Published in final edited form as:

J Biomech Eng. 2009 May ; 131(5): 054505. doi:10.1115/1.3116152.

EFFECT OF MECHANICAL LOADING ON ELECTRICAL CONDUCTIVITY IN HUMAN INTERVERTEBRAL DISC

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Abstract

Background—The intervertebral disc (IVD), characterized as a charged, hydrated soft tissue, is the largest avascular structure in the body. Mechanical loading to the disc results in electromechanical transduction phenomenon as well as altered transport properties. Electrical conductivity is a material property of tissue depending on ion concentrations and diffusivities, which are in turn functions of tissue composition and structure. The aim of this study was to investigate the effect of mechanical loading on electrical behavior in human IVD tissues. We hypothesized that electrical conductivity in human IVD is strain-dependent, due to change in tissue composition caused by compression, and inhomogeneous, due to tissue structure and composition. We also hypothesized that conductivity in human annulus fibrosus (AF) is anisotropic, due to the layered structure of the tissue.

Method of Approach—Three lumbar IVDs were harvested from three human spines. From each disc, four AF specimens were prepared in each of three principal directions (axial, circumferential, and radial), and four axial nucleus pulposus (NP) specimens were prepared. Conductivity was determined using a four-wire sense-current method and custom-designed apparatus by measuring the resistance across the sample. Resistance measurements were taken at three levels of compression (0%, 10%, and 20%). Scanning electron microscopy (SEM) images of human AF tissue were obtained in order to correlate tissue structure with conductivity results.

Results—Increasing compressive strain significantly decreased conductivity for all groups ($p < 0.05$, ANOVA). Additionally, specimen orientation significantly affected electrical conductivity in AF tissue, with conductivity in the radial direction being significantly lower than that in the axial or circumferential directions at all levels of compressive strain ($p < 0.05$, ANOVA). Finally, conductivity in NP tissue was significantly higher than that in AF tissue ($p < 0.05$, ANOVA). SEM images of AF tissues showed evidence of microtubes orientated in the axial and circumferential directions, but not in the radial direction. This may suggest a relationship between tissue morphology and the anisotropic behavior of conductivity in AF.

Conclusions—The results of this investigation demonstrate that electrical conductivity in human IVD is strain-dependent and inhomogeneous, and that conductivity in human AF tissue is anisotropic (i.e., direction-dependent). This anisotropic behavior is correlated with tissue structure shown in SEM images. This study provides important information regarding the effects of mechanical loading on solute transport and electrical behavior in IVD tissues.

Keywords

annulus fibrosus; nucleus pulposus; anisotropy; compression; tissue mechanics; electrical behavior; morphology; scanning electron microscopy

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INTRODUCTION

The intervertebral disc (IVD) is the largest avascular structure in the human body. The disc plays a primarily mechanical role, supporting large compressive loads and allowing for spinal flexibility. The mechanical and transport properties of the disc are related to its unique composition and structure. The primary components of IVD are water, proteoglycan (PG), and collagen [1,2]. The disc consists of the nucleus pulposus (NP), the annulus fibrosus (AF) and cartilage end-plates. In the present study, NP and AF tissues are investigated, see Fig. 1. The NP is composed of collagen fibrils arranged randomly in a proteoglycan gel, and is made up primarily of water (70–90%). The AF is formed by a series of concentric lamellae consisting of highly organized collagen fibers bundles [3,4].

Electrical conductivity, a material property of biological tissues, depends on ion concentrations and diffusivities within the tissue, which are in turn functions of tissue composition and structure [5–11]. The electrical conductivity of articular cartilage and animal IVD has been investigated [5–7,11–13,16–19]. Studies have shown that conductivity in cartilaginous tissues is sensitive to tissue hydration, but not fixed charge density at a physiological condition [9, 12]; conductivity has been linearly correlated with tissue hydration for animal IVD specimens with water content being greater than 70% [12,13,19]. The dependence of conductivity on hydration is believed to be due to changes in ion diffusivities with tissue water content [11–16]. Furthermore, our previous study has demonstrated that conductivity in bovine IVD is anisotropic and inhomogeneous [16]. However, to our knowledge, no previous work has investigated the electrical conductivity of human IVD or the effect of mechanical loading on conductivity in IVD tissues.

