Biological Effects and Health Implications in Magnetic Resonance Imaging

ALLAHYAR KANGARLU,1 PIERRE-MARIE L. ROBITAILLE2

1MRI Facility, 1630 Upham Drive, Columbus, OH 43210
2Center for Advanced Biomedical Imaging, Department of Radiology, The Ohio State University, Columbus, OH, 43210

ABSTRACT: In this work, the safety aspects of the Magnetic Resonance Imaging and Spectroscopy (MRI / MRS) systems are reviewed. Focus is placed on the interaction between the electric and magnetic fields generated by such instruments and the human body. An understanding of these interactions has become ever more important with the push to higher field strengths. Knowledge of MRI safety can not only guide RF coil and pulse sequence design but can also affect sequence selections, thereby ensuring safe and efficient system operation. Due to the signal to noise advantages of high field MRI systems, increases in the static magnetic field are inevitable. However, in addition to the static magnetic field, power intense sequences, fast gradient switching, and localized imaging / spectroscopy all have the potential of subjecting the human body to intense magnetic and electric field fluctuations. This further accentuates the need for a detailed understanding of the effects of exposure to these fields. In this work, some of the issues addressed are new, while others are well established. In either case, it is hoped that this compilation will enable all of us to pay greater attention to these matters and increase the current state of understanding through novel experimental studies. The discussion broadens the range of radio frequency effects to the microwave limit. This was accomplished in view of the latest efforts for realization of ultra high field (UHF) human MRI. In this regard, recently constructed ultra high field whole body systems will provide a new testing ground for safety issues. The proliferation of high field (1.0 – 3.0 tesla), very high field (3.0 – 7.0 tesla), and ultra high field (≥ 7 tesla) whole body MRI’s calls for a review of the safety literature that can guide future studies of critical health related issues. An effort has been made to present an up to date analysis of the biological effects within MR, covering a wide range of properties from cellular and physiological to clinical. © 2000 John Wiley & Sons, Inc. Concepts Magn Reson 12: 321 – 359, 2000

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INTRODUCTION

Instrumentation for MRI/MRS studies consists of subsystems that generate electromagnetic fields with vastly different characteristics. The main subsystems involved in MRI safety are (1) the whole body superconducting magnet, (2) the shielded gradient systems, and (3) the radio frequency (RF) transmit and receive coils. At field strengths of the order of tesla, the safety challenge from a physics and engineering standpoint is to study the effects of the deposition of energy by fields that vary in frequency by ten orders of magnitude and in strength by five orders of magnitude. This is an extraordinary range to cover. There are very few other human practices that employ natural phenomena of this expansive scope. While these effects all have the nature of the energy source in common, i.e., electric and magnetic fields, the rapidly varying electromagnetic waves from the RF coils are capable of inducing drastically different effects compared with the effect of the static field of the main magnet. In addition, the ever higher varying magnetic field strengths produced by the gradients (dB/dt) have an increased potential to interact with the human body. This requires a reexamination of these devices. Furthermore, future high field MRI systems will acquire and process NMR signals from the human body in a different range of the electromagnetic spectrum (Fig. 1). New findings in this area have the potential of guiding the evolution of the MR and have significant implications for the future of medical imaging and spectroscopy. Such studies will help refine current guidelines for the operation of MRI scanners and will hopefully help minimize the risk associated with such exams (see Tables 1 and 2).

The advantages of increasing field strengths include enhanced signal to noise and chemical shift dispersion. Indeed, the gains in these areas are so significant that, despite technological challenges, imaging and spectroscopy at ultra high fields have enjoyed an extraordinary progress. Analytical spectroscopy is now at the threshold of the first 1 GHz results and human imaging is now being performed at 340 MHz (1-3). Recent human images obtained at 8 tesla (see Fig. 2) demonstrate that all of the technological hurdles to ultra high field imaging can be overcome (4-9). Within the decade, human imaging at fields in excess of 10 tesla will most probably be achieved and such projects are now being planned. As such, there is an urgent need to better comprehend the implications of human exposure to ultra high fields (≥ 7 tesla).

THE BIOLOGICAL EFFECT OF THE STATIC MAGNETIC FIELD

To fully understand the physics of magnetic phenomena it is necessary to have recourse to quantum mechanics. Some of the basic phenomena, however, can be described in classical terms. Our knowledge of the interaction of static magnetic fields with biological tissue has guided us over two decades, thereby allowing an increase in magnetic fields for human MRI systems from 0.1 T to 8 T. There are basically two kinds of forces that act on electric charges placed inside electromagnetic fields. Electric fields exert a force \( \mathbf{F}_e = q\mathbf{E} \) proportional to the magnitude of the charge and the intensity of the electric field. This force is present regardless of the state of the motion of the charged object (see Fig. 3). The magnetic field, on the other hand, can only interact with moving charged objects. The magnitude of the magnetic force \( \mathbf{F}_m = q\mathbf{v} \times \mathbf{B} \) is controlled by the fact that unless the charge \( q \) is moving at a velocity \( \mathbf{v} \) in a non-parallel direction to \( \mathbf{B} \) it will experience no force. This is an important property of the Lorentz force, \( \mathbf{F}_l = \mathbf{F}_e + \mathbf{F}_m \), which prevents its magnetic component from contributing to the power deposition in a subject. This is due to the fact that the power generated by a force is given by \( P = \mathbf{v} \cdot \mathbf{F} \). Consequently, if this expression is used to calculate the power delivered by the Lorentz force, the following relationship will result: \( P = \mathbf{v} \cdot (q\mathbf{E} + q\mathbf{v} \times \mathbf{B}) \). The second term in this equation will vanish. Hence, apart from the diamagnetic susceptibility anisotropy (DSA) effects described below, the nature of the Lorentz force will only allow the electric component to contribute in the process of energy transfer into the subject. The distinction between the Lorentz force power deposition and the DSA mechanism is largely based...
Figure 1 Schematic representation of the electromagnetic spectrum. This figure displays a fifteen order of magnitude variation in energy. Typical applications are presented for each interval of the spectrum. The region used for proton MRI applications typically extends from 1 to 340 MHz. This figure was adapted from a drawing prepared by the Lawrence Berkeley National Laboratory.
Table 1  FDA Criteria for Significant Risk Investigations

Patient studies utilizing magnetic resonance diagnostic devices which are conducted under any one of the following operating conditions are considered significant risk investigations and require approval of an investigational device exemption (IDE) by the Food and Drug Administration (FDA) Center for Devices and Radiological Health (CDRH).

1. Main static magnetic field greater than 4 tesla;
2. Specific absorption rate (SAR) greater than
   a. 4 W/kg averaged over the whole body for any period of 15 min, or
   b. 3 W/kg averaged over the head for any period of 10 min, or
   c. 8 W/kg in any gram of tissue in the head or torso, or 12 W/kg in any gram of tissue in the extremities, for any period of 5 min;
3. time rate of change of gradient fields \( \frac{dB}{dt} \) sufficient to produce severe discomfort or painful nerve stimulation; or
4. peak unweighted sound pressure level greater than 140 dB or A weighted rms sound pressure level greater than 99 dBa with hearing protection in place.

These criteria apply only to device operating conditions. Other aspects of the study may involve significant risk and the study may therefore require IDE approval. (Taken from CDRH web page of the FDA, http://www.fda.gov/cdrh/ode/magdev)

The effect of magnetic fields on the orientation of molecules is the most important of the macroscopic effects. Magnetohydrodynamics, as another macroscopic effect, involves moving charged objects in large organized structures such as DNA and proteins. The orientation interaction has a low likelihood of posing an inherent hazard since the molecules in in-vivo cellular systems are in constant motion. This could further be explored by considering the anisotropic properties of the magnetic susceptibility tensor. These central issues related to static magnetic field interactions with biological materials are discussed below.

Of the three subsystems involved in magnetic resonance imaging, namely the static magnetic field, the time varying gradient magnetic field, and the RF coil and its associated power deposition, the static magnetic field is viewed as the most innocuous. There is no thermal absorption for static and low frequency fields. The magnetic field easily penetrates the human body. The exposure of human beings working in or around fields of up to 2 tesla for extended periods of time has been studied. Analysis of data taken on the health condition of workers in particle accelerators at the US National Labs (13) has shown no significant increase in health risk compared to the control subjects in the range of 0.5 mT to 2 T. There has not been a single unavoidable safety report due to the static field from some thirty 3 and 4 T human magnets in operation around the world for the past ten years.
Table 2  A Sampling of MRI Related Incidents from the MDR Database

<table>
<thead>
<tr>
<th>Incident Number</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDR-351516*</td>
<td>A patient with an implanted cardiac pacemaker died during an MR exam. (12/2/92)</td>
</tr>
<tr>
<td>MDR-175218*</td>
<td>A patient with an implanted cardiac pacemaker died during or shortly after an MR exam. The coroner determined that the death was due to the interruption of the pacemaker by the MR system. (9/18/89)</td>
</tr>
<tr>
<td>MDR-349790</td>
<td>A patient with an implanted intracranial aneurysm clip died as a result of an attempt to scan her. The clip reportedly shifted when exposed to the magnetic field. The staff apparently had obtained information indicating that the material in this clip could be scanned safely. (11/11/92)</td>
</tr>
<tr>
<td>MDR-100222</td>
<td>Dislodgement of an iron filing in a patient’s eye during MR imaging resulted in vision loss in that eye. (1/8/85)</td>
</tr>
<tr>
<td>MDR-454660</td>
<td>A patient complained of double vision after an MR exam. The MR exam as well as an X-ray revealed the presence of metal near the patient’s eye. The patient was sedated at the time of the exam and was not able to inform anyone of this condition. (12/15/93)</td>
</tr>
<tr>
<td>MDR-547886</td>
<td>An IV pole was attracted to the magnet and struck a patient, cutting his arm. The patient required stapling of the cut. (8/30/94)</td>
</tr>
<tr>
<td>MDR-405200</td>
<td>A pair of scissors was pulled out of a nurse’s hand as she entered the magnet room. The scissors hit a patient, causing a cut on the patient’s head. (8/2/93)</td>
</tr>
<tr>
<td>MDR-234698</td>
<td>A patient was struck by an oxygen bottle while being placed in the magnet bore. The patient received injuries requiring sutures. (6/2/91)</td>
</tr>
<tr>
<td>PRP-19168</td>
<td>Two steel tines (parts of a fork lift) weighing 80 pounds each were accelerated by the magnet, striking a technician and knocking him over 15 feet, resulting in serious injury. (6/5/86)</td>
</tr>
</tbody>
</table>

**RF Effects**

<table>
<thead>
<tr>
<th>Incident Number</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDR-711781</td>
<td>An electrically conductive lead was looped and placed against bare skin causing a burn on the patient’s upper arm. (5/19/95)</td>
</tr>
<tr>
<td>MDR-591457</td>
<td>A child received a burn to the right hand from a ECG cable while the patient was anesthetized. A skin graft was required to treat the affected area. (1/26/95)</td>
</tr>
<tr>
<td>MDR-246106</td>
<td>A patient received a 1.5&quot; × 4&quot; blistered burn to the left side of the back near the pelvis from an ECG gating cable. (9/23/91)</td>
</tr>
<tr>
<td>MDR-701219</td>
<td>A patient received blistered burns on the finger where a pulse oximeter was attached during MR scanning. A skin graft was required to treat the affected area. (2/27/95)</td>
</tr>
<tr>
<td>MDR-391667</td>
<td>A patient received small blistered burns to the left thumb and left thigh. Reportedly, the operator input an inaccurate patient weight resulting in an incorrect SAR value. (2/10/93)</td>
</tr>
<tr>
<td>MDR-149476**</td>
<td>A patient with an implanted insulin infusion pump was placed in an MR scanner resulting in movement of the device. The pump was removed from the patient and subsequently found to be non-functional. (1/13/88)</td>
</tr>
</tbody>
</table>

*These events may also be attributed to the pulsed RF fields.

**This event may also be attributed to the static magnetic field.

These data were obtained from the FDA CDRH.

