MAGNETIC RESONANCE IMAGING AND ASSOCIATED ALTERATION IN SOME BIOPHYSICAL PROPERTIES OF BLOOD

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Abstract. The safety aspects of the magnetic resonance imaging (MRI) requires an understanding of the interactions between the electric and magnetic fields generated by such instruments and the human body. Knowledge of MRI safety cannot only guide radiofrequency coil and pulse sequence design but also can affect sequence selections, thereby ensuring safe and efficient system operation. 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. Such an effect was evaluated for 25 patients subjected to MRI through measurements of some biophysical properties of erythrocytes. Results showed that there is a significant decrease ($p < 0.05$) in RBC membrane permeability, cellular membrane elasticity and erythrocytes sedimentation rate (ESR) during MRI, but post MRI there are not significant changes ($p > 0.05$). Scanning electron microscope (SEM) was used to follow the morphological modification of erythrocytes during MRI. It is concluded that a relatively large force (high magnet and RF) causes the membrane to undergo a continuous deformation. Removal of the force results in the cessation of deformation of the RBC membrane (reversible changes). These results confirm the safety of MRI.

Key words: erythrocytes, biophysical properties, MRI, SEM.

INTRODUCTION

Thresholds for physiological effects and for biohazards have been recognized since the late 1970s [3]. Early clinical nuclear magnetic resonance (NMR) imaging symposia and textbooks [16, 18] in the 1980s discussed the biological effects of NMR and proposed initial clinical operating guidelines. Recent efforts have led to a more detailed analysis of the practical health effects and safety issues and the definition of operating guidelines for magnetic resonance imaging (MRI) [11].

MRI has emerged as a leading diagnostic technique in clinical settings because it is non-destructive and yields a true volume rendering of the subject. An MR image is created by imposing one or more orthogonal magnetic field

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gradients upon specimen while exciting nuclear spins with radio frequency (RF) pulses, similar to a typical NMR experiment. After collection of data with a variety of gradient fields, de-convolution yields a one, two, or three-dimensional image of the specimen. Typically, the image is formed on the basis of the NMR signal from the protons of water, where the signal intensity in a given volume element is a function of the water concentration and relaxation times. Local variations in these three parameters provide the vivid contrast observed in MR images.

Modern imaging techniques require strong gradient fields to be switched rapidly for good resolution as explained by Schmitt *et al.* [20]. This places a patient within fields that can be considered extreme when compared to ordinary human environments. The interaction of these fields with biological tissue has thus been of great interest to the medical community in determining possible health risks associated with the use of MRI scanners.

Instrumentation for MRI studies consists of subsystems that generate electromagnetic fields with vastly different characteristics. The main subsystems involved in MRI safety are: the whole body superconducting magnet, the shielded gradient systems and the radiofrequency (RF) transmit and receive coils. Table 1 shows the principal mechanisms of interaction of the three magnetic resonance imaging energy fields with tissue.

Table 1

Principal mechanisms of interaction of the three magnetic resonance imaging energy fields with tissue

Magnetic resonance imaging energy field	Mechanism of interaction
Static magnetic field	Polarization
Transient magnetic field	Induced current
RF field	Thermal heating

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 have an increased potential to interact with the human body.

There are over 5000 human magnetic resonance imaging and spectroscopy systems in existence worldwide. These instruments have field strengths ranging from 0.1 to 1 tesla ($N\cdot m^{-1}\cdot A^{-1}$). In addition, there are now nearly thirty systems operating between 3 and 4 tesla [1]. 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 [17]. 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 principle biological effects of magnetic field [4] 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.

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. Studies in both animal and human subjects [12] demonstrated no demonstrable cardiac, physiological, or cognitive effects from exposure to the field strength of 8 T.

Clearly there is a need for additional studies to support the belief that extended exposure to magnetic fields during interventional MRI and related activities is not harmful. Therefore, the aim of the present study was to define whether there was a measurable alteration in some biophysical properties of human blood due to magnetic field exposure.

Blood rheological properties, RBC morphology and membrane properties were studied to determine if there was a measurable effect resulting from exposure to magnetic field strengths that might present a potential health risk to human subjects.

MATERIALS

The present study was conducted at the Kaser Al-Eine Hospital after the approval of the Nuclear Magnetic Resonance Department (Faculty of Medicine, Cairo University) and the Local Ethics and Research Committee. Written informed consent was obtained from each patient included in this study. All patients had normal hepatic and renal functions.

The biophysical properties of erythrocytes for twenty five subjects subjected to MRI, 19 males and six females, between the ages of 24 and 53 years (mean 35 years) were studied at different time intervals. Subjects were excluded based on routine safety standards [22] and the following criteria: subjects who suspected they may be or might have become pregnant; subjects with cardiac or known circulatory impairment and subjects with diabetes mellitus, heart disease, pulmonary disease or autonomic disorders. Subjects were asked to remove all metallic objects or clothing having any metallic components. Venous blood samples were obtained from internal jugular vein using heparinized plastic syringes at the following intervals: Pre-, during- (after 5, 10 and 18 minutes) and after MRI period.