Understanding how loading affects transport and electrical properties of IVD tissues is essential given the mechanical function of the disc. It is known that mechanical loading of the disc results in electromechanical transduction phenomenon, as well as altered solute transport [20]. Indeed, many studies have reported the effects of mechanical loading on water content, nutritional levels and solute transport in IVD [1,21–30]. Because conductivity is closely related to ion diffusivities, further comprehension of the effects of loading on the electrical behavior in IVD provides important insight into disc transport properties.

Many point to degeneration of the IVD as a primary etiologic factor leading to low back pain [31–34]; poor nutritional transport in the disc is thought to be a principal mechanism leading to degeneration [21,22,35–37]. During disc degeneration, there is a marked decrease in the PG content of the disc, resulting in decreased tissue hydration [38,39]. Due its sensitivity to tissue water content, electrical conductivity may be a good indicator of disc degeneration. Therefore, characterizing the electrical conductivity of human IVD and its relation to tissue composition and structure may be valuable for the future development of new techniques for diagnosing disc degeneration.

We hypothesized that the electrical conductivity of human IVD is strain-dependent, due to changes in water content caused by tissue compression. We also hypothesized that, due to the composition and structure of IVD, conductivity is inhomogeneous within the disc, and anisotropic in AF due to the layered organization of the tissue. Therefore, the objective of this study was to measure the electrical conductivity of human AF and NP tissues under three levels of compressive strain, as well as that of AF in three major directions (axial, circumferential, and radial). The present study is essential in more fully understanding of the effect of mechanical loading on the electrical and transport behavior in human IVD tissues, and is also useful in the development of novel methods for diagnosing disc degeneration.

THEORETICAL BACKGROUND

Under zero fluid flow conditions, the electrical conductivity (χ) of a charged porous material is related to the intrinsic Na^+ and Cl^- ion diffusivities ($D^{+/-}$) by [10,11,18]:

$$\chi = F_c^2 \phi^w (c^+ D^+ + c^- D^-) / RT, \quad (1)$$

where F_c is the Faraday constant, ϕ^w is the tissue water volume fraction (or water content), R is the gas constant, T is the absolute temperature, and c^+ and c^- are Na^+ and Cl^- ion concentrations, respectively. For negatively-charged tissues, such as IVD, the ion concentrations in tissue are related to the absolute value of the negative fixed charge density (c^F) through the electroneutrality condition, $c^+ = c^- + c^F$ [40,41]. The ion concentrations within cartilaginous tissues can then be calculated based on the ideal Donnan equation. The value of fixed charge density (FCD) within the tissue varies with tissue hydration by [42]:

$$c^F = \frac{c_o^F (1 - \phi_o^w) \phi_o^w}{(1 - \phi_o^w) \phi^w}, \quad (2)$$

where c_o^F and ϕ_o^w are FCD and water volume fraction at a reference configuration. Thus, the ion concentrations (c^+ and c^-) within the tissue also vary with water content.

Recently, a new constitutive model has been developed for solute diffusivity (D^i , where superscript “ i ” stands for species) in tissue [19]:

$$D^i = D_o^i \exp \left[-\alpha \left(\frac{r_s^i}{\sqrt{\kappa}} \right)^\beta \right], \quad (3)$$

where D_o^i and r_s^i are solute diffusivity in aqueous solution and solute Stokes’ radius, respectively; κ is the Darcy permeability of the tissue, α and β are two positive parameters that depend on the structure of the porous media. For example, $\alpha = 1.29 \pm 0.171$ and $\beta = 0.372 \pm 0.088$ for porcine AF tissue [19]. The value of κ in Eq (6) also varies with water content (ϕ^w) [43].

Since the water volume fraction of tissue (ϕ^w) is related to tissue dilatation, e , by:

$$\phi^w = \frac{\phi_o^w + e}{1 + e}, \quad (4)$$

the ion concentrations and diffusivities are all strain-dependent.

METHODS

Specimen Preparation

Three L3-L4 IVDs were harvested from three human lumbar spines (41 y.o. M, 45 y.o. F, 45 y.o. F, Thompson grades I, II, III, respectively). Discs were excised from spines, wrapped in plastic, and stored at -80°C until the day of experimentation. Cylindrical specimens (5 mm diameter, ~3 mm thickness) were prepared using a stainless steel corneal trephine (Biomedical Research Instruments, Inc., Silver Spring, MD) and sledge microtome (Model SM2400, Leica Instruments, Nussloch, Germany) with freezing stage (Model BFS-30, Physitemp Instruments

Inc., Clifton, NJ). Four AF specimens were excised in each of the three principal directions (axial, circumferential, and radial) while four NP specimens were prepared in the axial direction only, see Fig. 1. The specimen height was measured using a custom-designed current sensing micrometer [13]. A total of four groups of specimens were tested: three groups for AF in each direction ($n=12$ for each group) and one group for NP ($n=12$). A total of three conductivity measurements, corresponding to three levels of compressive strain (0%, 10% and 20%), were performed on each specimen.