Barring events such as projectiles effects, or the magnetic attraction of the ferromagnetic objects within a strong magnetic field, static magnetic fields are not known to have caused unavoidable injuries to subjects who are placed in their proximity. In order to increase the awareness of the MR practitioners, a brief section on projectiles is included at the beginning of this section. In general, the analysis of static magnetic field effects on human subjects has been classified in three categories. In one group, macroscopic effects, such as diamagnetic and paramagnetic effects, are presented. These are phenomena that do not amount to any sizable effects until a coherent collection of molecules or cells is involved in the process. The second group of effects are centered on the interaction of the static field at the molecular level or the interaction with
Figure 2  Axial gradient echo image of the human head obtained at 8 tesla. Acquisition parameters were as follows: field of view = 20 cm; matrix = 256 × 256; repetition time = 823 ms, time to echo = 17 ms, receiver bandwidth = 33 kHz, slice thickness = 2 mm.

Diamagnetic tissues and the consequences of paramagnetic nature of hemoglobin. The works on the effect of static field gradients on oxygen dissolution is also presented.

Projectile Effects

When paramagnetic and ferromagnetic materials are placed inside a magnetic field gradient, they experience a force \( \mathbf{F} \) that is proportional to the gradient strength as well as to the static magnetic field. The magnitude of \( \mathbf{F} \) is given by

\[
\mathbf{F} = \chi \mathbf{V}/\mu_0 \mathbf{d} \mathbf{B}/\mathbf{d}z,
\]

assuming that magnetic field variest in the \( \mathbf{z} \)-direction. This force could be of substantial magnitude depending on the size and susceptibility of the object. In order to offer a representative value for this force, a calculation is presented for an object, such as a stainless steel wrench of mass 100 g within the magnetic field of the 8 T system (Fig. 4) at the OSU. For this magnet, the magnetic-field-gradient product is plotted in Fig. 5. Given the highest field gradient, \( (\mathbf{d} \mathbf{B}/\mathbf{d}z)_{\text{max}} \) is 7.915 T/m, the maximum \( (\mathbf{B} \mathbf{d} \mathbf{B}/\mathbf{d}z)_{\text{max}} \) is 42.95 T²/m, and the \( \chi \) of the object is taken to be 0.01 with a density of 8
In this regard, the presence of the strong magnetic gradient fields can result in a torque being exerted on medical instruments such as aneurysm clips (14), cardiac pacemakers, metallic stents (15), implantable cardioverter defibrillators (16), and other metallic implants. These devices are usually evaluated based on the material, physical dimensions, mass, and the magnetic field strength. The evaluation of such devices has received much attention in the past and such products continue to evolve with the advent of new more MR-compatible materials.

**Magnetic Susceptibility and Orientation Interaction in the Static Magnetic Field**

The magnetic susceptibility $\chi$ of a tissue defines the extent of its induced elementary moment. For a molecule, the nature of electronic orbitals determines the electronic, optical, and magnetic properties. In turn, the non-symmetric characteristic of the susceptibility tensor for a sample is determined by the anisotropic chemical bond. If the values of the susceptibility are considerably different along one direction ($\chi_1$) compared to other directions ($\chi_2$) then a torque proportional to the difference in susceptibility ($\Delta \chi = \chi_1 - \chi_2$) could be experienced by the molecule. Typical values (17) for the difference in the susceptibility along the principal axes for cylindrically symmetric tensors are $\Delta \chi_{\text{C}} = -2 \times 10^{-30} \text{erg/G}^2$ for the C–C bond and $\Delta \chi_{\text{Ph}} = -100 \times 10^{-30} \text{erg/G}^2$ for the Phenyl ring. For diamagnetic material, $\chi$ is negative; that is, the induced magnetic dipole $m$ is opposite to the applied field $H$. Ionic and covalent molecules are diamagnetic, since they have atoms or ions with complete shells. The interaction of the magnetic field with the orbital motion of charged particles in a molecule can distort its charge distribution. This is the cause of their diamagnetic behavior.

As such, it is important to note that a torque will act on the anisotropic molecular aggregates in a uniform magnetic field. Biological molecules that orient themselves in a magnetic field are basically anisotropically shaped supermolecules. Their internal structure is the cause of the anisotropic susceptibility. The typical dimensions of these molecules are in the micron range. The muscle fibers are made of bundles of polypeptide chains of this type (18, 19).
Figure 5  Plot of magnetic field intensity, $B$, along the principal axis of the 8 T/80 cm MR scanner (A). Rate of change of the $B$-field, $dB/dz$, along the $z$-axis (B). Plot of $dB/dz$ along the principle axis of this scanner (C). $dB/dz$ will generate a force on objects placed within its range. Should a ferromagnetic object become accidentally lodged within the bore of the magnet, the two $dB/dz$ peaks on each side of the iso-center will act to trap the object within the bore and may present a huge resistance to any attempts at dislodging the object. Such attempts may result in placing substantial out of balance forces on the supporting rods of the magnet. These rods hold the magnet within the cryostat and are typically fragile due to the desire to maintain thermal isolation and sustain a low helium boil off rate. In order not to break the support rods, it is often necessary to de-energize magnets in order to remove foreign objects within their iso-centers.
The behavior of biological macromolecules in strong magnetic fields has been studied extensively. These studies have focused on magnetic reorientation as a result of anisotropic diamagnetic susceptibility. This is because such reorientation could, at high fields, create large effects. For instance, water, ethanol, and acetone as diamagnetic liquids have exhibited magnetic levitation in a magnetic field of more than 20 T. The surface of liquid helium has also been distorted at a magnetic field of 6.5 T. The dynamic properties of water have been demonstrated at a magnetic field of 8 T and magnetic field gradient of 400 T/cm. In this field, a bulk splitting of water was observed by the strong magnetic field and magnetic field gradient. This phenomenon, which resembled the story of Moses splitting the Red Sea, has been observed in other diamagnetic fluids such as agarose gels (Fig. 6).

Inhomogeneous fields could exert a translational force on isotropic particles as was analyzed above. The magnitude and direction of this force depends on the variation of the magnetic field across the particle, on the difference between the susceptibility of the medium, on the molecular environment, and on the particle volume. Due to the opposite effect of the magnetic field on the diamagnetic molecules compared to paramagnetic and ferromagnetic medium, they could experience forces in opposite directions and be physically separated. For efficient separation, however, the thermal force should be overcome. The viscosity of the medium controls the growth of this separative force. This method has been used in conjunction with high field gradients (magnetic field–field gradient product of about 100 T²/cm) to separate deoxygenated red blood cells from normal blood. However, this BdB/Δx will be much smaller for MRI applications.

Strong magnetic fields are, in fact, found to be useful in studying the structural properties of thermotropic liquid crystalline polymers. They can be used to study the orientation order parameter as a function of temperature near phase transition. In addition, strong magnetic fields can be used to study magnetic damping of the orienta-
Anisotropy. The magnetic field intensity $B$ in free space has a permeability result of magnetic induction $B$ up to $12 \, \text{T}$ fringes has been observed to be proportional to $25\, \mu\text{F}$ fluctuations could be achieved in a strong magnetic field. The magnetic field induced birefringence has been observed to be proportional to the magnetic field up to $12 \, \text{T}$.

Energy Transfer through Diamagnetic Susceptibility Anisotropy. The magnetic field intensity $H$ is the result of magnetic induction $B$ in free space. In turn, free space has a permeability $\mu_0 = 4\pi \times 10^{-7} \, \text{Hz/m}$. The magnetic dipole is calculated for $N$ atoms in a volume $V$. The quantity $M$, $M = \chi H$, is called magnetization. When a medium is placed in a magnetic field $H$, a magnetization $M$ is set up within the medium and consequently the magnetic induction inside the medium is given by $B = \mu_0 (H + M)$. Since $M = \chi H$, then $B = \mu_0 (H + M) = \mu_0 (1 + \chi) H$. This last expression is usually written in the form of $B = \mu H$, $\mu$ being the magnetic permeability of the body. Hydrogen and water are the two most widely used species in NMR and MRI studies. The magnetic susceptibility of $^1\text{H}$ is $-2 \times 10^{-9} \, \text{cm}^3$ and that of water is $-9 \times 10^{-5} \, \text{cm}^3$. It is important to notice that the expression

$$U = \left\langle - \int M \cdot B \, dv \right\rangle \quad [1]$$

which is taken to represent the energy of interaction between the magnetic dipoles and the external magnetic field, represents the total energy in the absence of the transient effects. The transient effects create fields that are time dependent. Outside this transient state, the steady state prevails and the atomic-level treatment could be applied. The interaction energy of a molecule with susceptibility along axial and radial direction as $\chi_a$ and $\chi_r$, respectively, within a field $H$ is given by the expression

$$U(\theta) = -\frac{1}{2} \left[ (\chi_a - \chi_r) \cos^2(\theta) + \chi_r \right] H^2 - \mu H \quad [2]$$

where $\theta$ is the angle between the axis of the susceptibility $\chi$ and the magnetic field $H$.

Notice that the second term is for paramagnetic materials with permanent magnetic dipoles. Since we are not dealing with paramagnetic materials the second term is ignored. For materials with large flexible molecules or isotropic material, $U(\theta) \ll kT$ for fields up to $10 \, \text{T}$. Therefore, there is very little energy transferred by a static magnetic field into these materials. In this picture, the average potential energy of a medium of magnetization $M$ in a magnetic field $H$ is given by

$$U(\theta) = -\frac{1}{2} (\chi_a - \chi_r) \cos^2(\theta) H^2 V \quad [3]$$

This energy is minimal when magnetic dipoles and $H$ are parallel, and hence, magnetic moments tend to line up with the field. Temperature causes random distribution of the orientation of the magnetic dipoles. The room temperature ($25^\circ\text{C}$) energy is about $kT = 4.1 \times 10^{-21} \, \text{J}$ and a $1 \, \text{K}$ temperature is equal the energy of a $2 \times 10^4 \, \text{MHz}$ photon. This should be compared to the interaction energy of molecules in human body when exposed to the static magnetic field ($27 \, \text{T}$). Calculations have shown (18) that this energy for a single alpha helical segment is about $10^{-22} \, \text{H}^2$ joules, with $H$ in tesla. At $10 \, \text{T}$, this corresponds to $10^{-23} \, \text{J}$, which is $4 \times 10^4$ times smaller than the room temperature energy. Even if all interactions with other protein aggregates were ignored, in order to cause any substantial orientation on the alpha helices one would require an unimaginable field of $2000 \, \text{T}$. This is simple evidence of the inability of magnetic fields up to $10 \, \text{T}$ to distort the protein structure. Another way of viewing the diamagnetic anisotropic interaction with the magnetic field is to estimate the number of parallel peptides within a protein assembly required to produce significant orientation. It has been shown that, even for large molecular diamagnetic anisotropy, not known to be possessed by many molecules, it requires $10^7$ peptides to modify the orientation of the segment at $1 \, \text{T}$. For any elongated proteins with a length of a few
microns and diameter less than 1000 angstrom, an axial orientation of a significant proportion of the alpha helical segment would be required for a substantial orientation to occur within a field of 1 T (27). As such, energy transfer through anisotropic susceptibility is likely in the in-vivo setting only for the circumstances such as large protein assemblies.

**The Effect of Strong Magnetic Fields on the Mechanism of Blood Coagulation.** The main blood coagulant is fibrinogen. These molecules are changed to fibrin monomers under the influence of the protease thrombin. They are then polymerized to long fibrin molecules that are diamagnetic and can interact with the magnetic field (28). In the absence of magnetic fields, the fibrin fiber appears to form a gummed up web. A magnetic field of 10 to 20 T is believed to be able to orient the fibrin fibers parallel to the field. Fibrin degradation product tests have shown (29) that under a magnetic field of 8 T, fibrinolytic processes produce on the average 15% more fibrin degradation products than the unexposed samples. If one considers the 190% higher fibrin degradation products in a 400 T2/m field gradient at 8 T compared to the control sample, this suggests that the magnetic field gradient is the main cause of this effect.

Fibrin gels have demonstrated a tendency to migrate to a region of lower field and fibrin had higher dissolution in a specific direction. Fibrin gels formed at 8 T have been shown (28) to be more soluble in water containing plasma than those formed in the absence of a field. However, the effect of the magnetic field should be separated from that of the field gradient. In this regard, homogeneous magnetic field studies on the enzymatic activities of plasmin conducted at a dB/dy < 4 T/m (30) showed no changes in the maximum velocity and the Michaelis constant of plasmin at 8 T. Consequently, it is unlikely that exposure to high magnetic fields will alter the blood coagulation process. Nonetheless, long term exposure to a static magnetic field (60 min at fields of 4–8 T), is believed to inhibit the hydrolysis of the synthetic substrate with plasmin (28–30).

