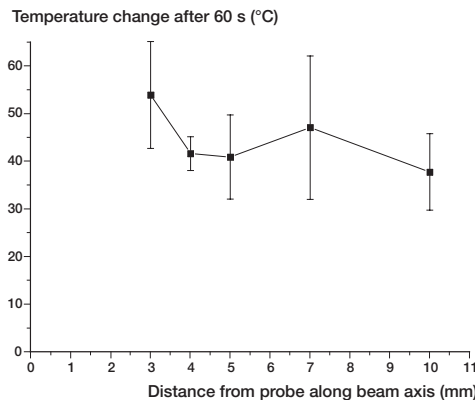
Figure 13. Temperature measured by thermocouples after 60 s exposure of the intervertebral disc to ultrasound at 2.5 W acoustic power, at different distances from the transducer.

In vivo animal experiments

Eight procedures were performed on 12-months old, healthy, slow-growing pigs. After pre-medication and anaesthesia, the probe was inserted to the lateral side of the disc, under radiographic control. The ultrasound probe was inserted with an introducer until the piezo-crystal was 1 mm from the disc surface. The probe was activated to provide an acoustic output of 2.5 W at 4 MHz for 60 seconds. This was repeated six times with the probe in different positions. The procedure was performed bilaterally on four discs. The animals were allowed to recover from anaesthesia, and were monitored for two weeks. Samples of disc, nerve root and muscle were dissected out from each treated region, together with control samples taken from non-treated regions of the spine. The samples were fixed, embedded, cut, and then stained for histology.

Results

The -6dB beam width was measured to be approximately 1.3 mm and the depth of field was estimated to be 21 mm. The intensity maximum was 9 mm from the transducer.

Sufficient temperature increases to produce collagen shrinkage were observed close to the focus of the ultrasound (Figure 13). Temperature measurements in vertebral endplates showed a temperature increase of only 4ºC after 60 seconds exposure of the disc.
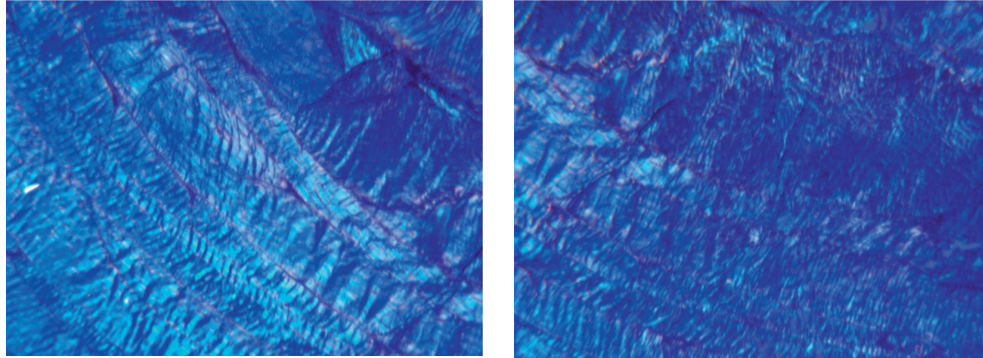
Figure 14. Examples of histological sections in the disc stained with toluidine blue from (left) an untreated control and (right) a thermally treated region of the intervertebral disc showing disorganised structure. Both images are magnified 10 times. See paper III, page 6, for colour versions of these figures.

The animals showed no sign of discomfort or abnormality of gait after the procedure. Histological changes in the disc consistent with collagen shrinkage were observed (Figure 14). No signs of thermal damage to the nerve roots or muscle could be found in any of the histology samples.

Conclusions

Sufficient temperature for collagen shrinkage was produced in the disc during HIFU treatment of bovine cadaver discs. Histology from the animal experiments also showed that temperatures high enough to produce tissue changes in the disc were achieved. No signs of thermal effects on the muscle or nerve tissue were seen.

Paper IV: Ultrasound attenuation and absorption in the intervertebral disc

Material and methods

Experiments were performed on bovine *annulus fibrosus* and pig muscle. The samples were stored in a freezer and thawed before the experiments, which were carried out at room temperature (22ºC), in degassed water. Both disc and muscle samples were placed with the orientation of the fibres in the sample perpendicular to the ultrasound.

Attenuation measurements

The transmission method was used to measure the ultrasound attenuation coefficient. Measurements were performed in a water bath containing degassed water. 5 mm diameter plane ultrasound probes were
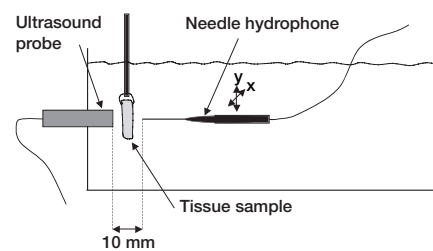
Figure 15. Experimental setup used in the attenuation experiments. The acoustic pressure was measured using a needle hydrophone in degassed water. A flat ultrasound probe (diameter 5 mm) was used as the ultrasound source and the pressure was measured in a 10×10 mm plane perpendicular to the propagation direction of the ultrasound.

used to provide the ultrasound at 2.1 and 4.3 MHz, (Figure 15). The ultrasound field was measured at a distance of 10 mm from the ultrasound probe with a 0.5 mm needle hydrophone (Precision Acoustics Ltd., Dorset, UK). A tissue sample with a thickness of 3 to 6 mm was placed between the ultrasound probe and the hydrophone. The samples had a minimal width and height of 6 mm and they were placed 2 mm from the hydrophone with the fibres orientated orthogonal to the path of the ultrasound. The ultrasound pressure field was measured with and without a specimen in the ultrasound field. The measurements were performed in a 10×10 mm plane which was scanned with a step size of 0.5 mm. The data from the hydrophone measurements were acquired by a PC, and the attenuation coefficient was calculated.

Absorption measurements

The transient thermoelectric technique was used to
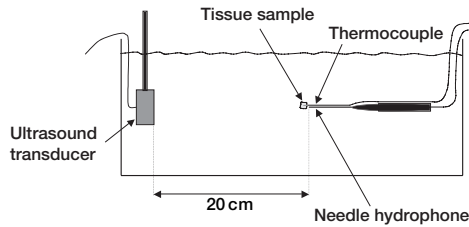
Figure 16. Experimental set up used in the ultrasound absorption experiments. A plane ultrasound transducer (5 mm diameter) is exposing a 5×5×5 mm^3 sample on a thermocouple. A needle hydrophone is used to measure the ultrasound intensity.

