ELECTRIC CURRENT DENSITY IMAGING OF BONE BY MRI

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Current density imaging (CDI) has been shown to be a feasible method to map spatial distribution of electric currents through bone structures and for studying osteoporosis and bone fracture models. For the osteoporosis model, bone sample was moistened in a solution of a sodium salt of ethylenediaminetetraacetic acid (EDTA) which causes chemical reaction with hydroxyapatite $Ca^{2+}$ ions and lowers the mineralisation degree of the solid bone. This enables clear visualisation of conventional magnetic resonance imaging and CDI. Sensitivity of conventional magnetic resonance and CD images of bone was improved by immersing the bone samples into physiological saline containing contrast agent Gd-DTPA prior to imaging. To simulate effects of bone fracture on electric current conductivity through bone, a transverse cut was made through the bone, and the resulting gap was filled with an insulator. Electric current density images under these conditions have shown that regions of strong conductivity can be distinguished from regions of no conductivity at the site where the insulator restricts electric current. Real bone fracture was imaged as well. To demonstrate influence of electrolyte concentration on electric current spatial distribution, the bone samples were imaged after being immersed in various saline concentrations. The same contrast in current density images was produced with the combinations of higher electrolyte concentrations and lower voltages. Our observations demonstrate the feasibility of the method in mapping current density in bone structures, which could have implications in understanding and monitoring the effects of the electrical stimulation. © 1997 Elsevier Science Inc.

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INTRODUCTION

The imaging of the spatial distribution of electric current density (Current Density Imaging, or CDI) is a recently developed magnetic resonance imaging (MRI) technique that has been experimentally demonstrated on phantoms$^1$ and, under microimaging conditions, on biological tissues.$^2$ Theoretical considerations of the sensitivity and resolution of CDI on a model system have shown that with the proper optimisation of the procedure, signal/noise ratios similar to those obtained in conventional MRI can be achieved in biologically relevant experiments.$^2,3$ The potential of CDI remains largely unexplored, except preliminary results in rabbit brain,$^4$ plant stems$^2$ and tumours.$^5$

The physical principle on which CDI is based utilises mapping of the quasistatic magnetic field $B_{\text{current}}$ produced by pulses of electric current flowing through the sample. This is done by synchronising two DC electric pulses applied to the sample with the conventional spin warp imaging sequence.$^1,3$ During the sequence, pulses are applied symmetrically about the II pulse with the first between the radiofrequency (RF) II/2 and II pulses, and the second between the RF II pulse and signal acquisition. The electric pulses have the same magnitude and duration, but opposite polarity. Since the currents are pulsed, a phase shift ($\varphi$) in the proton image is produced, proportional both to the component of $B_{\text{current}}$ in the direction of the static magnetic field and to the duration of the pulse. Imaging phase shift in nuclear precession provides a map of magnetic field change seen on the real component of the signal ($S$) as stripes superimposed on the image:

$$S = S_0 \sin \varphi$$

(1)

where $S_0$ indicates conventional magnitude image. Phase measurements only reflect the component of the induced field along the direction of the main magnetic field.
For the calculation of a two-dimensional electric current density map, two components of \( B_{\text{current}} \) are required. This is achieved by acquiring data with the sample in two perpendicular orientations. For example, calculating current density \( j_z \) in the \( xy \) plane requires that \( B_{\text{current}, x} \) and \( B_{\text{current}, y} \) must be determined from images in the \( xy \) plane in two sample orientations achieved by physical rotation of the object 90° about the \( z \) axis. The final step is to calculate the current density \( j_z \) on a pixel-by-pixel basis using Ampere’s law:

\[
  j_z = \mu_0 (\partial B_{\text{current}, y}/\partial x - \partial B_{\text{current}, x}/\partial y)
\]  

(2)

From the complex nuclear magnetic resonance (NMR) signal, phase image (in the module of 2 \( \pi \)) is obtained for two experiments: first in which \( B_{\text{current}, x} \) field is measured (\( B_x \) is parallel to \( x \)-axis of the sample) and second in which \( B_{\text{current}, y} \) field is measured (\( B_y \) is parallel to \( y \)-axis of the sample). The current density image is calculated as a difference between gradient in the \( x \)-direction of the \( B_x \) phase image and gradient in the \( y \) direction of the \( B_y \) phase image.