**Proteins and Lipids.** Protein and lipids constitute another group of magnetically sensitive biological structures. Ignoring the small set of proteins that have paramagnetic atoms at their centers, all the other proteins interact with the magnetic field through their diamagnetic properties. The diamagnetic anisotropy of proteins has long been known to be the cause of the orientation of the retinal rods and other membranous organelles in magnetic fields (31) as discussed above. A strong magnetic field can orient biological polymers such as sickle cell hemoglobin (32), actin (33), microtubules (34), and collagen (35). Deoxyhemoglobin S, a natural crystalline fiber, forms spontaneously in erythrocytes of the sickle cell anemia patients (27). The elongated shape of the sickle cell erythrocyte is caused by these packed fibers and strong magnetic fields could orient such cells (31). Nonetheless, under these conditions, the diamagnetic anisotropy is mainly caused by the heme group of hemoglobin as previously discussed. Accordingly, it is unlikely that exposure to high magnetic fields has real in-vivo implications for protein and lipid structures.

**Phosphenes.** Retinal rod outer segments and other organelles containing regular arrays of membrane (such as small membrane patches of bacteriorhodopsin) have been observed to align themselves in a magnetic field. These observations, however, are made in vitro through artificial purification from protein derivatives. In contrast, these molecules have a complex structure in vivo and this will highly affect their magnetic field orientation sensitivity. This is because diamagnetic susceptibility is the cause of the sensitivity to the magnetic field. As an example, this magnetic susceptibility is mainly due to the diamagnetic anisotropy within nucleotide base pairs. For instance, the base pairs in DNA are known to be oriented in a plane perpendicular to the double helix axis (18). Therefore, a convoluted structure will reduce or even eliminate the diamagnetic anisotropy. It is important to remember that within each cell in the retinal rod outer segment, however, there are some two billion prealigned rhodopsin molecules. Considering that there are seven alpha helical segments in each rod, this will give a total of $3.5 \times 10^{11}$ oriented peptides. This will make a magnetic field of only a few hundredths of a tesla sufficient for creating an orientational energy comparable to kT. In this manner, a complete orientation of the cells could be easily achieved. In a strong field, the total mechanical torque acting on the collection of aligned cells could become considerable. This is the cause of magnetic phosphenes. These magnetic phosphenes are detected as faint light flashes. They are produced when an abrupt change in orientation relative to an external field creates a tiny
mechanical stress which, in turn, generates the false excitations. The presence of magnetic phosphenes has been reported by few, but not all, individuals exposed to high magnetic fields.

**Red Blood Cells**

Hemoglobin is the major constituent of the erythrocyte, forming some 45% of its volume content (36). In addition to erythrocytes, human blood is known to contain a diverse variety of electrolytes and negatively charged proteins. Nevertheless, the rheological properties of blood are mainly determined by hemoglobin. In this light, changes in the valency and the spin state of hemoglobin confer a special characteristic to the erythrocytes. The ferrous deoxy-hemoglobin with its \( S = 2 \) spin state is responsible for the paramagnetic behavior of the deoxygenated erythrocytes. However, oxygenated erythrocytes have diamagnetic properties because of the \( S = 0 \) spin state of the oxyhemoglobin. All other erythrocytes are paramagnetic with different susceptibility depending on the spin state of the methemoglobin, high at \( S = 5/2 \) or low at \( S = 1/2 \).

The paramagnetic properties of erythrocytes have been used in early efforts to separate Malaria infected cells from healthy cells using a strong magnetic field gradient (37, 38). On the same basis, the paramagnetic attraction of the erythrocytes, under the effect of inhomogeneous magnetic fields, has been studied to better understand the effect of the static magnetic field on the blood circulation. These experiments confirmed the inhomogeneous magnetic field-induced attraction of paramagnetic erythrocytes (36, 39–41). This attractive force was found to be directly proportional to the magnetic field, field gradient, and hemoglobin susceptibility, and inversely proportional to the blood flow velocity. This is due to the fact that there are two forces acting on the flowing paramagnetic particle. One is due to the magnetic field which is given by \( \mathbf{F}_{m,z} = (\chi V/\mu)\mathbf{B}d\mathbf{B}/dz \) as was discussed earlier. Here \( \chi \) is the paramagnetic susceptibility and \( V \) is the volume of the particle. A second force, \( \mathbf{F}_t \), or frictional force or Stokes frictional force, provides resistance against motion along the \( z \)-direction. The magnitude of this force is given by \( \mathbf{F}_t = 6\pi\eta Ru \) in which \( \eta \) is the medium viscosity, \( R \) is the hydrodynamics radius of the moving particle, and \( u \) is the displacement velocity (36). Under steady state the frictional force will equate the magnetic force along the \( z \)-direction (Fig. 7).

![Figure 7](image)

**Figure 7** Schematic representation of the frictional force, \( \mathbf{F}_t \), or Stokes frictional force. This force presents resistance against motion along the \( z \)-direction. Under steady state conditions the frictional force will grow as large as the magnetic force along the \( z \)-direction.

Therefore, we could find the displacement velocity \( u \) in that direction, which would be given by \( u = (\chi V/6\pi\eta Ru)(\mathbf{B}d\mathbf{B}/dz) \). This quantity could then be used to calculate the displacement along the flow direction \( \mathbf{L} \), say the \( x \)-direction. Integrating the displacement velocity, \( u \), along the flow direction (\( x \)-axis) with substitution of the \( dt = dx/u \) will yield \( \mathbf{L} = (\chi V/6\pi\eta Ru)/(\mathbf{B}d\mathbf{B}/dz)dx \). This quantity is inversely proportional to flow velocity \( v \).

Inhomogeneous fields as low as 10 \( \text{T}^2/\text{m} \) were shown to produce a detectable attractive force on blood flow. As such, the biological effects of highly asymmetric fields (> 100 \( \text{T}^2/\text{m} \)) need to be closely examined to evaluate their safety consequences. Of relevance to biological systems, a typical \( \chi \) for oxygen molecules is \( 3449 \times 10^{-6} \) cgs at 300 K (21). For oxygen, under a static magnetic field of 8 T and gradient of 50 T/m, it takes an aggregate of 2000 molecules to transfer energy comparable to the thermal energy at 300 K.

An inhomogeneous magnetic field, which could be resolved in a uniform magnetic field and a superimposed gradient field, has been shown to be able to modify the flow of erythrocytes. However, it has been observed that this effect is saturated at 20 \( \text{T}^2/\text{m} \). It is interesting that high magnetic field gradients have been used for the separation of bio-micro particles from solutions. Also, small magnesium and chromium paramagnetic particles have been isolated using magnetic field gradients. Nonetheless, none of these effects are likely to be important under *in-vivo* conditions in magnetic resonance imaging.

As mentioned above, high magnetic fields have been used in structural determination studies of biological macromolecules (42, 43). It has long been known that, in a magnetic field of about 1 tesla, erythrocytes from sickle cell anemia patients become aligned with the field (44). The existence of the paramagnetic methemoglobin is
the reason for the torque experienced by the cell that brings it into alignment with the field. This effect has only been observed in vitro and does not seem to have any physiological consequences. Through microscopic observations, anomalous deformation of sickle cells has been observed (43). Their alignment is recorded in magnetic fields of only 0.35 T, with the long axis perpendicular to the field. No cellular lysis was observed after exposure of erythrocytes to a field of 0.79 T (46). There was a fourfold increase, however, in the irregularly shaped cells. Upon closer examination of the shape of the deformed cells by scanning electron microscopy (SEM), the cells were seen to be different from prelytic forms taking place in the irreversible lysis processes. The diamagnetic susceptibility of sickle cells was measured to be high due to the paramagnetic anisotropy of the heme group (32). Condensation of the hemoglobin molecules into a parallel fiber in the sickle cells, with the heme plane normal to the fiber, will cause their orientation normal to the field (47). Reports of more occurrences of the irregular erythrocytes upon exposure to fields of 1 T and damage to these cells of up to 10% at this field had generated expectations of full hemolysis at fields above 8 T. This was due to the nonlinear extrapolation of the actual measurements have shown, however, that after a 10 min exposure of blood to fields of up to 20 T, less than 1%, if any, of erythrocytes are hemolyzed. More recent experiments on normal individuals have demonstrated that the oxygenated erythrocytes align themselves within a uniform magnetic field of up to 8 T (48, 49). Glutaraldehyde-fixed erythrocytes in a uniform magnetic field of up to 8 T showed an orientation in which the plane of their disk was normal to the magnetic field (50). A significant contribution from the membrane-bound hemoglobin in paramagnetism was presented as explanation for the observation. But due to the circumstances in which these studies were carried out, more direct evidence of alignment is needed in order to conclude a similar outcome in vivo.

A recent experiment on the suspensions of human oxygenated erythrocytes has revealed an alignment tendency for these cells in a magnetic field of 7 T (51). The conversion of the hemoglobin to a paramagnetic form was credited for the alteration of the diffusion anisotropy of the sample. Since this study was performed in vitro, it is conceivable that in vivo factors such as flow will affect the outcome. This would largely depend on the direction of the flow with respect to the static field. Nonetheless, it is too early to attribute symptoms such as nausea and headache to these mechanisms as the authors of these studies invoke (51). These effects, if they do indeed occur, are being related to a modification in blood flow due to the erythrocyte alignment with the magnetic field (51). Nevertheless, we believe that this is unlikely in vivo.

**Oxygen Dissolution in Living Tissues**

The amount of oxygen dissolved in human tissues and cells is a fundamentally important quantity. The influence of the magnetic field on the mechanism of oxygen dissolution may therefore set a limit on the maximum static field applicable to human subjects. The paramagnetic nature of the oxygen molecule and the molecules it attaches to through the process of dissolution plays an important role in every form of life. There have been many works illustrating the role of oxygen in life (52). The fact that magnetic fields could affect the amount and mechanism of oxygen dissolution of living tissues has great ramification on the application of the magnetic field on these systems. In principle, a modulated high field could create spatial preference for the concentration of the dissolved oxygen. The magnetic field could cause a redistribution of the oxygen on the water surface at one atmosphere. This spatial redistribution of oxygen would cause modulation of the oxygen desorption–absorption rate. This has been observed for both absorption and desorption of oxygen at 1 T magnetic field under the direct contact of oxygen with the water surface (53).

The dynamics of oxygen dissolution in water has been studied by comparing the amount of oxygen concentration before and after exposure to a magnetic field (54). This was done for fields of up to 8 T for duration of up to 60 min. In these measurements, a range of initial concentration varying from 11 to 22 mg/l depicted an increase of 5% on the dissolved oxygen concentration. Considering that the force acting on an oxygen molecule is proportional to the product of the magnetic field and the field gradient, it is clear that the oxygen aggregates will be forced to move away from the center of the uniform magnetic field region. Comparing the acquired magnetic energy of an oxygen molecule at 8 T, $2 \times 10^{-24}$ J, to room temperature energy of $4 \times 10^{-21}$ J will indicate that it takes more than 2000 molecules of oxygen in a cluster to experience drift in any specific direction. Correspondingly, high gradient
effects may be substantial if there is a high local oxygen concentration. Consequently, it is unlikely that such effects will be of importance under in vivo conditions.

Interaction of the Magnetic Field with Blood Flow and Ionic Currents

It is well established that when major arteries of the circulatory system are placed in magnetic fields that an electric voltage is induced on the blood flow. Understanding of the mechanism of this interaction is important in order to determine the safe level for the magnitude of the applied field. Magnetohydrodynamics (MHD) involves the study of the electrodynamic interaction of the magnetic field with blood flow. The flow of conductive fluids of velocity $v = v_t + v_i$, where $v_t$ is the component of velocity parallel to $B$ and $v_i$ is perpendicular to $B$, within a magnetic field, will experience a force $F = q(v \times B)$. The motion of blood containing charged ions will therefore establish an electric current, parallel to the velocity $v$. In addition to this current, due to the magnetic force on the flow, there would be a lateral current $J = \sigma(v \times B)$, $I_i = J A_i$, that is parallel to $v \times B$ and so perpendicular to the magnetic field (Fig. 8). $I_i$ will interact with the magnetic field to create still another force proportional to $I_i \times B$. Considering the electric charge of the ions, this force will be in the $-v$ direction, which will oppose the flow of blood. By some estimates (55), in order to maintain the flow in the aorta this opposing magnetically induced force could raise the blood pressure by as much as 28% at 10 T. This expectation was proven erroneous (56) as no obvious slowing down of the blood flow was observed at 4.7 T. Moreover, in our recent studies of hemodynamics in dogs at 8 T revealed no elevation of blood pressure during 3 hours of exposure (57). According to MHD flow calculations (56), the change from the total hydrodynamic vascular pressure to the total magnetohydrodynamic vascular pressure is less than 0.2%. These calculations predict that there is no basis for any notable pressure effect on the human circulatory system for fields of up to 10 T. In addition to this MHD effect, the flow of ionic current of velocity $v$ in a static magnetic field within a vessel of diameter $d$ will induce an electric potential $V = \nu Bd$. Superposition of this induced potential (58–60) will modify the ECG's T-wave amplitude. This well established phenomenon has been observed in the ECG tracings of humans at fields up to 8 tesla as displayed in Figs. 9 and 10 (57).