Figure 17. Ultrasound attenuation coefficient in pig muscle and bovine annulus fibrosus at 2.1 and 4.3 MHz. The error bars represent the standard deviations.

measure the absorption coefficient, this was done by measuring the rate of temperature increase using small diameter thermocouples. A thermocouple was inserted into the tissue, which was exposed to an ultrasound field with a known intensity from plane 18 mm diameter ultrasound transducers. Given the tissue's density, specific heat capacity, sound velocity, the ultrasound intensity and the depth at which the thermocouple was placed, it was possible to calculate the ultrasound absorption. Measurements of the rate of temperature increase were performed in tissue samples in a water bath with degassed water (Figure 16).

Results

The attenuation coefficient in *annulus fibrosus* was measured to be 1.28 ± 0.57 dB cm^{-1} MHz^{-1} at 2.1 MHz and 1.05 ± 0.22 dB cm^{-1} MHz^{-1} at 4.3 MHz which was significantly higher than the attenuation coefficient measured in muscle tissue (Figure 17). The absorption coefficient in bovine *annulus fibrosus* was measured to only constitute 55% of the attenuation coefficient at 2 MHz and 40% at 4 MHz.

Conclusions

The measured absorption coefficients were lower than anticipated. This can be explained by the anisotropic nature of the *annulus fibrosus* which might lead to increased scattering of the ultrasound implying that ultrasound absorption coefficient becomes a smaller part of the attenuation coefficient.

Paper V: Heating of the intervertebral disc by high intensity focused ultrasound, evaluated with MRI

The possibility to use MRI to determine the treatment volume of the disc heated with HIFU was investigated. A bovine *in vitro* model was used in the experimental setting.

Material and methods

Bovine cadaveric discs were exposed to focused ultrasound using a 5 mm diameter focused ultrasound probe producing 2.5 W of acoustic power, operated at a frequency of 4.1 MHz. The setup, consisting of a water bath with a holder keeping the vertebral motion segment (vertebra-disc-vertebra) and the probe immersed in degassed water, was placed in the isocenter of a 3T Siemens Allegra MR scanner. MRI was performed using gradient echo phase images, which are sensitive to temperature induced changes of the proton resonance frequency. A reference MR scan was performed before the ultrasound exposure started and MR phase images were acquired every 15 seconds during the six minutes of heating.

From the MR phase pictures temperature change images were calculated using a program written in IDL (RSI, Boulder, CO, USA). The volume heated to 28ºC or more (corresponding to 65ºC starting
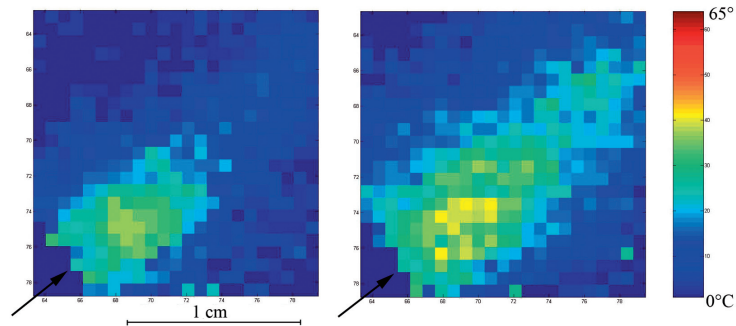
Figure 18. Magnetic resonance image of the temperature distribution in axial depiction of a bovine disc after 1 (left) and 6 (right) minutes of ultrasound exposure. The ultrasound probe was placed in the lower left corner of the image (arrow).
See paper V, page 2, for a colour version of this figure.

from normal body temperature) was calculated using Matlab (Mathworks Inc., Natick, MA, USA). This was performed for each time-point in the thermal experiment.

Results

The temperature change distribution measured with MRI in an image slice parallel to the probe after 60 seconds and six minutes heating is shown in Figure 18. The volume heated to 28ºC or more was 75 mm^3 after 60 seconds and 195 mm^3 after 6 minutes. The diameter of the treated volume was after 1 minute 4 mm and after 6 minutes 6 mm in a plane perpendicular to the probe. The treated volume increased sharply during the first 2.5 minutes and after this the curve leveled off.

Conclusions

Heating of a well-defined volume could be demonstrated with MRI, and the possibility to make comparisons with other physical characteristics in the future is evident.

Discussion

Minimally- and non-invasive treatment

The advantage of a non-invasive treatment is obvious but there are many practical problems in planning and monitoring the ultrasound treatment. In order to heat the disc non-invasively with ultrasound, it is important that the energy is limited to the disc and does not destroy the nerves or the soft tissue in front of the focus. The tissue between the ultrasound probe and the focus will be protected from harmful levels of ultrasound by administering the energy from a large area and focusing that on a small volume. However, the disc's adjacent vertebrae and the gaseous intestines on the anterior side limit considerably the possible ultrasound window into the disc. Two possible windows for ultrasound passage from the lumbar dorso-lateral sides have been identified. From the exposures of bovine motion segments in a water bath it was clear that the challenge was aiming the ultrasound field to the disc. This was difficult even with thermocouples in the disc which provided information on when the ultrasound beam was positioned correctly in the disc.

To combine two ultrasound transducers by letting their ultrasound fields overlap at the focus could lead to doubled ultrasound intensity in this volume. However, there is a risk of negative interference to occur in the overlap between two or more ultrasound beams (Lele, 1980). This means that the intensity in the overlap may be lower than in the individual ultrasound beams.

Another practical issue using focused ultrasound transducers is to choose the focal length of the probe. The distance to the disc from the skin varies a lot in patients with different body weights and muscle volume. Using phased array transducers instead of transducers with fixed focal lengths could solve this problem. The drawback is a much more complex ultrasound transducer demanding far more of the equipment exciting the many piezo crystals of the phased array probe.

An additional way to minimise the temperature in the tissue between the transducer and the focus could be to pulse the ultrasound. In some commercial systems for cancer treatment, the burst length is about one second, with an interval of the order of tens of seconds. This way, surrounding tissues with significant blood flow will have time to cool between each burst more effectively than the avascular disc.

The energy of the ultrasound must be limited to ensure that no damage occurs to the nerves or soft tissue surrounding the focus. This means that the temperature should not exceed 44ºC except in the focus, which must be positioned inside the disc. The heat in the focus will spread by heat conduction to a larger volume in the disc. Since bone is a good thermal insulator the heat will not spread into the vertebrae to a great extent. The vascular system outside the disc will have a cooling effect. Thus potential injury outside the disc associated with heat conduction from the disc should not be a problem.