Growing knowledge of electric current properties of tissues suggests that both naturally occurring currents and those caused by electrical stimulation play an important role in bone physiology.\(^6\) Naturally occurring currents in bone have been attributed to the piezoelectric effect—a potential difference that arises from deformation of tissues. Since this type of potential is associated with deformation—that is, with strain—and it persists in part as long as deformation is maintained,\(^10\) and it is called a strain related potential.\(^11\) The geometric relationship to strain is such that areas that are in compression, especially on concave surfaces, are negatively polarised with respect to areas of tension.\(^6\) In fact, a wide variety of animal and plant tissues display these polarisation; these tissues have in common a structured, generally fibrous organisation of a long-chain molecule, such as collagen, keratin, cellulose, and so on.\(^6\) All bone, as well as fracture callus,\(^12\) displays SRP. Furthermore, minute currents flowing in bone cause osteoblastic activity and increased bone deposition at compressed sites.\(^13\)

During electrical stimulation, an electric field is produced within the bone, that results in local production of electric currents that depend on the conductivity of the bone and surrounding tissues. At the areas of negative polarisation, bone deposition is increased, and this effect has been used therapeutically for osteoporosis, bone fracture and other bone diseases.\(^14,15\) Electrodes (usually of stainless steel, titanium and platinum alloys or silver-silver chloride systems) are placed within the tissue, in or near the location of desired stimulation, or externally on the opposite sides of the limb. The induced currents flowing through are of the order microamperes or milliamperes in magnitude. Several experiments on the electrical stimulation of bone growth have shown an increased calcification\(^9,16,17\) and osteoblastic deposition of bone.\(^18\) In a case of bone fracture, both the conductivity of bone and the local production of currents due to piezoelectricity are changed, since there is lack of physical stress on the bone.\(^6,13\) With electrical stimulation, negative polarisation is imposed on a delayed union or non-union, stimulating fracture healing. Osteoporosis is another disorder that, although perhaps not bioelectric in origin, is susceptible to electrical control. The disease, caused by increased osteoclastic activity, may be significantly retarded by suppressing osteoclasts with inducive signals.\(^19,20\)

In this study we present the use of CDI to map spatial distribution of DC electric currents through bone structures of comparable magnitudes to those used for electrical stimulation. We show that the technique can be used to (a) determine the current pathways of an osteoporosis model in which demineralisation has been simulated by soaking in EDTA, (b) determine the current pathways around a simulated bone fracture, (c) determine the current pathways around a real bone fracture, and (d) determine the effect that the conductivity of the immersion fluid has on the conductivity of the bone and bone marrow.

**MATERIALS AND METHODS**

**Bone Preparation**

Bone specimens were placed in a plastic holder and sealed with electrodes on both sides (10 mm apart) so that the electric currents were flowing in a direction parallel to the long axis of bone. The electrodes were connected to a DC voltage amplifier (0–300 V) which produced pulses with variable length, synchronised with the imaging sequence. The samples were inserted into a magnet with the axis perpendicular to the direction of the static magnetic field (Fig. 1).
Four fresh chicken femur bone samples with a diameter of 8 mm and length of 10 mm were cut transversally 2 mm from the centre to simulate bone fracture and for insertion of an insulator during imaging. The width of the gap was 0.1 mm, and it extended through 50% of the diameter (Fig. 1). For the osteoporosis model, two bone samples were immersed in 0.7 M solution of sodium salt of ethylenediaminetetraacetic acid (EDTA) for 24 h prior to being imaged. Two bone samples were broken to simulate real bone fracture. Four bone samples were used for experiments with different saline concentrations. First, all samples were immersed in physiological saline (0.9%) containing 50 mM contrast agent Gd-DTPA (Magnevist®, Schering, Germany) for 48 h prior to being imaged. Afterwards, the same procedure was repeated with those four bone samples, using 5%, 10% and 15% saline also containing contrast agent. Each bone sample was sequentially immersed in each of the different solutions. The samples were equilibrated in each solution for 24 h prior to each experiment.