Similarly, ionic currents will interact with the static magnetic field in the context of the Lorenz force mechanism. The action potential along the peripheral nerve fibers will be altered by this interaction along the loops in the central nervous system. It has been stated that a magnetic field of 24 T is required to induce a 10% reduction in conduction for nerve cells (61). Experimental measurements at fields up to 2 T have demonstrated that no significant effect is seen in the function of the peripheral nerves at such fields (62). At fields of up to 9.1 T, some perturbations were observed in the EEG trace of squirrel monkeys and rabbits (62). The effects were seen to be reversible within 20 to 30 min. This is an important observation requiring further study.

Static Magnetic Field and Binding Kinetics

The role of the static magnetic field on the interaction of ions with their binding site has been
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Figure 10 Representative lead II ECG tracings acquired outside the 50 gauss line before (first tracing) and after (second tracing) exposure to an 8 tesla field (57). Note that no significant changes are observed in the ECG tracing. Tracings 3 through 5 are representative lead II ECG outputs obtained from three separate subjects at 8 tesla. Although the QRS complex is consistently present, electrodynamic artifacts greatly distort the traces in all cases (used with permission).

studied (10, 11, 63). The viscosity, Lorentz force, spring force, and the Brownian force are the phenomena that may contribute to the displacement of the bound ions from their binding sites (12). These mechanisms have all been taken into account in solving the Lorentz–Langevin equation for kinetics of the bound ion. Such calculations are complex and can depend on whether the model takes into account the thermal effects or treats the binding site as a low viscosity environment. As such, different results for the role of the static magnetic field on the ionic binding dynamics can be obtained. Nonetheless, such calculations have shown that for an ion in an environment with the viscosity of water, a magnetic field of about ten million tesla is required to produce a Lorentz force comparable to the thermal force acting on the bound ions (64).

Nevertheless, it is known that the calcium–calmodulin dependent myosin phosphorylation is sensitive to $\mu T$ magnetic fields (65). It has frequently been speculated in this instance that a locally hydrophobic environment is created around the binding site as a result of the geometry of the site. This in turn results in the expulsion of the dipolar molecules leading to the depletion from the site of water molecules. The number of collisions for the ions in these regions will be drastically reduced as a result of the absence of water. This implies a much lower viscosity compared to that of water. As such, otherwise weak magnetic field effects could become the dominant effect.

Recently, attempts have been made to quantify thermal and magnetic field effects (12). Statistical mechanical approaches (12) were used to assess the ejection probability of ions from their binding sites after a bound lifetime. Through the use of the Lorentz–Langevin equation it was observed that an exceedingly low viscous environment is needed to decrease the thermal effects and keep the ion bound for lifetimes of the order of 1 s. Viscous damping smaller than that of water by several order of magnitude is required for lifetimes of the order of $\mu s$. This indicates that contribution of the other terms might not have been realistically represented. The ionic oscillation frequency, $\omega$, plays an important role in determination of the ionic displacement. The frequency of the bound-ion oscillation, $\omega$, as a coherent solution to the Lorentz equation for the ion in response to the magnetic field, along with the value for the viscosity at the binding site, will determine the nature of the interaction of the magnetic field with the ion. For $\omega$ in the $10^{12}$ range, magnetic fields of the order of 1 tesla and a viscosity of 1 are required for a substantial effect on dissociation kinetics.

Nonetheless, many questions remain to be addressed in regard to the actual viscosity in the binding regions. The extent of ion hydration and its implication on the collision rate and viscosity could be investigated. There has been speculation that structural changes in the binding process could also play in the solution of Lorentz–Langevin and significantly change the quantification methods for the interaction of the static magnetic field with the ion. Nonetheless, from existing models, it remains likely that magnetic fields which are much larger than those in use today for in vivo studies would be required to induce a sizable effect on binding process. Care, however, should be exercised in this conclusion as highlighted by the calcium–calmodulin interaction.
Embryonic Development and Genetic Effects

The influence of high magnetic fields on the early stages of the embryonic development is a topic of complex nature and the subject of several recent works (66, 67). Studies have focused primarily on the genetic effects of the static magnetic field. A study of mutagenic activity was conducted on a strain of mutant fruit flies without cellular DNA repair function capability (68). It was concluded that the mutagenic activity of a static magnetic field of 0.6 T was comparable to a conventional ultraviolet light of 15 W at 50 cm for 5 s, an energy density of 0.14 mJ/m². A lack of any static magnetic effect was observed in the control normal group. In addition, an 8% decrease in mutant genotype was observed. This was interpreted as DNA-induced damage on the repair-defective group rather than a more general physiological effect. Similar studies confirming this observation at higher fields have estimated mutagenic and co-mutagenic effects of strong static magnetic fields using bacterial mutagenicity (69). Bacterial mutagenicity studies did not reveal a potential by static magnetic field of up to 5 T to induce mutagenic effects.

Damages such as pyrimidine dimer formation or other DNA damages require dissociation energies of the order of a few electron volts. A low field magnet, 0.6 T, however, will interact with the electron spins generating an energy of the order of μeV at most. This is 10⁵ times smaller than the typical chemical bond dissociation energy. As such, it is understandable that a direct attack of the DNA molecule by low field magnetic fields (i.e., 0.6 T) has not been reported. Nonetheless, it may be important to consider mutagenic free radicals in the magnetic field. Singlet–triplet transitions of unpaired electrons are affected by magnetic fields. In a 0.6 T magnetic field (70), a many-fold increase in the lifetime of 2-naphthylphenyl radicals in polyoxyethylene dodecanol micelles was observed. Considering that micelles model true cells, a possible increase in free radical lifetime and its possible role in mutagenic activity is a viable option that calls for further clarification and well designed studies.

Developmental studies have also been important in understanding the potential health risks of high magnetic fields. Magnetic fields of up to 8 T have been used to study the embryo of *Xenopus Laevis* from the stage of precleavage through neurula for a duration of 20 hours. Considering that the most hazardous effect on the developing embryo at high fields is teratogenic, no such effect was found (71) when embryos were exposed to 8 T for 20 hours from the early fertilized-egg stage through neurula. Therefore it has been concluded, for *Xenopus Laevis*, that a static magnetic field of 8 T has no appreciable effect on the cleavage and the subsequent cell multiplication and differentiation. This is a remarkable observation since the sum of all biological effects at high fields does not seem to be of catastrophic consequence for the biological cell.

General

The principle biological effects of magnetic field of several tesla to tens of tesla (18) are related to orientation effects (as in crystals growing in a magnetic field). Orientation requires a constant field direction. This is not the case with blood cells circulating in the body and tissues. Theoretically, the major safety concerns when a living subject is placed within a strong magnetic field are related to the generation of electrical currents. Since blood is in motion, if the magnetic field is strong enough, an electrical current potentially could be generated. This is due to the fact that blood containing charged ions is susceptible to the Lorentz force generation. Also iron, as one of the paramagnetic elements in the body, has a dominant effect in comparison to the diamagnetic properties of the other constituents of the human tissues. The large paramagnetic susceptibility of iron makes it more vulnerable to magnetic interaction effects. Since neural activity is ionic, the presence of a subject in a strong magnetic field could be conceived as causing a discernable effect. Since the heart’s electrical control system is based on electrical nodes and electrical distribution patterns, it is plausible that motion of the myocardium in a strong magnetic field could generate electrical currents. The scientific community has tried to address many of these concerns over the past years.

In animal studies, exposure to very high magnetic fields of up to 9.4 tesla has been reported (72) to disrupt animal behavior. In excess of 4.6 tesla, performance of learned tasks by squirrel monkeys was reduced during the exposure (73). These studies, however, must be received with caution since the evidence from studies of nervous system response at these very high magnetic fields is actually equivocal. In addition, recent studies in rats at 9.4 tesla revealed no demonstra-
ble effects as a result of exposure of this field strength (74).

Nonetheless, in the range of 4 to 7 tesla, sinus arrhythmia and a temporary decrease in heart rate was reported (75) in one experiment in which squirrel monkeys were acutely exposed. No threshold between 4 and 7 tesla was identified that brought on this temporary decrease in heart rate. We have found no reports in the scientific literature that demonstrated any adverse effects other than innocuous transient phenomena associated with high static magnetic field exposure. Furthermore, physiological measurements of heart function in the swine at 8 T indicate no sign of arrhythmia or changes in cardiac output, heart rate, and blood pressure in these animals as a result of exposure to this field strength (57).

There are over 5000 human magnetic resonance imaging and spectroscopy systems in existence worldwide (NEMA 1996 statistics). These instruments have field strengths ranging from 0.1 to 3 tesla. In addition, there are now nearly thirty systems operating between 3 and 4 tesla (76–78). To date, no biological hazards to humans have been identified from exposure to high magnetic fields. The only sensation experienced at fields above 2 tesla is vertigo, due to movement by the subject, patient, or researcher while at the interface of the magnetic field. The vertigo is a transient effect caused by stimulation of the inner ear with motion and ceases after being removed from the gradient magnetic field. The reported effect of transient vertigo (77) associated with some subjects and researchers who work within the magnet’s bore are thought to be associated with stimulation of the vestibular controls. Within the ear, the semicircular canals provide signals to the brain, which confirm and correlate with visual information related to equilibrium. When the subject moves his head quickly in a magnetic field, it is possible that eddy currents are unequally generated in the endolymph flowing in the three semicircular canals of each middle ear. The hair cells sense this eddy current and confuse this stimulation with the normal flow stimulation by endolymph used to sense head motion and positioning. This effect is transient, not caused by time-varying magnetic fields of the system, but is generated by head motion in the static magnetic field. This uncomfortable feeling can be eliminated by restricting head motion in volunteer subjects and instructing researchers when working in the bore of the magnet to move their heads slowly to prevent this sensation of vertigo.

Most investigations with human volunteers (57, 79, 80) show that body temperature, blood pressure, heart rate, respiration, and other monitored physiological parameters are unaffected by chronic exposures to magnetic fields. However, one work (81) shows a slight drop in heart rate in humans exposed to a field of 2 tesla. The main concerns at higher fields are flow potentials, moving blood in the heart, and aorta generating currents. The existence of such potentials is known and well established, but their significance is less clear. Estimated maximum values (82, 83) at the human aorta range between 7 and 16 mV/T. At 8 tesla, estimated values range from 60 to 130 mV. These levels of voltage generated are several orders of magnitude below that which will cause heart fibrillation. Prior to human use of the first 4 tesla magnetic resonance systems, porcine studies were performed by Philips Research Laboratory in Hamburg, Germany (Philips Forschungs Laboratorium Hamburg). The studies at field strengths from 0 to 4.0 tesla on anesthetized adult pigs demonstrated no correlation between field strength and heart rate or production of sinus arrhythmia, extra systoles, or premature ventricular contraction abnormalities. We have obtained similar results at 8 tesla (57).

Due to the lack of reports on the effects of prolonged exposure to magnetic fields higher than 4 T on mammals it has proven difficult to measure the impact on safety. Nevertheless, it appears that an unusually long exposure time is needed in order to produce modifications at the molecular level. In one measurement (84) no effect was observed as a result of an hour long exposure of mice to a 14 T magnetic field. Due to the mechanism of interaction of magnetic fields with biological tissues, distinct from ionizing radiation capable of inflicting almost instantaneous damage, it is conceivable that an extremely high magnetic field might be required for an extended period of time for any damaging effect on biological systems. Nonetheless, in studies in which rats were exposed for up to 10 weeks to a field of 9.4 tesla, no static magnetic field effects were observed (74).