Using a mini-invasive method where a probe is inserted percutaneously to the disc without perforating the disc would minimise the problems of guiding the ultrasound to the disc. Apart from being an invasive method, the practical drawbacks of such a method is the size limitation of the ultrasound transducer to 5 mm in diameter for practical surgical reasons. Lafon et al. have earlier used small ultrasound transducers for invasive or intra-cavitational purposes (Lafon et al., 2002). To avoid the piezo crystal from reaching harmful temperatures (>44ºC) they introduced a water chilling system. It was decided that the issues regarding a delivery system for non-invasive system could comprise a thesis in itself, and in order to establish the effectiveness of ultrasound therapy for disc herniation subsequent work in this thesis would concentrate on a minimally invasive approach.

Specification of ultrasound parameters

Having established the feasibility of the concept in paper I, computer simulations were performed in paper II, in order to understand the important

parameters in defining detailed specifications for a prototype minimally-invasive device. In a clinical situation it may be desirable to maximise the treatment volume and minimise the treatment time. From this aspect a low frequency should be used; by decreasing the used frequency from 4 to 1 MHz the treated volume can be doubled. However, the output power from the ultrasound transducer needs to be increased three-fold in order to maintain the same peak temperature at 1 MHz compared to 4 MHz. Since the size of the ultrasound transducer has been set to 5 mm in diameter, this constrains the output power from the transducer. At 3 W total output from the transducer, the equivalent power density is 15 W cm^{-2}. For many piezo materials used in ultrasonic transducers, an operating power density of 10 W cm^{-2} is recommended, and a maximum power density of 30 W cm^{-2} is suggested by manufacturers. Therefore, the operating characteristics of a practical device may need to be a compromise between frequency and power output. The maximum heated volume was achieved at 1 MHz, but as this required 9 W total output it would require a power density that may be difficult to realise practically.

Traditionally, the herniation is reduced by reducing the volume of material that is bulging inward onto the *annulus fibrosus*. The volume of disc material removed during automated percutaneous discectomy is in the order of 1 cm^3 (Gill and Blumenthal 1991). The simulations indicated that peak temperatures occur 3 to 5 mm into the disc, well within the *annulus*, but that the focus will reach into the *nucleus* at its furthest extent. The treatment will not ablate tissue, as in laser discectomy. However, other mechanisms may contribute to therapeutic effectiveness. Although the mechanisms of non-ablative thermal treatment of chronic low back pain are not yet fully determined, they are believed to be either denervation of the nerve endings that detects painful stimuli (nociceptors) in the *annulus fibrosus*, collagen shrinkage of the disc or sealing of the fissures in the *annulus fibrosus*. Local shrinkage of collagen in the region of a herniation could lead to reshaping of the external contours of the disc, relieving pressure on nerve roots. Sealing of annular fissures could also contribute to reduction of pressure on the nerve roots and less leakage of pro-inflammatory *nucleus* material.

Bono and co-workers showed that temperatures greater than 65°C rarely were achieved at distances more than 2 mm from the heating catheter using IDET (Bono et al., 2004). Together with the fact that it has been difficult to show biomechanical changes of the disc after IDET (Bass et al., 2004) it is likely that pain relief is a result of denervation of nociceptors, in patients suffering from chronic low back pain. In this case, effectiveness will depend on the thermal dose delivered to the tissues, rather than reaching a threshold value for collagen shrinkage.

In general, thermal data for the intervertebral disc is based on a small sample population and shows wide variation (Houpt et al., 1996). Biological variations, differences in water content, and errors in the measurement model could explain the large deviation. The small size of the ultrasound transducer, in combination with the continuous mode it is operated at, leads to considerable self-heating of the piezo crystal. To prevent the temperature maximum occurring on the surface of the disc due to heat conduction from the piezo crystal, a cooling system with flowing water in front of the transducer can be used. For this reason, simulations with different transducer surface temperatures were performed. The temperature at this boundary affected the depth of the peak temperature, but had only minor effect on the size of the heated volume.

The effect of the geometrical focal length was also simulated. It was found that the focal length had a minor effect on both the depth of the temperature maximum as well as on the size of the treated volume. This is explained by the relatively small ultrasound transducer, the diameter of the transducer being less than the geometrical focal length.

Assessment of thermal effect *in vitro* and *in vivo*

The results presented so far indicate that significant heating occurs within the *annulus fibrosus*, with less heating effect occurring within the *nucleus pulposus*. One advantage of considering disc herniations for treatment is that the herniation can be visualised radiologically, providing a target for thermal therapy. It can be considered that local

shrinkage of collagen fibres can reduce pressure on the nerve root. It is also possible that the heat could produce local coagulation of pro-inflammatory proteins, or that heat shock proteins can be induced at the periphery of the treated region, which could then have an anti-inflammatory effect (Emohare et al., 2004).

In paper III, therefore, measurements of ultrasound intensity and *in vitro* and *in vivo* experiments were performed on discs, using a prototype device based on data provided by paper II. These results can be compared with the simulation results. The predicted acoustic pressure focal length at 4 MHz was 8.7 mm, and the position of the temperature maximum was at 4.5 mm depth. The simulated pressure focal length was slightly less than that measured with hydrophone. Apart from the problems associated with the Gaussian approximation, this discrepancy could be due to the values of ultrasound absorption coefficient used in the simulations; a value of 1.5 dB cm^{-1} MHz^{-1} was assumed based on published data for tendon. In general the temperature distributions are in line with the computational model, showing a well-focused treatment volume contained within the disc itself.

While it is necessary to produce sufficient therapeutic thermal dose in the targeted tissues, it is important to avoid thermal damage in the adjacent structures, most importantly the nerve roots, but also the vertebral endplates and surrounding muscle. It has been shown in a pig model that heating the nerve roots to 40°C for five minutes does not produce any changes in the tissue, heating to 50°C produces minor reversible changes, and heating to 60°C and 70°C for five minutes resulted in irreversible changes (Konno et al., 1994). In another study in rabbits, heating to 50°C for 45 s did not produce any damage to nerve fibres, heating to 55°C for 45 s destroyed approximately 50% of nerve fibres, and heating to 60°C for 45 s destroyed all nerve fibres (Frohling et al., 1998). As a guide, it is normally assumed that heating to 43°C for 240 minutes will produce complete cell death, and that the time is halved for each degree rise in temperature; thus 56°C will produce cell death after approximately 1.75 s. Measurements of temperature during laser ablation of the nerve root canal showed that temperature increases in the nerve root itself could be eliminated by appropriate use of irrigation fluid while still being effective at removing bone (Hafez et al., 2001).