Tissue Compression

Uniaxial, confined compression of the tissue specimen was carried out in a separate compression chamber, see Fig. 2a. The tissue was compressed between two porous plates in an acrylic chamber with inner diameter of 5 mm. Tissue compression was carried out in a separate chamber in order to avoid damage to Ag/AgCl electrodes in conductivity chamber, see Figure 2b. Initially, the tissue was compressed by 20% inside the chamber and then quickly moved to the conductivity apparatus and confined to 20% strain for resistance measurement. Following measurement at 20% compression, the specimen was allowed to swell uniaxially to the height corresponding to 10% compression in PBS solution while confined in the conductivity chamber (5 mm diameter, see below). After measurement at 10% compression, the tissue was then allowed to swell back to its initial height (0% compression) and resistance was measured.

Conductivity Measurement

The apparatus used was similar to the one previously reported [12,13]. Briefly, it consists of two stainless steel current electrodes, two Teflon-coated Ag/AgCl voltage electrodes, a spacer, and a non-conductive acrylic chamber (Fig. 2b). A four-wire sense-current method was applied using a Keithley SourceMeter (Model 2400, Keithley Instruments Inc., Cleveland, OH). The resistance, Ω , across the tissue sample was measured at a very low, constant current of 10 μ A. Electrical conductivity is related to resistance by:

$$\chi = \frac{h}{\Omega \cdot A} \quad (5)$$

where A is the cross-sectional area and h is the thickness of the sample. The distance between the electrodes, or the height of the specimen, could be controlled by the size of the spacers, see Fig. 2b.

Conductivity measurements were taken at 20%, 10% and 0% compression levels. For each level of strain, several resistance measurements were obtained at 10 minute intervals to ensure the tissue had reached equilibrium following compression or swelling. Measurements were repeated until the same resistance value (within 5%) was measured for two consecutive readings, signifying equilibrium had been reached (i.e., no fluid flow).

Measurement of water volume fraction (or water content)

The water volume fraction of specimens at undeformed state (ϕ_o^w) was determined using a buoyancy method published in literature [12,13,44]. Briefly, the specimens were weighed in air (W_{air}) and in PBS solution (W_{PBS}) using the density determination kit of a Sartorius analytical balance (Model LA120S, Goettingen, Germany); specimens were then lyophilized and weighed to determine the dry weight (W_{dry}). The water volume fraction was calculated by:

$$\phi^w = \frac{(W_{\text{wet}} - W_{\text{dry}}) \rho_{\text{PBS}}}{(W_{\text{wet}} - W_{\text{PBS}}) \rho_w}, \quad (6)$$

where ρ_{PBS} and ρ_w are the densities of PBS and water, respectively. The water volume fraction of tissue at different compression levels (ϕ^w) could be calculated by Eq. (4).

Scanning Electron Microscopy

Scanning electron microscopy (SEM) images were obtained in order to compare conductivity trends with tissue structure. Images of the axial, radial, and circumferential sections of the anterior region of human L3–L4 AF were acquired. Samples were fixed with a 2% glutaraldehyde (Electron Microscopy Sciences, Hatfield, PA, USA) in PBS, dehydrated in ethanol and dried by immersion in hexamethyldisilazane (Electron Microscopy Sciences, Hatfield, PA, USA) [45]. After sputter coating with Pd (Sputter Coater 108auto, Cressington, Watford, UK), high-resolution SEM images were obtained by a Scanning Electron Microscope (XL30 ESEM-FEG, FEI Company, Hillsborg, OR, USA) operating in high-vacuum mode.

Statistical Analysis

To investigate the effect of compression and direction on conductivity in human AF specimens, a two-way analysis of variance (ANOVA) was performed using SPSS software (SPSS Inc., Chicago, IL). The two factors were direction (three levels: axial, circumferential, and radial) and level of compression (three levels: 0%, 10%, and 20%). For human NP specimens, a one-way ANOVA was performed using SPSS software with level of compression being the factor (three levels: 0%, 10%, and 20%). Student-Newman-Keuls post hoc test was used for ANOVA analysis using SPSS software in order to determine between which levels of each factor the differences were significant. A student t-test was performed to compare conductivity values for NP and each group of AF specimens. For all tests, the significance level was set at $p < 0.05$.