Furthermore, exposure of the fetus in utero to about 1 tesla (85, 86) has had no significant effect on pre- or postnatal development. This suggests that possible pregnant researchers or staff working in the close proximity to the magnet room is not a safety concern. Insufficient data are available in the literature to determine the safety of, or hazard to, the human fetus in utero at 8 tesla.
levels; therefore pregnancy should be viewed as a contraindication for such devices until further research is completed with animals.

EFFECTS OF GRADIENT MAGNETIC FIELDS

It is well known that the need for spatial encoding in MRI necessitates application of gradient fields with time switching capabilities within about one FID time constant. Once time-dependent magnetic fields are utilized, many parameters must be considered. The waveform as well as the rise time and maximum field amplitude, $B_{\text{max}}$, will contribute to its interaction with biological systems.

There are two mechanisms of energy transfer through the operation of gradient coils in MRI systems. The first is the static magnetic field gradient. This gradient creates an opportunity to exert linear force on paramagnetic and ferromagnetic molecules and on moving charged particles and particles possessing magnetic dipoles within the body. The magnitude of this force was discussed in previous sections. The second is the effect of the pulsed gradient combined with the static magnetic field. The effect of the pulsed gradient magnetic field is not expected to become considerable for mammalians systems, with little magnetic material, especially noting that much lower $B/\text{dz}$’s are used in pulsed gradient magnetic fields compared to the static magnetic field gradients in MRI applications. For example, for a magnetic field of 8 T and pulsed gradient of 10 G/cm or 0.1 T/m, it would take $10^6$ molecules to impart a gradient-induced energy comparable to the thermal energy.

Extremely Low-Frequency Electromagnetic (ELFEM) Effect

The second mechanism of energy transfer to the tissues is through the operation of the gradient coils in MRI systems during the switching mode. In the same manner that rapid motion inside a magnetic field can generate electric potentials, changing magnetic fields can generate such potentials on a non-moving subject. Thus, time-varying magnetic fields can induce electric fields that create eddy currents in biological systems. These currents may affect normal cell function, particularly the function of electrically excitable nerve and muscle cells.

Typical gradient switching speeds are in the 200 µs or 5 kHz range. These frequencies fall within the ELFEM wave band. These waves have a long wavelength and penetration depth. Their temporal variation is so slow that their behavior can be approximated by quasistatic magnetic and electric fields. Nonetheless, while the mechanism of interaction between biological systems and low level electromagnetic fields is not completely understood, energy considerations could help clarify some main points of this interaction. The ELFEMs contain a minute amount of energy. As an illustration, for instance, in comparison with thermal energy of $kT = 25$ meV photons at 300 K, the energy of a 1000 Hz photon is $4.1 \times 10^{-12}$ eV. This means that ELFEM photons are 10 billion times less energetic than room temperature background thermal photons. Chemical bonds have a typical energy of a few electron volts. That is, 13 orders of magnitude higher than a 100 Hz ELFEM photon. Therefore, this amount of energy would not be close to being able to break the chemical bonds present in biological tissues and cells. There has been a growing amount of literature that these fields will not disturb or disrupt any chemical bond in biological molecules such as proteins and DNA. But the nature of the interaction remains unclear. The main source of confusion for the conflicting reports on the hazards of the weak electromagnetic fields is the complex nature of their interaction with biological systems. While there is no consensus on the primary governing factor of this interaction, all agree that frequency, magnetic field strength, electric field strength, and the nature and location of the exposed object are important.

Thermal Effects. Temperature variations can affect the rate of the chemical reactions. Using a classical outlook, it is currently held that the electric field component of higher frequency EM waves creates heating effects within biological systems. Low frequency ELFEM waves are incapable of producing such effects as discussed above. As a result, the biological effects of the gradient switching have always been considered as athermal in nature (87, 88).

The data on the thermoregulatory response of human subject to high intensity ELFEM waves have been sketchy and obscure. The low level ELFEM waves are known to cause nonthermal effects on the living organisms. A 1 V/m ELFEM wave can induce a specific absorption rate of $10^{-4}$...
ions, say Ca$^{2+}$ such, when the charge-to-mass ratio of biological channels. As true, this frequency effect of the that can alter the transport of ions through ion magnetic field of the switching gradients could be on the order of $dB/dt = 100$ T/s. When modeling the comparison between the induced eddy and displacement currents, where the permittivities of 310,000 and 130,000 were used for the heart tissue and skeletal muscle at 1 kHz, respectively, eddy currents were found to dominate the current distribution (89). The calculated eddy current for the same set of gradients reached 0.2 A/m$^2$ at 10 kHz. The eddy current still dominated the current density distribution. Therefore, from a classical perspective, it is important to notice that the induced electric field is probably the cause of the thermal interactions compared with direct magnetic field heating effects.

**Cyclotron Effect.** There have been speculations (90) that some combinations of DC and AC magnetic fields create cyclotron-resonance conditions that can alter the transport of ions through ion channels. If true, this frequency effect of the oscillating magnetic field on the ion channels could alter the kinetics of these channels. As such, when the charge-to-mass ratio of biological ions, say Ca$^{2+}$, has the right magnitude, the ions could become trapped into cyclotron resonance that couples effectively with the electromagnetic wave. According to the cyclotron-resonance equation, the resonance frequency is given by $f = (1/2\pi)B_0q/m$, where $B_0$ is the static magnetic field and $q$ and $m$ are the charge and mass of the ion. The predicted resonant frequency of the K$^+$, Ca$^{2+}$, and H$^+$ ions are 20, 40, and 760 Hz, respectively, in the 50 $\mu$T magnetic field of the earth. However, fluorescence based Ca$^{2+}$ measurements (91) have not confirmed any such resonance. The cyclotron-resonance hypothesis has been criticized (92) especially as related to the use of the equation describing the physical confinement of the ion to its helical path. As a general solution to the problem, restriction on the motion of the ion is not needed (63, 93). The most recent measurements (94, 95) have demonstrated no significant change in the channel traffic parameters as a function of the applied field for the most important ions of K$^+$, Ca$^{2+}$, and H$^+$.

**Chromosome Aberration.** There have been unsettling reports of threefold increase in chromosome gap and break frequencies under the effect of low frequency electromagnetic fields of 50 Hz and 30 $\mu$T$_{rms}$ sine wave for 3 days (96). In addition, there are reports of mutagenic and clastogenic effects of low frequency electromagnetic waves (97–101). Given the energies involved in ELFEM waves, these reports must be brought into question. For instance, Galt and co-workers (102) have reported “no increase in chromosome defects in the exposed cells” and rather “an opposite tendency was observed.” Lack of confirmation of the chromosome aberration by low frequency EM waves along with no indication of the exposure effects on the human amniotic cells is a major contribution in advancing the understanding of the ELFEM wave effects on the human body (102).

**Cardiac Stimulation.** The rapid switching of gradients can produce a large $dB/dt$ which, in turn, can generate a sizable electric field. Such electric fields induce excitatory responses in the subject according to the Faraday’s law. For a simple circular path of radius $r$,

$$E = -(r/2)dB/dt$$

for the induced electric field, $E$, around the path of radius $r$. For a maximum $dB/dt = 100$ T/s and a typical radius of 10 cm this equation gives an electric field of 5 V/m. As is evident from the induced $E$-field equation, the electric field is directly proportional to the radius of the object. Therefore, for smaller organs or parts of the body this electric field is smaller than 5 V/m. Ohm’s law, $J = \sigma E$, will give the magnitude of the current that will be generated. For a 5 V/m field and a typical conductivity of 0.11 $\Omega^{-1}$ m$^{-1}$ measured for the heart at a frequency of 100 kHz (103), a current density of 0.55 A/m$^2$ will be established. A 19.2 A/m$^2$ current density has been found to be the threshold required for heart stimulation for a pulse with 640 $\mu$s duration (104). It is clear from the above discussion that since the generation of $E$ fields is dependent on geometry that the potential hazards arising from $dB/dt$ can be reduced by altering gradient coil dimensions. For instance, this can be achieved by building shorter body gradient coils.

Excitation of cardiac muscles is based on the movement of charge from cell membrane. The
amount of this electric charge displacement should be above some critical value in order to cause stimulation of the tissue. In order to better understand these effects it is useful to reexamine some of the physiological basis of depolarization. It is well known that the resting membrane potential is reduced by $\Delta V$ as a result of depolarization \cite{105}. As soon as the resting membrane potential drops below some threshold potential $V_T$, the ion channels will open, allowing transmembrane flow of sodium and potassium ions. This will produce an action potential. It takes a finite time for a critical current density to establish in order to develop the $V_T$. This time is usually represented by a time constant $\tau$, in an equation commonly referred to as strength-duration equation \cite{106} given by

$$J = \frac{J_R}{(1 - e^{-t/\tau})}$$

in which $J$ is the current density, $J_R$ is the rheobase, and $\tau$ is the time constant. The rheobase is the current density required for excitation after a long time. Based on this equation, at $t = \tau$ the current density would acquire a value of $J = J_R/0.632$. Plotting this equation as a function of tissue time constant will give an indication of the role of stimulation time in establishing the current density across various membranes. As is shown in Fig. 11, a 10 $\mu$s pulse will require a current density larger than $200J_R$ to stimulate the heart tissue. This is based on the assumption of $\tau = 2$ ms for the heart tissue. This is in contrast with the motor nerve, with an assumed $\tau = 0.1$ ms, that would require 20 times less current density for the same pulse to induce stimulation \cite{105}. Because of the possibility of cardiac fibrillation and continuous muscle contraction, current densities of more than 1 $A/m^2$ should be handled with caution and viewed as a potential health hazard. It has been suggested that the average $J_R$ for heart muscle is 14.8 $A/m^2$ \cite{107}. Assuming a conductivity of 0.25 $\Omega^{-1} m^{-1}$ for the heart tissue, a rheobasic electric field of 60 V/m would be required for stimulation \cite{105}.

In addition, through induced electric fields during the switching period, energy transfer to ions in solutions can occur due to the Coulomb force exertion on the charged particles. This, in turn, manifests itself in increased drift velocity. The amount of energy transferred to an ion in a solution in a low level electric field, however, is negligible compared to the thermal energy. It is estimated that a field of 1000 V/m will induce a mean drift velocity of $5 \times 10^{-5}$ m/s on a sodium ion with a thermal velocity of 400 m/s \cite{108}. So the added thermal energy by drift velocity is $10^{14}$ times smaller than room temperature energy.

Since ELFEM waves produced by the gradients can induce electric fields in the body that could stimulate the heart, gradient-induced fields should not exceed the limit that could induce ventricular fibrillation. Since peripheral nerve stimulation is not life threatening, it is a convenient physiological indicator for the level of the

![Figure 11](image.png)

**Figure 11** Plot of strength of current induced versus pulse duration. This curve is important in understanding the thresholds of motor, sensory, and cardiac stimulation as related to pulse duration in MRI. This figure was adapted from Machawar et al. \cite{105}. 
induced electric field. Theoretical modeling of the effect of the magnetic gradient switching has been performed \((\text{109})\). For a cylinder with a 20 cm radius, a peak induced-electric field of 0.56 V/m was generated by a Z-gradient. This gradient was constructed from a pair of single-turn coils with a radius of 32.7 cm and with sufficient current to generate 1 gauss/cm gradients with a rise time of 500 \(\mu\)s. In the same calculation, a peak electric field of 0.82 V/m was found for the transverse gradients. In an experiment that exposed two subjects to pulsed sinusoidal fields of 1.4 kHz frequency, a 14 Hz repetition frequency, and a peak \(dB/dt\) of 86 T/s, a sensation in the lower back and facial regions was reported \((\text{110})\). According to calculations \((\text{111})\), excitation of human peripheral nerves could begin at 1.4 kHz. Assuming a stimulation of 0.5 ms duration, 4.5 times higher current density is required for heart stimulation compared to motor nerve stimulation. At higher frequencies, as shown in Fig. 11, significantly higher excitation is required for cardiac stimulation.