The *ex vivo* experiments reported in paper III used intact discs from bovine tails. These are smaller than human lumbar discs, and did not have blood perfusion in the end plates as a means of removing heat from bone. Reported figures for blood flow to the end plate are around 6 mL min^{-1} 100g^{-1} (Wallace et al., 1994). The disc is the largest avascular structure in the body, but the endplate is relatively well-perfused. It is therefore likely that the measured temperature increases in the endplate reported here, overestimate the changes that would occur in the human disc, due to the effects both of blood flow and the larger size of the human disc. The data can be compared with measurements made in cadaveric discs using an intradiscal catheter (Bono et al., 2004). Within the discs, temperatures above 60°C were measured between 2 to 4 mm from the device, 45°C was seen 9 to 14 mm from the device; however, temperatures in the endplate never reached more than 47°C. Temperatures of this order within the endplate would not be expected to produce thermal necrosis for exposure times of up to 10 minutes, and blood flow would lead to lower temperatures *in vivo*.

The *in vivo* experiments were designed as an initial assessment of safety for the procedure. As expected both from computations and *in vitro* experiments, no adverse effects were noted, neither from macroscopic examination of tissues, nor from histological examination of tissue sections. Although we were able to show changes consistent with collagen shrinkage in the disc, this does not prove a therapeutic effect. However, the histology demonstrates that sufficient temperatures were achieved *in vivo* to produce tissue changes that could lead to a therapeutic effect.

Ultrasound attenuation and absorption in the disc

In paper IV the attenuation coefficient in muscle was shown to coincide well with those earlier reported (Colombati and Petralia, 1950, Shore et al., 1986, White and Wambersie, 1998, Lehmann and Johnsson, 1958). At 2 MHz, the measured absorption coefficient for muscle is 60% higher

than the corresponding value reported by ICRU (White and Wambersie, 1998) but it agrees for the 4 MHz case. Our measurements of absorption coefficient in muscle are similar to the values of attenuation coefficients at 2 MHz, and slightly lower than the attenuation coefficient at 4 MHz. This suggests that scattering becomes more important in muscle at higher frequencies. The results for the *annulus fibrosus* samples are lower than the reported value for tendon for both the ultrasound attenuation and the absorption coefficient.

In many tissues the ultrasound absorption is comparable to the ultrasound attenuation. Our results show that the ultrasound absorption in *annulus fibrosus* only accounts for approximately half of the attenuation coefficient. The anisotropic nature of the *annulus fibrosus* might lead to increased scattering of the ultrasound, which leads to decreased ultrasound absorption compared to ultrasound attenuation. Skeletal muscle (muscle that is attached to bone), nerve and tendon are known to be anisotropic (Duck, 1990). The attenuation in muscle has been demonstrated to be 2 to 3 times as great along the fibres as across the fibres. Dussik et al. (1958) reported amplitude attenuation coefficients in human and bovine tendon of 4.1–6.3 dB cm^{-1} MHz^{-1}. Goss et al. have measured the absorption coefficient in bovine tendon to 0.96–1.7 dB cm^{-1} MHz^{-1}. Attenuation in the longitudinal direction in tendons is at least an order of magnitude greater than in the transverse direction (Miles et al., 1996). From measurement of backscattering it was also stated that absorption is the primary mechanism for attenuation in the longitudinal direction in tendons (Dussik et al., 1958). However, it was also shown that attenuation is an order of magnitude lower in the transverse direction, and that back scattering is an order of magnitude larger in the transverse direction. Scattering in tendons is thought to occur by scattering from the interfaces between the fascicles. In general, tendon has a similar composition as *annulus fibrosus*, and we had anticipated that we would obtain similar values in the *annulus fibrosus* as in the tendon. However, our results indicate that both the attenuation and absorption coefficient are smaller in the disc than in tendon, and scattering appears to contribute significantly to attenuation.

Tendon fibres are of the order of 20 microns, and these are bundled into fascicles approximately 1 mm in diameter (Vogel, 2003). The *annulus fibrosus* of the human disc comprises fibre bundles of the order of 0.1 mm and interbundle gaps of approximately 0.05 mm (Marchand and Ahmed, 1990). Maximum reflectivity of ultrasound, with wavelength λ, from a flat plate with thickness *l*, occurs when *l*/λ = 0.25 (Miles, 1996). At 2 and 4 MHz, wavelengths are approximately 0.8 mm and 0.4 mm respectively, producing conditions for reflection and scattering within the disc. It therefore appears that the detailed structure of the *annulus fibrosus* is more conducive to produce ultrasound scattering at these frequencies than is the tendon.

Errors associated with the transient thermoelectric method result initially from viscous heating around the interface between the thermocouple and the tissue, and later from heat conduction away from the heated region. To avoid these artefacts the temperature measurements were performed immediately after the beginning of the irradiation. Errors also arise from calibration errors in the hydrophone, which is quoted to be 14% by the manufacturer (Precision Acoustic, Dorchester, UK). As any such experimental errors would affect measurements of both muscle and *annulus fibrosus* absorption coefficients, and given that our values for muscle are comparable with those published in the literature, we consider that our measurements for disc are valid.

The data from paper IV allows a better understanding of both the ultrasound and temperature distributions within the disc, leading to optimisation of treatment conditions. The measured values are different to those used in the simulations in Paper II. The effect of these lower values of absorption coefficient is to reduce the rate of temperature increase, and lead to a deeper point for peak temperature.

Alternative assessment of heating

Clinical pilot studies have been performed with the equipment and parameters described in paper III. However, it is not obvious that these are the optimal parameters, concerning the length of treatment and energy emitted. A main concern is the safety

margin of treatment. The treatment should aim at a defined volume of the disc without risking thermal injury to the end plates or to the adjacent nerve roots. It has been possible to estimate temperatures at specific sites using thermocouples inserted into the disc and surrounding tissues, but measuring the distribution of energy dissipation in real time during HIFU heating would allow a better understanding of the mechanism.