**MRI and CDI Measurements**

MRI was performed on a 100 MHz Bruker Biospec system, equipped with microimaging gradient coils and a saddle RF coil with a diameter of 20 mm, with the imaging conditions: repetition time (TR) = 1000 ms, echo time (TE) = 30 ms, field of view = 2 cm, slice thickness = 3 mm, MATRIX = 256 × 256, number of averages = 4, τ = 18 min. Conventional MRI of the central transverse slice 0.5 mm above the partial gap was followed by MRI in the presence of electric current with and without insulator. For CDI, samples were imaged at two perpendicular orientations to construct the map of electric current density (j in the xy plane) spatial distribution as required by theory (Eq. [2]). Voltages used in our protocol were 50, 40, 30 and 20 V for 0.9%, 5%, 10% and 15% saline concentrations with conductivities ranging from 1.44 to 17.1 Ω⁻¹m⁻¹. Duration of electric current pulses was 12 ms. Voltages were chosen so that the average electric current density through the bone was practically the same: j = 1800 ± 10% A/m² (no insulator–gap filled with a conducting saline) and j = 2200 ± 10% A/m² (with inserted insulator).

**RESULTS**

Figure 2 shows cross-sections through chicken femur as seen by conventional MRI and CDI. Bone samples were moistened for 24 h in physiological saline (a and b), for 48 h in physiological saline containing 50 mM Gd-DTPA (c and d) and for 24 h in 0.7 M EDTA solution (e and f). Conventional MR images (Figs. 2a,c,e) show high signal intensity on the region of bone marrow interspersed with areas of no signal due to air voids in the sample. The mineralised solid bone is partially visible. High signal can be seen on the border where water diffused into the porous bone. Some nonuniformity seen as lower signal on the sites compared to the top and bottom is detected due to structural differences on the border of the bone (Fig. 2a). Sensitivity of the solid part of the bone was improved with longer diffusion time and presence of Gd-DTPA, which shortens T1 relaxation time (Fig. 2c), or presence of EDTA, which demineralises the bone (Fig. 2e). CDI images (Figs. 2b,d,f) show similar patterns of contrast as conventional MRI. Both bone marrow and dense bone appear as regions of comparable signal intensity j = 1800 ± 10% A/m² and j = 1500 ± 10% A/m². Relatively high current noise on CD images is associated with low signal-to-noise ratio, estimated from conventional MR images. An inspection of CD images without electric current present showed that the bright regions correspond to the presence of the electric current.

To simulate the effect of bone fracture on electric current conductivity through bone, a transverse cut was made through the bone, which was immersed in a saline solution containing Gd-DTPA, and the resulting gap was filled with an insulator to prevent electric current conductivity (Fig. 1). Figure 3a shows the electric current density image under these conditions. A region of strong conductivity with a high signal intensity (bright region) can be easily distinguished from the region of no conductivity (dark region) at the site where insulator restricted electric current. There is no such contrast in Fig. 3b, which shows the CD image in the same plane after the insulator was removed and conductivity through the entire bone reestablished. This image is similar to the image in Fig. 2d. For a real bone fracture model, a bone sample was immersed in saline solution containing Gd-DTPA and mechanically broken. Fig. 3c shows a conventional MR image of fractured bone. At the fracture site, electric current conductivity pattern is changed compared to the rest of the bone sample. CD image (Fig. 3d) demonstrates this effect as a bright region due to higher electric current density on the side of the fracture. Again, relatively high current noise on CD images is associated with low signal-to-noise ratio estimated from conventional MR images. An inspection of CD image without electric current present shows that the bright region corresponds to the presence of the electric current.