Using magnetic stimulation, a direct measure of the myocardial response to gradient pulses in MR can be obtained. In order to understand the thresholds of such excitations a strong magnetic pulse is usually used that delivers stimulation to the target. A powerful pulse applied to the vagus causing a temporary stoppage of the canine heart has been used to inquire into this interaction \((\text{105})\). Stimulation with a pulsed magnetic field was sufficient to restart the heart. In comparison, to stimulate fibrillation using an electric field, a 10 ms long persistent pulse was required. To accomplish the same task with an MRI gradient, a \(dB/dt\) as high as 6000 T/s would be required. As a result, recent studies indicate that most modern MRI systems operate at much below the onset of the myocardial stimulation \((\text{104, 112})\). Nevertheless, a more in depth understanding of the induced electric fields in human myocardium by MRI gradient coils is an important undertaking for the MR community and is now being pursued \((\text{104, 105, 112})\).

A recent finite element study \((\text{113})\) has used conductive anatomy to model a detailed human thorax. This has resulted in acquiring a more refined approximation of the MRI gradient-induced spatial distribution of the electric field in myocardium. This work demonstrates that simple model approximations of magnetically induced electric fields over-estimate the peak myocardial field by 44%, 39%, and 30%, for X, Y, and Z gradient coils, respectively. For a typical echoplanar MRI, a gradient of 2.5 gauss/cm (1 kHz, \(dl/dt = 1.5 \times 10^6\) A/s) induced peak electric fields of 2.75, 1.86, and 1.68 V/m through the action of the X, Y, and Z coils, respectively. This amounts to a factor of 35 decrease in the previously estimated threshold of 1 V/cm for magnetic stimulation of the canine heart \((\text{104, 105, 114})\). Considering that present MRI devices are operated well below the limits for cardiac stimulation, this indicates that there is room for theoretical and experimental work with stronger gradient coils both for low and high field MRI systems.

**Phosphenes**

More than a century ago, the visual sensation produced from magnetophosphenes was first reported by D’Arsonval \((\text{115})\) as a result of exposure to low frequency magnetic fields. Phosphen induction manifests itself as perceived light flashes. This effect is totally reversible upon termination of the exposure. Since 1896 \((\text{115})\), visual sensations have continued to be experienced due to the exposure to oscillating magnetic and electric fields \((\text{116})\). The application of electrode induced currents to the scalp \((\text{117})\) suggested that a strong frequency-dependent minimum current threshold is required for the induction of visual sensations. This was performed for currents of less than 8 mA over the 0 to 200 Hz band. The exact frequency appeared to have an effect on the quality of the visual sensation. The minimum current to induce this effect was found to be 10 mA and it is now known that at lower current densities, between 10 and 100 mA/m\(^2\), phosphen induction is likely to occur. Exposure of the human head to this level of current density at low frequencies, below 100 Hz, is believed to cause this effect.

In MRI, phosphen induction can occur above a threshold of 5–10 mT at 20 Hz. A faint flickering phenomena is detected in the eyes, similar to a dark adapted person closing his eyes and pressing lightly on the orbits. This most sensitive transient response is also noticed to be due to the occurrence of magnetic phosphenes. They are believed to result from tiny induced currents affecting the retina. Magnetic phosphenes have been confirmed \((\text{118–120})\) to result from currents induced by various time-varying magnetic fields. This transient electrochemical phenomenon is not
considered to be hazardous to humans for the range of variation of the gradient fields.

Nerve Stimulation

A mild sensation in the lower back has been reported (121) in individuals who have been subjected to a peak longitudinal field of 60 T/s over a range of 600 to 2000 Hz. The perception thresholds in these experiments were determined to be proportional to frequency. In a measurement when the palm was brought close to an induction coil, which pulsed at 3.8 kHz with a field of 16 to 48 mT, a rise time of 130 μs and dB/dt of 150 T/s, a bold pain and decreased blood flow were observed (122).

Interestingly, the possibility of stimulating the diaphragm prompted a test of the effectiveness of a pulsed magnetic field, applied from outside the lateral abdominal region, to act as a respirator (123). The minimum pulse for the contraction of the abdominal muscles and deep diaphragm was found to be a dB/dt = 560 T/s with a rise time of 250 μs.

Clearly, it is known that dB/dt and pulse duration can stimulate living systems. However, muscles and nerves are unable to respond to short-duration EM fields, even if they have high dB/dt. Hence, pulse width should be examined while setting an upper bound on the magnitude of the applicable peak value of a time-varying magnetic field. This problem can be addressed at a simple level as follows: For a trapezoidal gradient pulse shape where the ramping part of the pulse could be approximated by a linear relationship such as B = R t, for 0 < t < t r and 0 < B < B max, where t r is the duration of gradient ramp (rise or fall) and B max is the maximum value of the gradient magnetic field strength, then \( R = \frac{dB}{dt} \) would be given by \( B_{max}/t_r \). Using this pulse shape with \( t_r = 100 \mu s \) and a plateau time (t p) of 200 μs for a total pulse duration t s = 2t r + 4t p of 800 μs, it has been shown that a threshold of 300–400 T/s was required for nerve excitation around the clavicle of human volunteers (124). The threshold for the sensation at the middle of the forehead was found at 80–100 T/s for the same pulse width.

In a more general model, the stimulus threshold is described as a function of duration of the gradient pulse. In this model, the equation

\[
\frac{dB}{dt} = \left( \frac{dB}{dt}_0 \right) \left( 1 - \exp(-t/\tau) \right)
\]

is found to give the best approximation to experimental data (109). Integration of the above equation yields (111), \( \frac{B}{B_0} = (t/\tau)/(1 - \exp(-t/\tau)) \). Here \( dB/dt \) is the threshold value, \( (dB/dt)_0 \) is the minimum value for long-pulse threshold, and \( \tau \) is a time constant (109). For \( t \ll \tau \), the approximate expression

\[
(dB/dt)t = (dB/dt)_0\tau = B_{max}
\]

has been suggested (125). This relationship between the stimulation threshold for gradient magnetic field strength (B max) and the pulse width applies to monophasic square/trapezoidal waveforms. For long pulses, the minimum of the threshold value of dB/dt for peripheral nerve stimulation is approached, while a minimum of B occurs for short pulses. A theoretical threshold value of 6.2 V/m has been hypothesized for a square pulse for stimulation of 20 μm nerve fibers, known to be among the largest fibers (105, 126). The 6.2 V/m value is rather typical for a relatively sensitive nerve. The minimum threshold for a sine wave is estimated at 7.3 V/m (128). The myelinated nerve model has predicted a τ = 120 μs for the uniform excitation field threshold (127). In close agreement, a time constant of 148 ± 39 μs was obtained in the MR setting for the human sensory threshold (129). Using a value of 6.2 V/m as the threshold level for both nerve and cardiac stimulation for square pulses, dB/dt values of 72.1 to 38.3 T/s were found for long duration pulses (> 10 ms) on different body locations. This myelinated nerve model also predicts that the excitation threshold of peripheral nerves and the heart converge as pulse duration increases (111, 127).

The human threshold of perception for peripheral stimulation has been established at about 200 T/s in volunteers whose forearms (130) were exposed to time-varying magnetic fields. High frequency fast time-varying magnetic fields can stimulate nerves at a lower level. A very short pulse (180 μs at 2.2 tesla) was able to stimulate the median nerve (131) of the forearm. However, it is difficult to induce high enough currents with existing human sized magnets in order to easily assess such effects. Nonetheless, a wealth of literature exists related to the direct electrical current stimulation of tissues. From such a database, one can approximate hazardous levels of induced eddy currents resulting from time-varying magnetic fields. It is known for instance that direct stimulation of nervous and muscular tissue occurs with
current densities in the range of 1 to 10 A/m² (132). A 3 A/m² and 50/60 Hz stimulation is reported to cause cardiac fibrillation (133). The World Health Organization (13) and others (120, 130) conclude that at current densities above 1 A/m², adverse health effects from nerve or muscle stimulation may result. Nevertheless, taking into account the anisotropic and inhomogeneous nature of biological material it has been estimated that the maximum current density for whole body exposure is in the range of 0.4 A/m² (134). Eddy current calculations (127) suggest that peripheral nerve and cardiac muscle stimulation can be avoided by an adequate margin of safety if the time-varying magnetic field does not exceed 20 T/s for monophasic single pulses, and for repetitive pulses of widths greater than 3 ms (see Fig. 11). The normally assumed time constant for cardiac muscle is 3 ms, whereas that for nerve conduction is 120 µs. As the pulse width narrows, between 3 ms and 120 µs, the safe level increases exponentially to 1000 T/s as the pulse duration changes between 10 and 1 µs (135), where heating from eddy currents starts to have an effect (127). These values have been found to be in agreement with experiments (127, 135) considering the circumstances of the stimulation and conditions of the experiment. Accordingly, they present an insight into the order and nature of the events involved in subjecting human to time-varying magnetic fields. A positive report is independently reproducible (155). The results of several groups with negative reports are independently reproducible (155). The results of several groups with negative reports are independently reproducible (155). The results of several groups with negative reports are independently reproducible (155). The results of several groups with negative reports are independently reproducible (155).

Cellular Effects
In cellular studies, where cell cultures are exposed to gradient magnetic fields for hours, the results show a lack of time-varying magnetic fields effects. In fact, there were no statistically significant effects (151) observed when 3 and 4.32 T static magnetic fields were combined with a gradient field of 25 mT/m in 300 ms and a 4 W/kg specific absorption rate (SAR) exposure to 126 and 180 MHz RF pulses (152). No significant effects on sister chromatid exchange rates were found when human lymphocytes (153, 154) were exposed to time-varying fields of up to 220 μT. A comprehensive review of the published studies of potential genotoxicity of electromagnetic fields over a time span of five years encompassing 23 published studies has concluded that none of the positive reports are independently reproducible (155). The results of several groups with negative studies in several exposure categories (case 1 = ELF magnetic fields, 150 microT–5 mT; case 2 = combined ELF electric and ELF magnetic fields, 0.2 mT, 240 mV/m; and case 3 = static magnetic fields of 1–3.7 T) have been confirmed (155). The lack of effects suggest that time-varying magnetic fields are unlikely to act as carcinogens. Several in-vitro studies reported increased DNA synthesis in human fibroblast (156) with exposures of 300 to 560 μT at 4 to 15 kHz. Altered levels of protein synthesis and enhanced DNA transcription were observed in Drosophila salivary glands.
with exposures of 2.3–3.5 mT at 1 to 71 Hz. Nonetheless, altered transcription, translation, or DNA syntheses rates do not necessarily demonstrate that time-varying magnetic fields promote the appearance of cancer. However, it is clear that caution should be exercised in this regard and additional studies are needed.

Acute exposure (90 min) to low ELF magnetic fields in mice has been shown (161) to enhance the analgesic response to morphine. It was later demonstrated (162) that this effect on the mouse opioid system was largely due to gradient-coil induced ELFMF. The site of interaction of ELFMF waves has been associated (163) with the mechanism of maintaining the intracellular calcium ion concentration. The indirect nature of the inference of Ca\(^{2+}\) as the primary site for ELFMF engagement with the living tissue during an MRI session prompted some investigators to seek more direct evidence (164). A 20% increase in calcium ion concentration was observed (164) during a 23 min MR imaging procedure through fluorescence measurements. This proved that the increase in intercellular Ca\(^{2+}\) was exclusively due to the gradient field switching. Even though these results point to the possible harmful aspects of chronic ELFMF exposure, it is not clear if they should be of concern in the context of MRI time scale exposure to ELFMF. This is especially true in the light of the apparently reversible nature of these effects. Once again, however, caution should be exercised in light of these findings.

**Human Safety of Gradient Fields and Government Guidelines**

Three “warning” signals related to the effect of time-varying magnetic fields on human volunteers exist. They are the occurrence of magnetic phosphophes, the presence of nerve and muscle cells stimulation, and the excitation of the inner ear. Two of these warning signals are due to gradient switching and the third one is due to sudden motion of the head inside a magnetic field gradient. The switching gradients used in MRI are not strong enough to cause inner ear excitations. The static magnetic field gradients used in MR scanners or found around MR spectrometers, however, are capable of inducing inner ear excitations depending on the rate of change of head position when the individual is within the field gradient.

The acoustic sound due to the gradient switching has long been a non-life-threatening but inconvenient aspect of MRI systems. Studies in the quantification of the gradient magnetic-field-induced acoustic noise levels are implemented that mostly deal with the fast and ultra-fast techniques. The noise due the echo planar imaging (EPI) and three-dimensional fast spin echo pulse sequences has been measured for 1.5 T systems under “worst case” acoustic noise levels to be a maximum of 114–115 dB compared to the highest ambient noise levels of 67–78 dB measured for various MR systems (165). These levels, while high, are within the permissible levels recommended by federal guidelines.