In clinical use, the ultrasound probe is designed to be sequentially rotated around its probe axis during treatment. Since the transducer surface is tilted 10° in relation the probe axis, the treated volume is increased by this rotation. The disc is treated for 1 minute in one position, rotated 60º, and treated again for 1 minute. This is repeated until a full 360° is covered, i.e. six different positions will be treated during 1 minute each. Since the six heated volumes to some extent overlap, the total treatment volume will not be increased by a factor of six. On the other hand, the heat conduction in the disc will imply that the heating will start from higher temperatures in each position and therefore heat a larger volume every time the exposure is repeated in the new position. The calculations from the MR images suggest that the treatment volume after 1 minute of ultrasound exposure is 75 mm^3. Repeating the treatment in six different positions will increase this volume and it will be dependent on the time interval between each treatment and to what extent the treatment volumes will overlap.

MRI has not been used before to map the temperature distribution within the disc during ultrasound treatment. The temperature measurements are reasonably fast (scan time of 15 s) and the precision is in the order of ±1°C (1 SD measured in a homogeneous region of a temperature image) with a volume resolution of approximately 1 mm^3. This is sufficient for the present application making the measured temperature distributions and dynamic characteristics useful to investigate and to further optimise HIFU heating of intervertebral discs. The absolute accuracy depends on the temperature coefficient of the proton resonance frequency shift (Ishihara et al., 1995). Deviations from the actual temperature can be caused, for example, by susceptibility effects which are dependent on the actual experimental geometry (Peters et al., 1999)

and will become larger with increasing temperature changes. It is therefore possible that the temperature increase is under- or overestimated a few degrees at higher temperature increases, which will influence the estimated treatment volumes presented in this work.

For HIFU treatment, information is available on how to plan, target, monitor and follow the treatment with MRI (Hynynen et al., 2001b, Huber et al., 2001, Stewart et al., 2003, Hindley et al., 2004). MRI makes it possible to monitor real-time temperature change in tissue, non-invasively, with the drawback of being an extremely resource and time consuming method. Diagnostic ultrasound has also been used to monitor HIFU treatments of tumours (Wu et al., 1998, Souchon et al., 2005, Rabkin et al., 2005, Wu et al., 2004, Visioli et al., 1999, Kohrmann et al., 2002). The advantages with ultrasound imaging are that it is inexpensive, available, flexible, can be used to image organs that are moved by the respiratory system, and can be performed with real-time imaging. The disadvantage with ultrasonography is the poorer image resolution compared to MRI. There is also an important physical difference between the methods. While MRI record phase shifts due to the temperature change in the tissue, the diagnostic ultrasound will record changes in the ultrasound attenuation due to effects of temperature changes such as coagulation necrosis in the tissue.

Clinical observations

Although clinical studies are not reported in this thesis, there are some interesting clinical findings that are worthwhile to discuss. Clinical trials are underway in Sweden, Germany, Italy, Turkey and South Korea. Initial results from these trials are reported to be promising. The symptoms for many patients treated with mini-invasive HIFU for disc herniation are improved. Anecdotally, back pain seems to improve immediately after treatment, while the leg pain remains longer. These preliminary findings suggest that there are two primary mechanisms involved. Chronic back pain, which is probably due to nerves growing into the disc, here the HIFU generated heat is ablating the ingrown nerves locally with immediate effect. Sciatic leg

pain, results from pressure on the nerve root, and heating induces a remodelling process, which leads to relieved pressure on the nerve root/roots over a period of time. However, it must be noted that the clinical findings are most preliminary and have not been reported in the literature so far.

Conclusions and future work

Conclusions

- It was shown that it is possible to heat intervertebral discs with HIFU delivered by 50-mm-diameter ultrasound transducers. The smaller (5 mm diameter) invasive ultrasound transducers reached high temperatures at the surface during treatment. It was concluded that a chilling irrigation system in this transducer was necessary.
- Finite element studies indicated that it would be possible to heat the disc to a temperature of 65ºC or above through an extradiscal minimally invasive procedure. However, the depth of the treatment volume is shallow, and it is not possible to increase this by increasing the focal length.
- Computational studies were in general validated by experiments. *In vivo* studies revealed no sign of discomfort or abnormality to the treated animals. Histological changes due to collagen shrinkage in the discs were found, and no damage to the nerve or muscle tissues could be found.
- The attenuation coefficient in bovine *annulus fibrosus* was found to be in the range of 1.1 to 1.3 dB cm^{-1} MHz^{-1} and the absorption coefficient 0.4 to 0.7 dB cm^{-1} MHz^{-1}, which is approximately half of the attenuation coefficient. This indicates that a significant proportion of the ultrasound is scattered, due to the anisotropic nature of the *annulus fibrosus*.
- Using magnetic resonance thermometry in a bovine *in vitro* model, the possibility to measure the temperature distribution in the disc during HIFU treatment was demonstrated. This method can be used to evaluate future ultrasound transducers and treatment protocols.

Future work

It has been shown that it is possible to heat parts of the intervertebral lumbar disc to temperatures where denaturation of collagen starts, using a minimally invasive approach. Future work may involve further ultrasound transducer designs in order to optimise the size, shape, and position of the treatment volume.

The main advantage of HIFU is its possibilities for non-invasive treatment and the ultimate HIFU treatment of the intervertebral disc would of course be totally non-invasive. In order to achieve this it is necessary to monitor the temperature changes in the disc in real time during the treatment. Today only one non-invasive temperature monitoring method exists, magnetic resonance imaging. However, diagnostic ultrasound might also be a useful tool for monitoring the effects of HIFU, based on changes in attenuation coefficients due to collagen denaturation.

Acknowledgements

I am very grateful to everyone who has contributed to the making of this thesis. Especially I would like to thank:

Lars Lidgren, my supervisor, for introducing me to the field of orthopaedics and for making this work possible.

Ian McCarthy, my co-supervisor, for all the scientific guidance, support and English corrections done over the years.

Björn Strömqvist, my co-supervisor, for support and for performing the HIFU treatments in the animal study.

Carina Forslund, who has provided me with numerous disc samples and been my colleague in the business of measuring temperature in the discs.

Eskil Hansen, Numerical Analysis, Lund University, for great teamwork and in the help of setting up the FE model.

Johan Olsrud, Diagnostic Radiology, for mastering the MRI machine in both good and bad "electromagnetic days".

Bjarne Madsen Härdig, Department of Cardiology, for advice and help in the art of hydrophone measurements.

Mats Christensson, for mounting ultrasound transducers and producing excellent testing equipment.

Inger Mårtensson, for preparation of histology samples.

Kaj Knutson, for help with the layout of the thesis.

All the people in the Biomechanical laboratory over the years. Special thanks to Fred Kjellson for proofreading this thesis.

