Ultrasound in Med. & Biol., Vol. 40, No. 1, pp. 244–257, 2014

0301-5629/$ - see front matter

http://dx.doi.org/10.1016/j.ultrasmedbio.2013.08.015

● *Original Contribution*

3-D HIGH-FREQUENCY ULTRASOUND BACKSCATTER ANALYSIS OF HUMAN ARTICULAR CARTILAGE

Nils Männicke,* Martin Schöne,* Matthias Gottwald,† Felix Göbel,‡ Michael L. Oelze,§ and Kay Raum*‖

*Julius Wolff Institute and Berlin-Brandenburg School for Regenerative Therapies, Charité-Universitätsmedizin Berlin, Berlin, Germany; †Department of Surgery, Hospital Köln-Holweide, Cologne, Germany; ‡Department of Orthopaedics and Traumatology, Carl-von-Basedow-Klinikum, Merseburg, Germany; §Bioacoustics Research Laboratory, Department of Electrical and Computer Engineering, University of Illinois at Urbana-Champaign, Urbana, Illinois, USA; and ‖Department of Orthopedics, Martin Luther University of Halle-Wittenberg, Halle, Germany

(*Received* 19 *April* 2013; *revised* 13 *August* 2013; *in final form* 16 *August* 2013)

Abstract—High-frequency ultrasound is a promising method for non-invasive characterization of cartilage degeneration. Surface reflection and integrated spectral parameters are often used. In the work described here, human cartilage samples with varying degrees of degeneration were measured using a 40-MHz transducer. Backscatter signals originating from the superficial and transitional zones of cartilage were analyzed using amplitude, spectral and envelope statistical parameters and related to degenerative changes of the matrix given by the Mankin score. The results indicate an increased sensitivity of spectral slope and envelope statistical parameters to early matrix degeneration compared with conventional amplitude parameters. Furthermore, moderate correlations of chondrocyte number with backscatter amplitude and envelope statistics were observed, suggesting that at high frequencies, cells are one important scattering source in cartilage. An application of spectral and envelope statistical parameters to intra-articular ultrasound arthroscopy is conceivable and could improve the diagnostic potential of these examinations. Future studies are necessary to clarify the contributions of chondrocytes, extracellular matrix and collagen content to ultrasound backscatter to further improve the diagnostic potential of ultrasound for cartilage assessment. (E-mail: kay.raum@charite.de) **© 2014 World Federation for Ultrasound in Medicine & Biology.**

Key Words: **Backscatter, Cartilage, Degeneration, Envelope statistics, High-frequency ultrasound, Osteoarthritis, Quantitative ultrasound, Spectral slope, Ultrasound bio-microscopy, Ultrasound spectroscopy.**

INTRODUCTION

Osteoarthrosis (OA) is the most prevalent joint disease and results in considerable economic hardship and a decrease in quality-adjusted life years (Pinto et al. 2012). OA involves progressive degenerative changes in cartilage surface, matrix and subchondral bone. One of the first signs of OA is cartilage tissue softening, leading to cartilage fibrillation and disruption of the collagen network in later stages (Schöne et al. 2013). To date, none of the established non-invasive imaging modalities are able to assess these degenerative tissue alterations concurrently. Therefore, the gold standard is still histologic evaluation, for example, the Mankin (Buckwalter and Mankin 1998), Osteoarthritis Research Society International (Pritzker et al. 2006) and International Cartilage Repair Society II (Mainil-Varlet et al. 2010) scores. Non-invasive determination of different stages of degeneration is of high interest. In particular, the detection of the earliest signs of matrix degeneration, which are not associated with collagen destruction, could aid in the development of treatment strategies that aim to arrest the degeneration process (Brown et al. 2012; Yang et al. 2004).

In principle, high-frequency ultrasound is able to provide distinct information on the cartilage surface, cartilage matrix and subchondral bone boundary through temporal and inclination-controlled separation of the reflected and backscattered signals (Schöne et al. 2013). The use of ultrasound for the detection of early degenerative changes has been proposed in previous studies (Nieminen et al. 2009). The temporal variability and

Address correspondence to: Kay Raum, Julius Wolff Institut & Berlin-Brandenburg School for Regenerative Therapies, Charité-Universitätsmedizin Berlin, Augustenburger Platz 1, 13353 Berlin, Germany. E-mail: kay.raum@charite.de

intensity of signals reflected from the cartilage surface are related to cartilage surface roughness and stiffness, respectively, which are associated with collagen depletion (Nieminen et al. 2002; Wang et al. 2010), surface fibrillation (Saarakkala et al. 2004; Schöne et al. 2013) and biomechanical competence (Gelse et al. 2010) of the tissue. However, several researchers have noted that careful control of normal sound incidence is required for reliable estimation of reflection intensity and roughness parameters (Kaleva et al. 2009; Schöne and Raum 2011; Schöne et al. 2013). With increasing surface inclination, the fraction of specular reflection that is received by the transducer decreases, and the first detected signals become increasingly composed of sub-surface backscatter signals. Moreover, the intensity of the reflection from the interface between cartilage and subchondral bone has been observed to increase in OA samples, it has been suggested that this increase is due to a sclerosis-related increase in bone density (Jaffre et al. 2003; Laasanen et al. 2006; Saarakkala et al. 2006). As discussed by Saarakkala et al. (2011), the measured intensity from this interface is also subject to changes caused by alterations in sound attenuation in the cartilage matrix. Hence, *a priori* information on the acoustic properties of the matrix, that is, speed of sound and acoustic attenuation, is necessary to enhance the accuracy of parameters derived from the subchondral bone interface.