The International Electrotechnical Commission (IEC) Safety Standards (166) do not limit the level of field gradients. Instead, it is recommended that an indication should be provided that the device is in an investigational mode of operation when used at levels above those provided in a graphical table of slew rate and pulse duration of the form represented in Fig. 11. As a cautionary note, however, there have been reports (FDA, MDR [Medical Device Report]) that on some magnetic resonance systems, a 60 T/s level caused peripheral muscle stimulation.

For high gradient strength and slew rate studies (such as EPI), the FDA guidelines suggest that (in commercial clinical systems) the gradient field use be limited by monitoring perception of the pain threshold caused by peripheral nerve stimulation. The investigator should then limit gradient strength and slew rates to below this threshold. The perception of the pain threshold level is at least an order of magnitude below any level that could cause electrical eddy currents in the body. This latter level might induce heart fibrillation. Therefore, by operating just below the pain threshold, the investigator establishes an upper level (in the range of 50 to 100 T/s) which is both safe and comfortable for the volunteer.

Following current FDA magnetic resonance guidelines for \(dB/dt\) (see Table 1), a study of controlled higher levels of gradient fields will be advisable (167). This will allow one to explore peripheral nerve stimulation with animal studies, and for controlled human studies of gradient sensation. This system should be designed to carefully and cautiously determine at what level subjects begin to elicit the perception of nerve or muscle stimulation or the perception of stimulation that can be considered approaching the sensation of pain. It is conceivable that the result of these kinds of studies could be a new maximum \(dB/dt\) level. As we are approaching this limit,
safety mechanisms should be designed that will conform to the results of a comprehensive gradient study while adhering to the FDA guideline of operation below the threshold of any sensation of pain. Such a safety mechanism would involve a system that prevents the gradient level from going above safe levels (currently about 100 T/s) with both software (dB/dt calculated limits) and hardware (slew rate limited) safeguards.

STUDIES LINKED TO RADIO FREQUENCY DEPOSITION EFFECTS

Experiments with animals have clearly demonstrated that body temperatures can be elevated with exposure to radio frequency (RF) energy, and physiological effects have been noted at high levels of RF exposure in animals. With a 17 W/kg exposure in rabbits (168) and a 10 W/kg exposure in mice (169) there was a significant decrease in barbiturate-induced sleeping times. At 10 to 15 W/kg, rabbits (170) and anaesthetized rats (171, 172) demonstrated increased cardiac output and heart rate and elevated blood pressure with rectal temperatures of 40.5°C. At 3 to 4 W/kg, with core body temperature raised by more than 1°C, an increase in plasma cortical levels was observed in primates (173) and an increase in corticosterone was found in rats (174).

It is also clear that increased heat loads result in decreased mental function. Performance of learned tasks by primates (175–177) was significantly reduced by exposures to 2.5 to 5 W/kg RF energy for 1 hour with a 1°C rise in rectal temperature. Similar transient responses while at higher body temperature have been observed in rodents (178–181).

Certain organs such as the eyes and testes are particularly sensitive to heat due to lack of perfusion or because they exist normally at lower temperatures than body temperature. The lens of the eyes of anaesthetized rabbits exposed for over 2 hours at 41 to 44°C developed lens opacities or cataracts (182–186). The corresponding SAR was about 100 W/kg. In a work on unanaesthetized rabbit that were irradiated by 2.45 GHz CW microwave for 160–240 min with a SAR of 26.5 W/kg, the corneal surface temperature increment was 3.0°C for 15 min. This resulted in conjunctiva edema which disappeared within a week after exposure (183).

The testes are normally cooled several degrees C below body temperature by thermal isolation and through perspirant radiant cooling. Elevated temperatures adversely affect male germ cells undergoing meiosis. Male germ cells were depleted in the testes of anaesthetized mice and rats exposed to 30 W/kg (187) and 8–10 W/kg (188), respectively. However, if not anaesthetized, conscious mice acutely exposed to 20 W/kg (189) and conscious rats exposed up to 9 W/kg (190) had no changes in testicular function. Chronic exposure of male rats to 5.6 W/kg (191), producing a testicular temperature of 37.5°C for a total of 80 hours over a 4 week period, resulted in transient infertility.

Maternal heating is known to cause abnormalities in embryo and fetal development (192, 193). Raising maternal rat temperature to 43°C with 11 W/kg exposure was sufficient to induce embryo and fetal death, and/or developmental abnormalities (194–196). Chronic exposure of maternal rats to 6–7 W/kg producing 39–41°C during pregnancy induced growth retardation and subtle behavioral changes in the offspring (197, 198). However, the transient exposures of humans to RF power levels that do not increase the maternal temperature above 39°C are not likely to adversely affect the human embryo or fetus. More studies with animals would be required in this area.

Cellular Effect

In vitro exposure to a 147 MHz carrier wave has been shown to result in the enhancement of the calcium ion efflux from brain tissues (199, 200). Cultured neuroblastoma cells exposed for 30 min to a 145 MHz carrier amplitude modulated at 16 Hz were reported to have enhanced calcium ion efflux and acetylcholine esterase activity (201). In erythrocyte based cation permeability studies, RF radiation was found to select the plasma membrane as the interaction site. Exposure to RF radiation at 1 kHz, 2450 MHz, and 8.3 GHz frequencies appears to alter the membrane transport of K⁺, Rb⁺, and Na⁺ in the plasma membrane of the erythrocytes (202). Frequency and electric field effects on the membrane K⁺/Na⁺ ATPase are thought to be the cause of altered K⁺ transport in erythrocytes. At 100 MHz, a field strength of 400 V/m was required to induce hemolysis in erythrocytes in blood suspension (203). In order to achieve the same effect, a field strength of at least 900 V/m was required when using 10 MHz radiation. This importantly points
to a varying tolerance to RF power as a function of frequency.

RF heating may also have implications in DNA replication and transcription. The rate of electron flow within the stacked bases of DNA is estimated at $10^6$ s$^{-1}$ (204). Considering the charge of an electron and the cross-sectional area of a DNA molecule (2 nm diameter), a current density of 50,000 A/m$^2$ is flowing through the molecule under normal circumstances. It is reasonable to assume that currents of this magnitude are required to disrupt transcription at an electronic level. Considering the small magnitudes of the electric field components of the RF excitation used in MR systems (maximum 1 mV/m), the high resistivity of human tissues (up to $10^5$ Ωm), and the improbability of local eddy currents over an extremely small area, it is unlike that the requirements for the establishment of a transient current of this magnitude can be established.

Cell culture study evidence suggests that RF exposure does not cause an increase in mutation or chromosome aberration frequency in male germ cells when normal temperatures are maintained (191, 205, 206). Human lymphocytes acutely exposed in-vitro to up to 200 W/kg showed no effect on sister chromatid exchange rates (207). The lack of evidence for a mutagenic effect of RF exposure suggests that within the MRI context RF is unlikely to be carcinogenic.

In addition to the evidence of the non-thermal cellular effect of RF radiation it is clear that the frequency, field intensity, and duration of exposure play an important role in determination of the extent of the interaction. This suggests the need to study these interactions on a more general basis than simple tissue heating.

**Thermal Effects**

The human thermoregulatory response to RF exposure in MRI has been extensively studied. It has been calculated that a patient, with normal thermoregulatory ability, lightly clothed, in a normal comfortable indoor temperature and humidity, when exposed to 4 W/kg of RF energy would experience a rise in body temperature of up to 0.6°C at 63 MHz (208). These calculations are fairly well supported by studies of the thermoregulatory response of normal volunteers and patients exposed to an SAR of 4.0 W/kg. However, the magnitude of the temperature rise is generally smaller than the predicted 0.6°C. When examining the thermoregulatory response, perspiration becomes an important cooling mechanism. This mechanism requires increased blood flow to the skin. However, the associated surface vasodilation often requires increase in cardiac output. In accordance with this observation, heart rates were reported to increase by three beats per minute in volunteers exposed to 0.8 W/kg for 17 min with minimal effect on blood pressure at 63 MHz (209). A study of 50 volunteers exposed to 0.4–1.2 W/kg demonstrated an average body temperature rise of 0.2°C, with average heart rate and blood pressure remaining unaffected (210).

In other studies at 63 MHz (211, 212), the average increase in body temperature of volunteers exposed to 4.0 W/kg for 20 min was 0.3°C, with heart rate minimally affected. A high whole-body-averaged SAR, 6.0 W/kg at 63 MHz, applied to evaluate the physiologic responses of six volunteers to a MR procedure resulted in no deleterious effects to the subjects (213). This conclusion was reached as a result of major vital sign monitoring, i.e., tympanic membrane temperature, skin temperature at seven sites, heart rate, blood pressure, oxygen saturation, and cutaneous blood flow, for 16 min during, and immediately after the MR scan.

Even though homogeneous RF fields are often desirable for uniform imaging, transmitting surface coils and other specialty coils can often produce non-uniform RF fields. As such, localized heating, in contrast to core body temperature changes, has also been studied. With surface coils and specialty coils exposure to RF is often maximal in the skin and superficial tissues (213, 214). However, since perspiration and perfusion are important cooling mechanisms for the skin, maximum temperatures will not necessarily be on the surface of the patient (215). Calculations suggest that the temperature of the vitreous humor of the eye is unlikely to rise by more than 1.6°C during 1-hour exposure of the head to 3.2 W/kg at 63 MHz (216). In calorimetric experiments, where eight volunteers immersed their hands and wrists in warm water (equivalent to the heat from 20 W/kg exposure), the local temperature induced was not in excess of 40°C (217).

Scientists have also proposed that as the frequency of the irradiation approaches the so called “resonance frequency” (corresponding to a wavelength that is nearly 2.5 times the long axis of the body) that higher SARs are usually observed. There have been many (218, 219) observations of the difference between the heating efficiency near this theoretical resonant frequency compared with...
SAR Computational Techniques. In magnetic resonance, the extent to which RF power can lead to heating has been analyzed only classically using approaches based on Maxwell’s equations. While such approaches can provide initial insight, it should be remembered that they remain classical in nature and ignore the quantized nature of heat transfer. In order to calculate the absorbed power by a biological sample using classical methods, one needs an accurate representation of the E-field distribution. Classically the SAR, or specific absorption rate, is given by

\[ \text{SAR} = \frac{\sigma |E|^2}{2\rho} \]  

where \( \sigma \) is the tissue conductivity, \( \rho \) is the tissue density, and \( E \) is the electric field within the tissue. The magnitudes of \( E \) and \( B \) are solutions to Maxwell’s equations that are made of four coupled partial differential equations. Only two of these equations

\[ -\frac{\partial B}{\partial t} = \nabla \times E \]  

\[ -\mu \frac{\partial H}{\partial t} = \nabla \times E \]  

\[ \varepsilon \frac{\partial E}{\partial t} + \sigma E = \nabla \times H \]

are sufficient to uniquely define \( H \) (here \( B \)-field of the coil), the magnetic field, and \( E \), the electric field, assuming that conservation of charge is maintained. An analytical solution to the Maxwell equation for sources with the complexity of the MRI coils and for human head as the object of interest are impractical to obtain. This will leave only computational methods as the technique of choice for solutions in these situations. Various techniques have been used in the past for this purpose. Among them, the finite element method (FEM), the method of moments (MoM), the finite difference in time domain (FDTD), and the finite difference in frequency domain (FD) are among the most widely used. The FDTD has recently produced the most realistic results \((220–223)\) among all the numerical analysis techniques. In this technique the time dependent Maxwell equations are adopted for a lattice of cubic cells. The solutions of \( E \) and \( B \) are sought within the cells by modeling the propagation of an electromagnetic wave into a volume containing material with specific dielectric properties as defined by the sample. This is done by repeatedly solving for a finite-difference analogue of the Maxwell’s equation within each cell of the lattice. By arriving at a steady state behavior for the \( E \) and \( B \) fields within each cell as a result of the tracking of an incident wave and its interaction with the medium which could include current induction, dispersion, penetration, and diffraction, FDTD presents a numerical solution to Maxwell’s equation.