All the people at BMC, C12, for scientific discussions as well as other discussions. Special thanks to Anna-Karin Wihlborg, Åsa Ström and Anders Olin for mentioning me in their thesis acknowledgements.

Family and friends, for being family and friends.

Populärvetenskaplig svensk sammanfattning

Ultraljud

Ljud utbreder sig som en vågrörelse och får partiklarna i mediet att vibrera kring sitt jämviktsläge. Ljud brukar klassificeras beroende på dess frekvens (tonhöjd) enligt:

- Infraljud – frekvensintervallet 0 – 20 Hz
- Hörbart ljud – frekvensintervallet 20 Hz – 20 kHz
- Ultraljud – ljud med frekvens större än 20 kHz. Medicinskt ultraljud brukar vara i frekvensintervallet 1–10MHz.

Ultraljud brukar oftast förknippas med diagnostiska metoder såsom fosterdiagnostik men kan även användas för terapeutisk behandling. Terapeutiskt ultraljud bygger på att ljudet absorberas i vävnaden och därigenom ger upphov till en ökad temperatur. Temperaturökningen är beroende av ultraljudets intensitet samt ultraljudsabsorptionen i den aktuella vävnaden. Genom att fokusera ultraljudet är det möjligt att öka intensitet i en begränsad volym och på så sätt behandla djupt liggande vävnad utan kirurgi. Högintensivt fokuserat ultraljud, så kallat HIFU efter engelskans High Intensity Focused Ultrasound, används idag för att behandla tumörer, olika ögonsjukdomar samt hjärt- och hjärnsjukdomar.

Diskbråck

Mellan varje ryggkota finns en disk som tillåter viss rörelse mellan kotorna och samtidigt fungerar som en stötdämpare. Disken är den största strukturen i kroppen som saknar blodtillförsel och består till 90% av vatten. Den inre gelé-liknande vävnaden kallas *nucleus pulposus* och är omgiven av den något fastare *annulus fibrosus*. När disken åldras tappar den gradvis sin vätskeupptagningsförmåga vilket gör att disken blir skörare. Detta kan leda till sprickor i *annulus fibrosus* och *nucleus pulposus* kan då tryckas ut i dessa sprickor och orsaka en utbuktande disk. Om denna utbuktning trycker mot nervrötter kan ischiassmärta (som strålar ut i ena benet) uppstå.

Diskbråckspatienter ordineras vila och sjukgymnastik under minst två månader innan operation övervägs, detta eftersom spontanläkning är vanlig. Vid konventionell diskbråcksoperation perforeras disken och en del av *nucleus pulposus* plockas ut så att diskvolymen minskas och utbuktningen går tillbaka. För att minimera ingreppet används mikrokirurgi. Vid ultraljudsbehandling av diskbråck behöver disken inte perforeras varvid ingreppet minimeras ytterliggare. När den kollagenrika disken värms upp med ultraljud krymper kollagenfibrerna i *annulus* vid 65°C. Även eventuell nervvävnad som kan ha växt in i den yttre delen av den åldrade *annulus* kommer att förstöras vid denna temperatur. Genom dessa båda mekanismer kan smärta orsakad av diskbråck minskas eller upphävas.

Kortfattat om artiklarna

Syftet med detta arbete har varit att studera och optimera HIFU-behandling av disken, ur ett fysikaliskt perspektiv.

I den inledande studien visades att det går att värma disken med HIFU. Två storlekar av ultraljudsgivare studerades, den större (50 mm i diameter) var avsedd för att användas utanför kroppen utan att något kirurgiskt ingrepp genomförs (icke-invasivt). En icke-invasiv ultraljudsbehandling av disken kräver övervakning av ultraljudets väg in till disken så att inte närliggande muskel- eller nervvävnad skadas. Ett sätt att undvika detta problem är att utföra en så kallad mini-invasiv behandling, därför studerades även mindre ultraljudsgivare (5 mm i diameter). Ytan på de mindre ultraljudsgivarna nådde höga temperaturer under behandling och slutsatsen drogs att vattenkylning av dessa var nödvändig.

För att optimera designen av en mini-invasiv ultraljudsgivare gjordes en beräkningsmodell av en disk vilken exponeras för fokuserat ultraljud. Med hjälp av finita-element-metoden löstes värmeledningsekvationen vilket gav möjligheten att studera dels givarspecifika och dels vävnadsspecifika

parametrars påverkan på temperaturfördelningen i disken. Modellen indikerar att det är möjligt att värma upp delar av disken till 65°C eller mer med en ultraljudsgivare på 5 mm i diameter. Den uppvärmda volymen blir dock liten och ytlig även om fokallängden ökas.

Ultraljudsgivare tillverkades med frekvens och fokallängd baserade på resultaten från tidigare nämnd beräkningsmodell. Denna ultraljudgivares intensitetsfält i vatten uppmättes, *in vitro* och *in vivo* experiment utfördes på diskar. Temperaturökningar tillräckliga för att uppnå krympning av kollagenet i disken observerades samtidigt som temperaturökningen begränsades till måttliga 4°C i de omgivande ändplattorna och kotorna. Djurförsöken syftade till att bedöma säkerheten i behandlingen. Inga tecken på termiska skador på nervrötter eller muskelvävnad observerades, däremot hittades histologiska förändringar konsistenta med kollagenkrympning i disken.

När ultraljud passerar genom vävnad dämpas (attenueras) intensiteten på grund av absorption och spridning i vävnaden. Storleken på attenueringen respektive absorptionen är olika för olika vävnader och mättes i vårt fall i *annulus* från oxsvansar. Mät-ningar utfördes även på muskelvävnad från grisar för att kunna konfirmera modellens giltighet eftersom attenuerings- och absorptionskoefficienterna för muskelvävnad är känd sedan tidigare. Resultaten visade att absorptionskoefficienten endast utgjorde cirka hälften av attenueringen i *annulus*. Detta innebär att ultraljudsspridningen är stor i *annulus* beroende på dess anisotropa uppbyggnad.

För att få en bättre bild av temperaturfördelningen i disken under HIFU-behandling än den som enstaka temperaturgivare ger, undersöktes möjligheten att med magnetresonanstomografi (MR) mäta temperaturen. Disk med omgivande kotor (oxsvans) monterades i ett vattenbad som placerades i en magnetresonanskamera. Fasbilder i flera plan togs före, under och efter HIFU-behandling och temperaturändringen beräknades på de resulterande bilderna. Volymen som upphettats till 28°C eller mer (vilket motsvarar sluttemperatur på minst 65°C när utgångstemperaturen är normal kroppstemperatur) beräknades till 75 mm^3 efter 60 s och 195 mm^3 efter 6 minuters behandling. Metoden är lämplig för att mäta temperaturförändringar och utvärdera behandlingar vid HIFU behandling av disk.

