Osteoarthritis and Cartilage 22 (2014) 1784–1799

Osteoarthritis and Cartilage

Review

The potential utility of high-intensity ultrasound to treat osteoarthritis

H.J. Nieminen †, A. Salmi †, P. Karppinen †, E. Hæggström †, S.A. Hacking ‡ § *

† Department of Physics, University of Helsinki, Finland
‡ Department of Orthopaedics, Massachusetts General Hospital, Boston, MA, United States
§ Harvard Medical School, Boston, MA, United States

ARTICLE INFO

Article history:
Received 7 April 2014
Accepted 29 July 2014

Keywords:
Ultrasound
Osteoarthritis
Cartilage
Bone
Drug delivery
Orthopedic surgery

SUMMARY

Osteoarthritis (OA) is a widespread musculoskeletal disease that reduces quality of life and for which there is no cure. The treatment of OA is challenging since cartilage impedes the local and systemic delivery of therapeutic compounds (TCs). This review identifies high-intensity ultrasound (HIU) as a non-contact technique to modify articular cartilage and subchondral bone. HIU enables new approaches to overcome challenges associated with drug delivery to cartilage and new non-invasive approaches for the treatment of joint disease. Specifically, HIU has the potential to facilitate targeted drug delivery and release deep within cartilage, to repair soft tissue damage, and to physically alter tissue structures including cartilage and bone. The localized, non-invasive ultrasonic delivery of TCs to articular cartilage and subchondral bone appears to be a promising technique in the immediate future.

Introduction

Articular cartilage covers the surfaces of synovial joints where it prevents direct bone to-bone contact and enables pain-free articulation of the joint. Osteoarthritis (OA) is a degenerative disease that affects the joints and surrounding tissues. Radiographically, OA is commonly described as a loss or thinning of cartilage at the articulating surfaces of long bones. However, the process of cartilage degeneration also includes changes in the joint structure and surrounding tissues. Symptomatic patients with OA often experience joint pain, stiffness, and a loss of joint mobility[1]. The development of OA involves distinct morphological changes[2], depending on the extent of degeneration. Trauma, or more specifically mechanical damage to the cartilage, can also induce degradation and OA[3–5].

All cartilage-covered joints are susceptible to OA and there is no cure for this disease. OA is a global problem that reduces quality of life and results in significant economic impact[6,7]. Worldwide, 9.6% of men and 18% of women over 60 years suffer from symptomatic OA and the disease is expected to be the fourth leading cause of disability by 2020[8]. Post-traumatic OA, accounts 12% of all OA[9], as young as 30 years of age can lead to symptomatic OA[10]. Because of OA's wide-reaching implications, there is a persistent interest in developing new approaches to prevent, retard, halt or potentially reverse the progression of OA[11–13]. Currently, the most successful treatment for advanced OA is to replace articulating surfaces with mechanical components in a procedure known as total joint arthroplasty (TJA)[14,15]. While successful, the need for TJA may be delayed by more efficient disease-modifying treatments for OA, which would be the preferred option in especially young knee injury patients likely to develop OA[10].

Background

Unique properties of osteochondral tissue

In individuals with healthy joints, articular cartilage forms a low friction surface about 1–3 mm thick. As a material, cartilage is a fiber-reinforced hydrogel with tortuous nano-sized pores [Fig. 1]. More specifically, cartilage is a fibril-reinforced poroviscoelastic cushion[16] that retains liquid during fast loading while permitting liquid flow during static loading[17]. The unique and dynamic material properties of cartilage result from its structure and

* Address correspondence and reprint requests to: S.A. Hacking, Laboratory for Musculoskeletal Research and Innovation, Department of Orthopaedics, Harvard Medical School and Massachusetts General Hospital, 55 Fruit St, Rm. GRJ 1120, Boston, MA 02114, United States. Fax: 1-617-726-3883.

E-mail addresses: heikki.nieminen@helsinki.fi (H.J. Nieminen), ari.salmi@helsinki.fi (A. Salmi), pasi.karppinen@gmail.com (P. Karppinen), edward.haeggstrom@helsinki.fi (E. Hæggström), ahacking@yahoo.com (S.A. Hacking).