RESULTS

The results for electrical conductivity measurements in human IVD tissue at 21.5°C are shown in Fig. 3. Results are shown in mean $\pm$ SD, with $n=12$ for all groups. Values for water content at reference configuration (i.e., 0% compression) and under compression are shown in Table 1. Electrical conductivity in the NP specimens was significantly higher than that in the AF specimens for all tissue orientations at all levels of compressive strain (t-test, $p < 0.05$). For both AF and NP specimens, there was a significant decrease in electrical conductivity with increasing compressive strain (ANOVA, $p < 0.05$). Furthermore, in AF tissue, specimen orientation was shown to have a significant effect on electrical conductivity, with values in the radial direction being significantly lower than those in the axial or circumferential directions (ANOVA, $p < 0.05$).

DISCUSSION

The primary objective of this study was to investigate the behavior of electrical conductivity in human IVD tissues. More specifically, we directed our investigation at determining the effect of mechanical strain on conductivity in human IVD as well as the anisotropic trend for conductivity in human AF. Our results for electrical conductivity in human IVD are comparable with previously reported values of conductivity in human articular cartilage (6–10 mS/cm) [9,11]. The results also indicate that electrical conductivity in human IVD is dependent on both tissue composition and structure.

The significant decrease in conductivity with increasing mechanical loading indicates that electrical conductivity in human IVD is strain-dependent. To our knowledge, this is the first study showing this behavior for human IVD tissues. The decrease in conductivity with increasing strain is mainly due to a reduction of water content caused by increasing compression (see Theoretical Background). Previous studies have shown that electrical conductivity increases with increasing tissue hydration [12,13,19], which has been attributed to an increase in ion diffusivities with increasing tissue hydration [11–16]. Tissue compression causes fluid exudation and a corresponding decrease in tissue water content, as is evidenced by water content values for uncompressed and compressed tissue shown in Table 1. This results in decreased ion diffusivity in the tissue, leading to subsequent decreased electrical conductivity. Similar strain-dependent behavior has also been found for glucose and oxygen diffusivity in bovine AF [29,30] and water diffusivity in IVD tissue [27,28]. Our results also qualitatively agree with the theoretical prediction of monotonically decreasing conductivity with increasing tissue compression [5,18].

Our theoretical model, shown in Eq. (3), could quantitatively predict the experimental results for strain-dependent electrical conductivity, Fig. 4. Note that in Fig. 4, the conductivity (χ) is normalized by the conductivity of bathing solution (χ_o). The averaged fixed charge density of IVD specimens was estimated to be $c_o^F=0.20$ mEq ml⁻¹ at the corresponding water volume fraction of $\phi_o^w=0.72$, based on results for human IVD found in the literature [46]. Ion diffusivities were calculated based on Eq. (3), using $\alpha = 1.29$ and $\beta = 0.372$, as well as our previous model for hydraulic permeability [19,42]. It should be noted that these values were determined for porcine AF tissue with axial orientation; values for these parameters are not known for human AF and NP tissue. The values for Stokes' radii for Na⁺ and Cl⁻ ions ($r_s^+=0.197$ nm and $r_s^-=0.142$ nm) and Na⁺ and Cl⁻ ion diffusivity in water ($(D_o^+=1.16 \times 10^{-9}$ m²/s and $D_o^-=1.61 \times 10^{-9}$ m²/s)) were obtained from the literature [19, 47]. The model reasonably predicts strain-dependent conductivity behavior in human IVD tissues, as is shown in Fig. 4. The model also predicts strain-dependent conductivity behavior in human NP tissue. However, the prediction appears to overestimate conductivity values for radial AF, indicating that the material parameters (α and β) for axial AF would be different from those for radial AF (i.e., anisotropy). Nonetheless, it is evident that the model is capable of predicting strain-dependent conductivity behavior in human IVD tissues. It is likely that prediction accuracy would be greatly improved if the values for α and β for human NP and AF tissues are determined for each of the three major orientations (axial, circumferential, and radial).

The findings of this investigation also indicate that the electrical conductivity in human AF tissue is anisotropic, i.e., direction-dependent. To our knowledge, this is the first study reporting the anisotropic behavior of electrical conductivity in human IVD. The values for conductivity in the radial direction were significantly lower than those in the axial or circumferential directions for all levels of compression. This anisotropic trend is in agreement with previous findings for electrical conductivity in bovine AF [16], as well as with findings for diffusion coefficient of water [27,48], glucose [29] and fluorescein in IVD [49].