The influence of electrolyte concentration on electric current spatial distribution is shown in Fig. 4. The conductivity of bone structures (σ) was obtained with Ohm's law from regions of interest in CD images consisting of at least 20 pixels (j) deviated by applied electric field (E):

\[ \sigma = \frac{j}{E} \]  

(3)
where $E$ is applied voltage ($U$) divided by distance between the electrodes ($l$). In Fig. 4 the values of $\sigma$ of bone marrow ($\sigma_{BM}$) and bone ($\sigma_{B}$) are presented as a function of conductivity of immersion fluid ($\sigma_f$). The bone is modeled with a circuit with two parallel resistors: bone and bone marrow. Each is parallelly divided into a component having a conductivity proportional to surrounding fluid and a component that is independent of the conductivity of the surrounding fluid:

$$\sigma_B = 0.00086\sigma_f + 6.8m\Omega^{-1}m^{-1} \quad (4a)$$
Fig. 3. Upper row—model bone fracture experiment: CD images of a partially cut bone. (a) insulator is inserted in the gap—arrow shows high current density on the opposite site of the gap; (b) no insulator in the gap—arrows show high current density through the entire bone. Bottom row—real fracture model experiment: (c) conventional MRI and (d) CD image. Fracture site is indicated by an arrow.

\[
\sigma_{\text{BM}} = 0.00045\sigma_p + 3.4m\Omega^{-1}m^{-1}
\]

(4b)

By dividing the slopes of Eq. (4a) and (4b), a coefficient of 1.91 ± 1.2% is obtained that is independent of the conductivity of the immersion fluid.

**DISCUSSION**

The results show that electric current density imaging of bone structures by MRI is feasible. This is true despite the fact that the solid part of the bone, consisting of hydroxyapatite crystals deposited on collagen fibers, has both low intrinsic MRI intensity and low electric conductivity. This problem can be partially overcome by immersing the bone for at least 24 h in physiological saline, or additionally with the use of contrast agent to shorten the proton relaxation time. The use of EDTA lowers bone mineralisation by bonding Ca\(^{2+}\) ions in Ca-EDTA chelats and also improves sensitivity.\(^2\) This osteoporosis model demonstrates the feasibility of the method in detecting electric current density distribution in areas of changed solid bone structure due to lack of Ca\(^{2+}\) ions and increased porosity. The bone fracture model demonstrates the sensitivity of the method in detecting electric current density distribution and that regions of undisturbed current can be clearly distinguished from the regions of no current due to insulator in
the fracture gap. The increase in conductivity on a site of a real mechanical fracture is probably due to filaments of the fracture filled with a conducting fluid. Immersion of the bone in a range of saline concentrations agrees with previous data on large samples of bone that electrical conductivity in vitro is directly and linearly proportional to the conductivity of the saturating fluid. In addition it shows on a pixel-by-pixel basis that varying saline concentrations has no effect on contrast in CD image, which is in accordance with scanning electron micrograph data on bone structures, showing that pores are primarily responsible for the observed conductivity.

The mechanism of bone healing by electrical stimulation is not well understood. Several possibilities have been proposed, including stimulation due to the strain-related potential, changing of the bioelectric potential, and electrochemical reactions in the vicinity of the electrodes. The ability to nondestructively map the distribution and magnitude of electrical currents within a bone sample should greatly facilitate research in this area. Furthermore, the ability to observe the effect of therapy on the healing process as it takes place would have significant clinical importance. Bone CDI may provide the means of accomplishing these goals.

However, bone CDI does have significant limitations which must be addressed. Bone inherently has very low signal intensity due to its solid state, and it usually is apparent as a signal void bounded by water- and fat-containing tissue and marrow. Current flow within the bone matrix is also limited by the low level of interstitial water. Thus adequate signal-to-noise ratio may require long acquisitions and/or high applied potentials that could limit the application of this technique. In addition, the required two orthogonal spatial orientations would limit the application of CDI to small animals, or to the extremities of large animal or human subjects in conventional magnets. However, open-architecture magnets and dedicated orthopedic imaging systems may allow the use of this technique. Finally, the presence of conducting electrodes within the imaging system may cause artefacts and/or pose a safety hazard in the presence of magnetic and RF fields.

In conclusion, we have demonstrated that CDI can generate maps of spatial distribution of electric currents through bone structures and we have shown the feasibility of the method in studying osteoporosis and bone fractures. We think that the limitations of the method discussed can be largely overcome, and that the method can potentially be used in real fracture models and in the investigation of the effect of the electrical stimulation.

REFERENCES