http://dx.doi.org/10.1016/j.joca.2014.07.025
1063-4584/

High-intensity ultrasound terminology

Absorption	loss of acoustic energy converted into other forms of energy such as heat.
Acoustic discontinuity	spatially abrupt change in e.g., *speed of sound* or *acoustic impedance* at an interface between two materials.
Acoustic impedance	material property that describes how much *pressure* is generated in a medium from spatial displacement of its molecules at a given frequency. Sound is reflected at an interface between two materials with different acoustic impedances.
Acoustic radiation force	force induced by sound impinging on sound-absorbing material (e.g., tissue) or acoustic interfaces (e.g., fluid–tissue or gas–fluid interface).
ARFI, i.e., Acoustic Radiation Force Impulse imaging	an elasticity imaging technique in which acoustic radiation force produces spatial tissue displacement, which is recorded by *ultrasound* imaging device. The detected spatial displacement are converted into spatial elasticity images that can be used to diagnose e.g., hard tumors deep in the body that are difficult to palpate.
Acoustic streaming	streaming of fluids induced by *absorption* of sound into the medium.
Attenuation	loss of acoustic energy due to *absorption*, sound scattering at *acoustic discontinuities* and spreading of the sound beam (geometric attenuation).
Cavitation (stable, inertial)	interaction of acoustic *pressure* variation and gas *micro-bubbles* leading to radial bubble oscillation (stable cavitation). This can induce fluid streams around the bubble and shear forces on cells. Combining intense sound and micro-bubbles allows producing micro-implosions or fast and hot water-jets at the micro-scale that can micro-machine material (inertial cavitation). Cavitation is a threshold phenomenon that can be controlled by adjusting frequency, maximum negative sound pressure amplitude, and duration of the applied sound pulse.
Displacement	in *ultrasound* wave, molecules oscillate coherently around their rest position. The distance of molecules from their rest position is called a displacement. In longitudinal or shear waves the displacement of molecules occur along or perpendicular to the direction of ultrasound propagation, respectively.
HIU	high-intensity *ultrasound* or power *ultrasound* has $\geq$1 W/cm^2 *intensity*.
HIFU, i.e., High-Intensity Focused Ultrasound	High-Intensity Focused Ultrasound is *HIU* that is produced by geometrically and/or electrically focusing ultrasound energy into a small volume. In medicine, HIFU is typically used to *thermally ablate* tumor tissue.
Intensity	power of sound per unit area perpendicular to the direction of *ultrasound* propagation (SI unit: W/cm^2). Ultrasound intensity is directly proportional to the square of ultrasound *pressure*.
Lithoptripsy	method for breaking gallstones or other calculi by strong *shock waves*.
LIU	low-intensity *ultrasound* or low power ultrasound has $\lesssim$1 W/cm^2 *intensity*.
Longitudinal wave	see *displacement*.
Micro-bubble	a micron sized gas bubble. When a micro-bubble interacts with sound, a phenomenon called *cavitation* may occur. Micro-bubbles are used in medicine as *ultrasound* imaging contrast agents (enhanced scattering of sound) and in therapy applications (enhanced cavitation effects). Nano-bubbles have shown promise to act as ultrasound contrast agents.
PRF, i.e., pulse repetition frequency	the rate (Hz) at which *ultrasound* pulses or bursts is generated.
Pressure	ultrasonic pressure appears as a traveling density disturbance of material oscillating at a frequency >20 kHz.
Reflection	reflection of sound occurs when sound meets an *acoustic impedance* mismatch (see *acoustic discontinuity*), which is greater in size than the wavelength (e.g., collagen bundle). When the discontinuity is of same size or smaller than the wavelength of the sound wave, *scattering* occurs instead of reflection. Collagen at superficial articular cartilage or inside cartilage is known to be a strong reflector or scatterer of ultrasound, respectively.
Scattering	see *reflection*.
Shear wave	see *displacement*.
Speed of sound	a property of a sound wave describing the traveling speed of a wave. In articular cartilage, the *ultrasound* speed is typically 1600–1700 m/s in MHz domain.
Shock wave	a traveling acoustic wave with steep temporal and spatial gradients in *pressure*. This is typically a short impulse-like acoustic wave with high pressure amplitude and broadband spectral content. Its propagation speed depends on *intensity*.
Thermal ablation	removal of tissue by heat. This strategy is used e.g., in *HIFU* surgery, where tumor cells are killed by heating tissue with focused *ultrasound*.
Ultrasonic actuation	a process of using *ultrasound* to modify, machine or micro-machine material such as tissue. Common examples of ultrasound actuation are: *cutting*: ultrasonic knife with vibrating blade to enhance surgical cutting of tissues. – *homogenization*: ultrasound can be used to homogenize tissue by typically combining low-frequency ultrasound with strong inertial *cavitation*. – *milling, abrading or polishing*: in these industrial actuation techniques high-intensity ultrasound is applied to milling,