To further investigate the anisotropy of electrical conductivity and its related ion diffusivity, AF structure was studied using scanning electron microscopy (SEM) and compared with trends found in conductivity results (Fig. 5). The SEM images of axial and circumferential specimens in Fig. 5b–d distinctly show microtubes running parallel to the collagen fiber bundles. By contrast, the radial specimen image shown in Fig. 5a illustrates the structure of collagen fiber bundles, but microtubes are not obviously visible. Several previous studies have presented SEM images showing a similar microtube structure in rat tail IVD [50] and bovine tail IVD [29,49]. The presence of microtubes may provide explanation for the anisotropic behavior of

electrical conductivity in AF. It is possible that the organization of these microtubes along collagen fibers may provide a preferred pathway of transport in the axial and circumferential directions; on the other hand, because the microtubes do not appear to be contiguous between adjacent lamellae, no such direct path appears to exist in the radial direction.

The significant difference between conductivity values in NP tissue as compared with those in AF tissue indicates that electrical conductivity in IVD tissues is inhomogeneous. The regional variation in conductivity results from the distinct composition and structure of AF and NP tissues. Differences in tissue composition are evidenced by the variation in tissue water content shown in Table 1. These findings are in agreement with our previous study which demonstrated the inhomogeneous behavior of electrical conductivity in bovine IVD [16].

In summary, the effect of mechanical compression on the electrical behavior in human IVD tissues was investigated by measuring strain-dependent electrical conductivity. Our results indicate the conductivity in human IVD depends on both tissue composition, i.e., water content, and structure. It was determined that electrical conductivity in human IVD is strain-dependent due to tissue compositional changes (i.e., decreased water content) caused by compression. Furthermore, we also determined that conductivity in human IVD is inhomogeneous, with that in NP tissue being higher than AF tissue. Finally, it was found that electrical conductivity in human AF is anisotropic, most likely due to the microtube structure of the tissue. The results of this investigation are important in further understanding transport properties and nutritional pathways in IVD, as well as mechanical-to-electrical transduction phenomena in IVD tissues.

ACKNOWLEDGEMENTS

This project was supported by a grant from the NIH NIAMS (AR50609). The authors also wish to thank Mr. Larry Hazbun and Mr. Andre Castillo for their assistance in apparatus machining.

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Figure 1.

Schematic of intervertebral disc showing sites and orientations of test specimens. AF indicates annulus fibrosus, NP indicates nucleus pulposus.

Figure 2.
Schematic diagrams of (a) compression apparatus; and (b) apparatus for measuring strain-dependent electrical conductivity.

Figure 3.

Variation of electrical conductivity with increasing compressive strain for annulus fibrosus (AF) and nucleus pulposus (NP) tissues. For AF tissue, results for conductivity in three directions are shown: axial (A), circumferential (C), and radial (R). Variation bars signify standard deviation (SD). Statistical analysis showed a significant difference ($p < 0.05$) between conductivity values for all groups except axial AF and circumferential AF (at all levels of compressive strain).

Figure 4.

Model prediction of normalized conductivity in human AF and NP tissues compared with experimental data. The value of FCD was assumed to be 0.2 mEq/ml at water volume fraction of 0.72. Values for α and β were taken from the literature [19].

Figure 5.

Scanning electron microscopy (SEM) images showing no obviously visible microtubules in the radial section of human AF (a), the clear presence of microtubules in the axial ((b) and circumferential sections (c), along with magnified view of microtubule (d).

Table 1

Water volume fraction for IVD tissue specimens at three levels of compression. Values at reference configuration (i.e., compression = 0%) were measured using buoyancy method. Values for water volume fraction of compressed (10% and 20%) tissue were calculated from Eq. (4) using ϕ_o^w . Values expressed in mean $\pm$ SD. For all groups, n=12.

	ϕ_o^w (0%)	ϕ^w (10%)	ϕ^w (20%)
Axial AF	0.80 $\pm$ 0.02	0.78 $\pm$ 0.02	0.75 $\pm$ 0.03
Radial AF	0.79 $\pm$ 0.04	0.77 $\pm$ 0.05	0.74 $\pm$ 0.05
Circumferential AF	0.79 $\pm$ 0.02	0.77 $\pm$ 0.03	0.74 $\pm$ 0.03
Axial NP	0.86 $\pm$ 0.02	0.85 $\pm$ 0.03	0.83 $\pm$ 0.03