References

Bass E C, Wistrom E V, Diederich C J, Nau W H, Pellegrino R, Ruberti J, Lotz J C. Heat-induced changes in porcine annulus fibrosus biomechanics. J Biomech 2004; (37): 233-240.

Boden S D, Davis D O, Dina T S, Patronas N J, Wiesel S W. Abnormal magnetic-resonance scans of the lumbar spine in asymptomatic subjects. A prospective investigation. J Bone Joint Surg Am 1990; (72): 403-408.

Bono C M, Iki K, Jalota A, Dawson K, Garfin S R. Temperatures within the lumbar disc and endplates during intradiscal electrothermal therapy: formulation of a predictive temperature map in relation to distance from the catheter. Spine 2004; (29): 1124-1129.

Colombati S, Petralia S. Assorbimento di ultrasuoni in tessuti animali. La Ricerca Scientifica 1950; (20): 71-78.

Duck F A. Physical properties of tissue. A comprehensive reference book. Academic Press, London 1990.

Dussik K T. On the possibility of using ultrasound waves as a diagnostic aid. Neurol Psychiat 1942; (174): 153-168.

Dussik K T, Fritch D J, Kyriazidou M, Sear R S. Measurements of articular tissues with ultrasound. Am J Phys Med 1958; (37): 160-165.

Dyson M, Pond J B, Joseph J, Warwick R. The stimulation of tissue regeneration by means of ultrasound. Clin Sci 1968; (35): 273-285.

Edler I, Hertz C H. The use of ultrasonic reflectoscope for continuous recording of the movements of the heart walls. Kungliga Sällskapet i Lund Förhandlingar 1954; (24): 1-19.

Emohare O, Hafez M I, Sandison A, Coombs R R, McCarthy I D. Laser-induced thermal stress and the heat shock response in neural cells. Acta Orthop Scand 2004; (75): 610-617.

Filipczynski L, Kujawska T, Wojcik J. Temperature elevation in focused Gaussian ultrasonic beams at various insonation times. Ultrasound Med Biol 1993; (19): 667-679.

Freeman B J, Fraser R D, Cain C M, Hall D J, Chapple D C. A randomized, double-blind, controlled trial: intradiscal electrothermal therapy versus placebo for the treatment of chronic discogenic low back pain. Spine 2005; (30): 2369-2377.

Frohling M A, Schlote W, Wolburg-Buchholz K. Nonselective nerve fibre damage in peripheral nerves after experimental thermocoagulation. Acta Neurochir (Wien) 1998; (140): 1297-1302.

Fry W J, Fry F J. Fundamental neurological research and human neurosurgery using intense ultrasound. IRE Trans Med Electron 1960; (ME-7): 166-181.

ter Haar G. Therapeutic ultrasound. Eur J Ultrasound 1999; (9): 3-9.

Hafez M I, Zhou S, Coombs R R, McCarthy I D. The effect of irrigation on peak temperatures in nerve root, dura, and intervertebral disc during laser-assisted foraminoplasty. Lasers Surg Med 2001; (29): 33-37.

Hayashi K, Markel M D. Thermal capsulorrhaphy treatment of shoulder instability: basic science. Clin Orthop 2001; (390): 59-72.

Heckman J D, Ryaby J P, McCabe J, Frey J J, Kilcoyne R F. Acceleration of tibial fracture-healing by non-invasive, low-intensity pulsed ultrasound. J Bone Joint Surg Am 1994; (76): 26-34.

Hill C R, Rivens I, Vaughan M G, ter Haar G R. Lesion development in focused ultrasound surgery: a general model. Ultrasound Med Biol 1994; (20): 259-269.

Hindley J, Gedroyc W M, Regan L, Stewart E, Tempany C, Hynynen K, McDannold N, Inbar Y, Itzchak Y, Rabinovici J, Kim H S, Geschwind J F, Hesley G, Gostout B, Ehrenstein T, Hengst S, Sklair-Levy M, Shushan A, Jolesz F. MRI guidance of focused ultrasound therapy of uterine fibroids: early results. Am J Roentgenol 2004; (183): 1713-1719.

Holm S. Ultrasim – a toolbox for ultrasound field simulation. Nordic Matlab conference 2001.

Houpt J C, Conner E S, McFarland E W. Experimental study of temperature distributions and thermal transport during radiofrequency current therapy of the intervertebral disc. Spine 1996; (21): 1808-1812.

Huber P E, Jenne J W, Rastert R, Simiantonakis I, Sinn H P, Strittmatter H J, von Fournier D, Wannenmacher M F, Debus J. A new noninvasive approach in breast cancer therapy using magnetic resonance imaging-guided focused ultrasound surgery. Cancer Res 2001; (61): 8441-8447.

Hynynen K, Clement G T, McDannold N, Vykhodtseva N, King R, White P J, Vitek S, Jolesz F A. 500-element ultrasound phased array system for noninvasive focal surgery of the brain: a preliminary rabbit study with ex vivo human skulls. Magn Reson Med 2004; (52): 100-107.

Hynynen K, McDannold N, Vykhodtseva N, Jolesz F A. Noninvasive MR imaging-guided focal opening of the blood-brain barrier in rabbits. Radiology 2001a; (220): 640-646.

Hynynen K, Pomeroy O, Smith D N, Huber P E, McDannold N J, Kettenbach J, Baum J, Singer S, Jolesz F A. MR imaging-guided focused ultrasound surgery of fibroadenomas in the breast: a feasibility study. Radiology 2001b; (219): 176-185.

Ishihara Y, Calderon A, Watanabe H, Okamoto K, Suzuki Y, Kuroda K, Suzuki Y. A precise and fast temperature mapping using water proton chemical shift. Magn Reson Med 1995; (34): 814-823.

Kohrmann K U, Michel M S, Gaa J, Marlinghaus E, Alken P. High intensity focused ultrasound as noninvasive therapy for multilocal renal cell carcinoma: case study and review of the literature. J Urol 2002; (167): 2397-2403.

Konno S, Olmarker K, Byrod G, Nordborg C, Strömqvist B, Rydevik B. The European Spine Society AcroMed Prize 1994. Acute thermal nerve root injury. Eur Spine J 1994; (3): 299-302.