Only a few studies have investigated acoustic backscatter originating from the cartilage matrix for detection and characterization of cartilage degeneration, and so far, only integrated spectral amplitudes of the received signals have been considered, that is, apparent integrated backscatter (*AIB*). For example, Cherin et al. (1998) suggested that variations in *AIB* reflect changes in shape, size and/or density of scatterers in the cartilage matrix and could also be related to constitutional and structural changes in the extracellular cartilage matrix. However, until now, the origin of acoustic backscatter from cartilage tissue has not been fully identified. Experimentally, it has been found that *AIB* is not affected by depletion of proteoglycans (Pellaumail et al. 2002), but decreases with age in patellas of Wistar rats (Cherin et al. 2001) and after an acute impact injury in bovine bone (Viren et al. 2012). In contrast, a massive increase in *AIB* was observed in repair tissue as compared with intact hyaline cartilage (Gelse et al. 2010; Viren et al. 2010).

Much of ultrasound backscatter arises from sub-wavelength structures. In contrast to specular reflections, the spectrum of backscattered waves is usually not equivalent to that of incident waves. The spectrum of a backscattered signal received by an ultrasound probe from a scattering tissue is determined by distribution, geometry and acoustic impedance mismatch between scatterers and the surrounding medium. Outstanding work has been conducted in both theoretical formulations (Insana and Hall 1990; Lizzi et al. 1983) and experimental applications (Oelze and O'Brien 2006; Oelze et al. 2004) to use quantitative backscatter parameters, for example, the ultrasonic backscatter coefficient, to enhance the diagnostic power of clinical ultrasound scanners (Nam et al. 2012). However, for cartilage tissue, incorporation of spectral features more sophisticated than integrated intensity has not been achieved. One reason is that estimation of the backscatter coefficient requires locally homogeneous and uniform scattering properties in the direction of sound propagation, with axial dimensions on the order of several pulse lengths. The layered cartilage structure consisting of three thin layers, in which cells and collagen fibrils gradually change geometry, density and orientation (Fig. 1), leads not only to a pronounced dependence of acoustic backscatter on depth (Gelse et al. 2010), but also to gradual changes in bulk properties, for example, speed of sound and attenuation (Agemura et al. 1990).

To overcome these limitations, we applied 3-D high-frequency ultrasound in combination with depth-dependent spectral analysis using short time gates to the analysis of healthy and degenerated human cartilage samples. To separate specular surface reflections from components backscattered from cartilage matrix, we

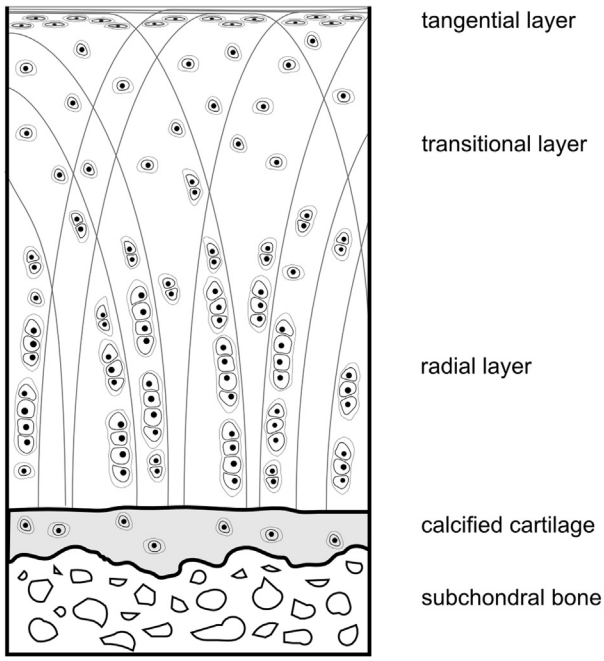

Fig. 1. Layered structure of healthy articular cartilage. The superficial zone is characterized by a large number of small disk-shaped chondrocytes. Fewer and more isotropic chondrocytes can be observed in the transitional zone. In the radial zone, chondrons contain multiple chondrocytes. Cell density is lowest and the cell size is large. Note the arch-like structure of collagen, with the fiber orientation parallel to the surface in the superficial zone and perpendicular to the surface in the radial zone.