It has been claimed that results of the FDTD computations agree with the experimental findings within \( \pm 1 \text{ dB} \) \((220)\). Such analysis provides the energy deposition within the object which once normalized for the object mass will give the specific absorption rate (SAR) as is widely used for medical applications. In addition to the SAR calculations one needs to compute the thermal redistribution in order to present a complete picture of the thermal effect of the interaction of the EM fields with biological tissues. This step, however, will be common to all heat transfer problems. As a result, only the SAR calculations and their prediction of the energy deposition into the human body during MRI scans will be reviewed.

From a classical approach, the SAR calculations depend on the geometry as well as electromagnetic characteristics of the source, here the RF coil. In addition, the structural characteristics of the object as related to the source, such as distance from the source and orientation with respect to different polarization axis, will strongly influence the outcome. In MRI, the object is exclusively within the near field of the source. This places more demand on the computational method as compared to the far-field solutions where relatively simple plane waves could be used to decrease the required computational power. Since FDTD was first proposed \((224)\) it has demonstrated an efficiency in computer memory usage that has made it attractive for complex lossy media such as the human body. Accordingly, it has been used for various applications such as hyperthermia for cancer treatments and SAR calculations for the cellular phone industry. Whole-body averaged SARs calculations from an FDTD approach in a 5628 cell anatomically based model of the human body exposed to a plane wave from 20 to 100 MHz, have resulted in a maximum SAR in the 50 to 60 MHz range \((225)\).

SAR and \( B_1 \)-field calculations for the bird caged coil have produced results for frequencies up to
Figure 12  Computational analysis of specific absorption rates (SAR) distribution for an axial slice obtained from the human head using a finite difference time domain (FDTD) model. In this case, the SAR profile was obtained by modeling the head in the presence of an eight struts transverse electromagnetic (TEM) resonator at 362.5 MHz using four-port excitation. The head model has a resolution of $3 \times 3 \times 3$ mm$^3$.

400 MHz ($221\text{--}223$). It has been advanced ($221$) that SARs at 128 and 256 MHz are increased by a factor of 5 and 10, respectively, compared to 63 MHz for linearly driven birdcage coils. Also, the quadrature drive has an advantage over the linear drive by a factor of 2 for average SAR and a factor of 3 for maximum SAR ($221$). Unfortunately, the value of these calculations is limited since they do not account for the interaction between the RF coil and the human head ($221$). In addition, such calculations remain classical in nature.

In Fig. 12, results of the SAR calculated for a head model ($222$) loading a transverse electromagnetic (TEM) resonator using an integrated coil and subject is shown. Integration of the coil and subject allows a realistic modeling of the interaction of the coil and subject and gives a more accurate representation of the SARs for MRI settings ($222$). The coupling of the coil with the sample will play an important role in the determination of the $B_1$ field distribution. The cases of the strong coupling of the single drive have demonstrated high SAR values ($222$). The high SAR values are mostly concentrated around the regions where drivers are located. Increasing the number of drivers has been found ($222$) to be a way of reducing the SARs. This is the result of a more homogeneous $B_1$ distribution. As such, selection of drive mechanisms and considerations of the coil designs with coil–subject coupling as a parameter for uniform distribution of the field will help to minimize the formation of hot spots and in lowering unnecessary RF power deposition within the body.

**Cardiovascular and Respiratory Stimulation**

As has been shown above, there are distinct whole-body average and local temperature increases as a result of exposure to RF energy. This determines the primary animal physiologic thermoregulatory responses. Classically, the frequency of the wave is a decisive factor in determining the extent of the temperature increase. At low frequencies, it is known that the body is transparent to the magnetic component of the electromagnetic field. As the frequency increases, it has been proposed that the body’s long axis length will near the half wavelength. This could act to strengthen the coupling between the wave and the irradiated body. There may be higher whole-body energy deposition for strongly coupled electromagnetic waves of this wavelength region to the irradiated body. This aspect of the interaction of the electromagnetic microwaves with human body has been previously analyzed ($226, 227$). This so called resonant condition needs to be reexamined in the context of magnetic resonance however, where real changes in internal body temperature can be mapped with diffusion based methods. Much of this work therefore needs to be questioned and reevaluated. Nonetheless, sub-resonant body heating effects have been hypothesized in the rat ($228$). In this regard, it has been stated that the rat displays increased peripheral body heating at 350 MHz with an average power density of 38 mW/m$^2$ and average whole-body SAR of 13.2 W/kg compared to 700 MHz (resonant) exposure. This phenomenon has not been broadly confirmed and requires more understanding.

During a 1°C colonic temperature increase, a significant heart rate and mean arterial blood pressure elevations were reported. There has been no report of considerable change in the respiratory rate. Through a series of measurements from 700 MHz to several GHz (at power levels sufficient for 1°C colonic temperature increase) certain irradiation frequencies were found to correspond to more efficient peripheral heating ($229\text{--}232$). In these studies, it was observed that
stimulation of the cutaneous thermoreceptors produced an increase in heart rate. Deep heating of the internal organs is hypothesized to be caused by frequencies much lower than whole-body resonance frequency (at sub-resonant frequency) (233). Once again such a hypothesis needs to be reexamined. This is especially true in light of the fact that indications of limits to RF penetration have not yet been observed for the human head, despite the fact that we are now in the ultra high frequency (340 MHz) range.

It is interesting that while rats respond when exposed to 0.5 mW/cm² at 2450 MHz (234) there is an absence of measurable response in insects at 100 mW/cm². Nonetheless, while rats and insects display pronounced differences in response, there remains a great deal of value in relating tests in animals to humans. At the same time, it is clear that complementary in-vivo measurements in humans provide important data for a more comprehensive analysis.

At fields above 6 T, MRI systems are operating in EM terms within the near field, i.e., within a distance of 2D²/λ or about 40 cm from the coil. In this region, all EM waves behave within the near field constraints. Classical EM field theory predicts that the field coupling with the sample depends on the source size and geometry when operating in near field. It has been shown that currents induced by RF magnetic fields are the dominant contributor to SAR in close proximity of resonant RF current sources (235). However, an improvement in the present understanding of the interaction of RF energy with biological tissue is needed. There have been recent experimental measurements that have disputed our past understanding of the physical properties of biological systems.

Higher conductivity and dielectric constants are observed for bones (236). High SARs, up to 100 W/kg, are used in cancer hyperthermia (237). This suggests that SAR dosimetry studies, such as brain SAR data, based on the computer tissue modeling, could have overlooked mechanisms such as source–object interaction and used dielectric properties for the modeling tissue that is not an accurate in-vivo representation of the human body. The role of the quantized nature of heat transfer has also been ignored.

The thermal load produced by RF excitation requires cardiac accommodation. The maximum skin blood flow rate in a 63 kg person is 150 mL/100 g/min (238). This blood flow to the body surface could dissipate 1296 W for a skin temperature 4 degrees below the core temperature (239). This corresponds to 20.6 W/kg of power during maximum blood flow. Calculation of the cardiovascular stress for exposure of 4 W/kg required only about 5% elevation in cardiac output (238). Experimental measurements on humans exposed to 4 W/kg SARs for 20 min showed that the heart rate increased by 5.7% (240).

IEC Safety Standards (166) recommend that for an SAR above 2.0 W/kg, the scanner should provide indications that the subject should have normal thermoregulatory capabilities, i.e., the ability to cool through perspiration evaporation. Above 4.0 W/kg averaged over the whole body, the device should alert the operator that the device is in an investigational mode, if it is imaging the head or body. Peripheral exposure level is two to three times the body level depending on location. Current commercial equipment has FDA 510(k) clearance to operate at 4.0 W/kg averaged over the whole-body weight.

CONCLUSION

Perhaps the most innocuous component of the MRI exam is the magnetic field strength. Studies of more than 100 million individuals worldwide at 1.5 T have revealed no unavoidable effects from static magnetic field exposure at this level. The same can also be said for the thousands of subjects that have now been studied at fields of 3 and 4 tesla. Our initial studies in both animal and human subjects (57) demonstrated no demonstrable cardiac, physiological, or cognitive effects from exposure to the field strength of 8 T. Interestingly, man has only been exposed to magnetic fields of 1 to 8 T in whole-body systems for two decades. Nonetheless, in light of these discussions, it appears that long term effects to human health from exposure to strong magnetic fields are unlikely. In addition, now that magnetic resonance has been in existence for over one generation, it is being viewed as a standard medical diagnostic modality. This popular familiarity should help reduce that anxiety associated with MRI exams. Importantly, more than an entire scientific generation has now completed nearly a half a century of work with strong magnets. Still, no scientific evidence has been identified that points to long term health effects. As a result, it appears that MRI at fields much above 4 T will share the same primary safety concerns that exist...
at lower fields, namely RF power deposition and pulsed field gradients.

It is clear that RF power deposition presents the greatest risk for patient injury in MRI. All scientists and regulators agree that a core body temperature increase of 1°C in a healthy individual with normal thermoregulatory capability is absolutely free of risk. This increase in temperature can be reached with a constant specific absorption rate (SAR) of RF energy of 4 W/kg averaged over the body weight. In addition, since higher RF energy may be required, FDA procedures and IEC Standards provide sound guidelines for safe exposures. An SAR of 8 W/kg or higher could be utilized as necessary at high magnetic field strength to acquire data, but for short enough exposures to produce a no more than 1°C core body temperature increase. In terms of simple safety provisions, it would be desirable that every clinical MR system be equipped with fail safe sensing which could shut off the power to the RF source when necessary. This may become even more important with the proliferation of systems operating in excess of 1.5 tesla.

The second most significant risk in magnetic resonance imaging arises from the use of pulsed field gradients. Excessive slew rates and elevated gradient strengths can cause peripheral stimulation that can be painful, although not harmful, to the subject. The duration and shape of the gradient pulse can significantly alter this response. Importantly, peripheral stimulation occurs in the 50–100 T/s range, well below the level required for potentially dangerous cardiac stimulation.

In summary, due to the thermogenic effects of electromagnetic fields, RF energy is the primary biological hazard of magnetic resonance. It is capable of depositing an unsafe amount of energy into the human body. Unlike the static magnetic field, the parameters controlling the RF pulse could deviate from the intended value in at least two ways, hardware and software. Appreciation of the multiple opportunities for deposition of excessive RF energy into the subject has resulted in a flurry of activities in achieving a better assessment of the mechanism of interaction of RF energy with the biological tissues. While still classical in nature, our models of human organ or whole human power deposition are being refined and much work is still needed in this area. High magnetic field systems are slowly flourishing and their growth and safe use speaks loudly for the safety of lower field systems. In this regard, it is important to note that the very high field systems operating at 4 tesla have completed a decade of operation with no unavoidable safety incidents inherent to MR.

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Allahyar Kangarlu received his undergraduate education in Physics at the Arya Mehr University in Tehran, Iran and completed his Ph.D. degree in Physics at the University of Missouri at Columbia in 1987. Upon graduation, he accepted a position as an Assistant Professor of Physics at the University of Dayton, where he established a laboratory for spectroscopic studies under high pressure. He joined the Department of Radiology at The Ohio State University in December 1995. He has been involved with the design and assembly of the 8 Tesla human magnetic resonance imaging (MRI) scanner since its inception. In addition, he has taken the lead in all the human safety aspects of this project. He has consequently conducted an exhaustive review of the safety literature over the past 4 years. This work is in large part a compilation of these efforts. Furthermore, for nearly 15 years, he has worked on the interaction of a wide range of electromagnetic radiation with matter. He is presently using that experience in developing diffusion/perfusion imaging at high fields for application to multiple sclerosis, cancer, and stroke.

Pierre-Marie L. Robitaille received his M.S. degree in Biochemistry from Iowa State University at Ames in 1984. He received his Ph.D. degree in 1986 from the same institution, completing a double major in Inorganic Chemistry and Zoology. Prior to becoming an Assistant Professor at The Ohio State University and the Director of Magnetic Resonance Research in 1989, he undertook 3 years of postdoctoral training in biophysics at the University of Minnesota, Minneapolis. He was responsible for the conception and implementation of the 8 Tesla MRI project at OSU, guiding the engineering, experimental, and theoretical aspects of the project. He is currently a Professor and is a member of the biophysics, chemical physics, and biomedical engineering programs at OSU. He holds academic appointments in molecular and cellular biochemistry and radiology. Dr. Robitaille is a member of the International Society of Magnetic Resonance in Medicine and a life member of the American Physical Society.