Kossoff G. Analysis of focusing action of spherically curved transducers. Ultrasound Med Biol 1979; (5): 359-365.

Lafon C, de Lima D M, Theillere Y, Prat F, Chapelon J Y, Cathignol D. Optimizing the shape of ultrasound transducers for interstitial thermal ablation. Med Phys 2002; (29): 290-297.

Lee L A, Simon C, Bove E L, Mosca R S, Ebbini E S, Abrams G D, Ludomirsky A. High intensity focused ultrasound effect on cardiac tissues: potential for clinical application. Echocardiography 2000; (17): 563-566.

Lehmann J F, Johnsson E W. Some factors influencing the temperature distribution in thighs exposed to ultrasound. Arch Phys Med Rehab 1958; (39): 347-356.

Lele P P. Induction of deep, local hyperthermia by ultrasound and electromagnetic fields: problems and choices. Radiat Environ Biophys 1980; (17): 205-217.

Marchand F, Ahmed A M. Investigation of the laminate structure of lumbar disc anulus fibrosus. Spine 1990; (15): 402-410.

Mayer H M, Brock M, Berlien H P, Weber B. Percutaneous endoscopic laser discectomy (PELD). A new surgical technique for non-sequestrated lumbar discs. Acta Neurochir Suppl (Wien) 1992; (54): 53-58.

Miles C A. Ultrasonic properties of tendon: velocity, attenuation, and backscattering in equine digital flexor tendons. J Acoust Soc Am 1996; (99): 3225-3232.

Miles C A, Fursey G A, Birch H L, Young R D. Factors affecting the ultrasonic properties of equine digital flexor tendons. Ultrasound Med Biol 1996; (22): 907-915.

Mixter W, Barr J. Rupture of intervertebral disc with involvement of the spinal canal. N Engl J Med 1934; (211): 210-214.

Nationellt Kompetenscentrum för Ortopedi. Indikationer för behandling inom ortopedi, 2005, ISBN 91-975284-8-X.

Olmarker K, Blomquist J, Strömberg J, Nannmark U, Thomsen P, Rydevik B. Inflammatogenic properties of nucleus pulposus. Spine 1995; (20): 665-669.

Pauza K J, Howell S, Dreyfuss P, Peloza J H, Dawson K, Bogduk N. A randomized, placebo-controlled trial of intradiscal electrothermal therapy for the treatment of discogenic low back pain. Spine J 2004; (4): 27-35.

Peters R D, Hinks R S, Henkelman R M. Heat-source orientation and geometry dependence in proton-resonance frequency shift magnetic resonance thermometry. Magn Reson Med 1999; (41): 909-918.

de Poorter J, de Wagter C, de Deene Y, Thomsen C, Ståhlberg F, Achten E. The proton resonance frequency shift method compared with molecular diffusion for quantitative measurement of two dimensional time dependent temperature distribution in a phantom. Journal of Magnetic Resonance 1994; (103): 234-241.

Rabkin B A, Zderic V, Vaezy S. Hyperecho in ultrasound images of HIFU therapy: involvement of cavitation. Ultrasound Med Biol 2005; (31): 947-956.

Saal J A, Saal J S. Intradiscal electrothermal treatment for chronic discogenic low back pain: prospective outcome study with a minimum 2-year follow-up. Spine 2002; (27): 966-973.

Schenk B, Brouwer P A, Peul W C, van Buchem M A. Percutaneous laser disk decompression: a review of the literature. Am J Neuroradiol 2006; (27): 232-235.

Shore D, Woods M O, Miles C A. Attenuation of ultrasound in post rigor bovine skeletal muscle. Ultrasonics 1986; (24): 81-87.

Sluijter M E. The use of radiofrequency lesions for pain relief in failed back patients. Int Disabil Stud 1988; (10): 37-43.

Souchon R, Bouchoux G, Maciejko E, Lafon C, Cathignol D, Bertrand M, Chapelon J Y. Monitoring the formation of thermal lesions with heat-induced echo-strain imaging: a feasibility study. Ultrasound Med Biol 2005; (31): 251-259.

Spangfort E V. The lumbar disc herniation. A computer-aided analysis of 2,504 operations. Acta Orthop Scand Suppl 1972; (142): 1-95.

Stewart E A, Gedroyc W M, Tempany C M, Quade B J, Inbar Y, Ehrenstein T, Shushan A, Hindley J T, Goldin R D, David M, Sklair M, Rabinovici J. Focused ultrasound treatment of uterine fibroid tumors: safety and feasibility of a noninvasive thermoablative technique. Am J Obstet Gynecol 2003; (189): 48-54.

Strömqvist B, Jönsson B, Fritzell P, Hägg O, Larsson B E, Lind B. The Swedish National Register for lumbar spine surgery: Swedish Society for Spinal Surgery. Acta Orthop Scand 2001; (72): 99-106.

Thijssen J M. The history of ultrasound techniques in ophthalmology. Ultrasound Med Biol 1993; (19): 599-618.

Visioli A G, Rivens I H, ter Haar G R, Horwich A, Huddart R A, Moskovic E, Padhani A, Glees J. Preliminary results of a phase I dose escalation clinical trial using focused ultrasound in the treatment of localised tumours. Eur J Ultrasound 1999; (9): 11-18.

Vogel K G. Tendon structure and response to changing mechanical load. J Musculoskelet Neuronal Interact 2003; (3): 323-325.

Wallace A L, Wyatt B C, McCarthy I D, Hughes S P. Humoral regulation of blood flow in the vertebral endplate. Spine 1994; (19): 1324-1328.

White D R, Wambersie A. Tissue Substitutes, Phantoms and Computational Modelling in Medical Ultrasound. ICRU Report 61 1998.

Wood R W, Loomis A L. The physical and biological effects of high frequency sound waves of great intensity. Phil Mag 1927; (4): 417-436.

Wu F, Wang Z B, Chen W Z, Zou J Z, Bai J, Zhu H, Li K Q, Xie F L, Jin C B, Su H B, Gao G W. Extracorporeal focused ultrasound surgery for treatment of human solid carcinomas: early Chinese clinical experience. Ultrasound Med Biol 2004; (30): 245-60.

Wu F, Wang Z B, Wang Z L. Changes in ultrasonic images of tissue damaged by high-intensity focused ultrasound *in vivo*. J Acoust Soc Am 1998; (103): 2869.