ERYTHROCYTE MEMBRANE PROPERTIES

RBC membrane properties were estimated using the osmotic fragility test [5]. In the differential osmotic fragility curves, C% is the NaCl concentration at which hemolysis starts to occur. This value indicates the relative permeability of RBC membrane. Also, the width at half maximum (W_{hmax}) of the differential curves is observed to estimate the relative elastic limit of the RBC membrane.

Erythrocyte sedimentation rate (ESR) was measured using Westergreen's method [5].

SCANNING ELECTRON MICROSCOPY

The morphology of RBC was studied using the scanning electron microscope (SEM) according to Kaul *et al.* [13] as follows:

Blood samples were collected into 50 μ/ml heparin, stored at 4ºC and protected from light. Erythrocytes were separated from plasma and buffy coats by centrifugation at 600×g for 10 min at 4ºC and washed three times with: ice cold 5 m mol/l sodium phosphates, 145 mmol/l NaCl (pH 7.4) and post fixation in osmium tetroxide 1% respectively. Blood aliquot was fixed with 2.5% glutaraldehyde immediately after collection.

For observation, the erythrocyte samples were diluted in a solution of ethanol and propylene oxide (1:1, v/v), a drop was deposited directly onto the microscope support, air dried, coated with gold (by sputtering) and examined in SEM, Model Philips XL30 with accelerating voltage 30 kV, magnification of 10× up to 400.000× and resolution for w (3.5 nm).

To evaluate the erythrocyte shape changes quantitatively, stages of morphological alterations were estimated (as percentages) on electron micrographs as shown in classification of Hsu *et al*. [10], as echinocytes 1, echinocytes 2, echinocytes 3 and spheroechinocytes. The spiculated RBC with short, equally spaced projections over entire surface, are progressing from the "crenated disc" (echinocyte I) to the crenated sphere (echinocyte IV) with nearly complete loss of spicules.

The morphological index was calculated according to Fujii *et al*. [6] as follows:

Morphological index = Σ(morphological score) × [(number of distorted cells)/(total cell number)]

where, morphological scores of +1, +2, +3 and +4 correspond to each shape stage referred to above, respectively, the discocytes score was considered as 0. Approximately 500 cells were counted, distributed in five randomly selected fields.

RESULTS AND DISCUSSION

In the present study, there is non significant change in the preoperative characteristics for the patients.

Blood is known to be non-Newtonian fluid with non-linear stress – strain rate relationship [14]. As the RBC constitutes more than 99% of the particulate matter in the blood, they govern the flow properties of blood. The rheological properties of RBC play a significant role in determining the fluidity of blood [2].

The two special features of RBC that underlie the non-Newtonian rheological behavior are cellular deformability and aggregation. Deformability is the ability of the entire cell to adopt new reversible shape in response to deforming force [9].

Assessments of the osmotic fragility, defined as the sensitivity of RBC to the osmotic shock, are widely used to elucidate mechanisms of ionic and molecular transport across the plasma membrane and for diagnosis of certain hematological diseases [5]. As shown in table 2 there is a significant decrease ($p < 0.05$) in RBC membrane permeability (C% values) and cellular membrane elasticity (W_{hmax} value) during MRI, but post MRI there are non significant changes ($p > 0.05$).

Tvedten and Weiss [25] showed that anything that disrupts the interaction of the proteins within the lipid bilayer of the membrane, or the surface area to intracellular volume ratio will lead to decreased deformability and increased osmotic fragility of the cell.

Table 2

Parameters of the differential osmotic fragility curves for RBCs of the studied group

Variable	Pre MRI	During MRI (after 5 min)	During MRI (after 10min)	During MRI (after 18 min)	Post MRI (after 30 min)
C%	73 ± 2.53	60 ± 1.3	53 ± 1.3	45.5 ± 2.3	*67 ± 2.3
	72 ± 2.3	46 ± 2.3	36 ± 2.3	32 ± 2.3	*66 ± 2.3
$W_{hmax.}$	15 ± 2.19	12 ± 2.6	11 ± 1.6	10 ± 1.23	*14 ± 1.5
	15.5 ± 2.19	8 ± 2.6	6 ± 1.6	6 ± 1.23	*13 ± 1.5

* Non significant change ($p > 0.05$).

As presented in Table 3, there is a significant decrease ($p < 0.05$) in erythrocyte sedimentation rate (ESR) during MRI, but post MRI there are non significant changes ($p > 0.05$).The decrease in ESR is due to RBC aggregation, which is preferentially among more deformable cells [24]. The aggregation of RBC may produce reduction in microcirculation of blood flow and tissue perfusion [22].

When an electrically conducting fluid, such as blood, flows in an applied magnetic field a transverse electromotive force (EMF) is developed. This leads to a small induced current density in the tissues, which in turn leads to a small electric voltage on the body surface which may affect the erythrocyte morphology.

Table 3

ESR results for RBCs of the studied group

Variable	Pre MRI	During MRI (after 5 min)	During MRI (after 10min)	During MRI (after 18 min)	Post MRI (after 30 min)
ESR (mm) First hour	12 ± 0.44	7 ± 0.29	6 ± 0.45	5 ± 0.23	*10 ± 0.2
	10 ± 0.44	2 ± 0.29	2 ± 0.45	3 ± 0.23	*10 ± 0.55
ESR (mm) Second hour	24 ± 0.9	14 ± 0.74	12 ± 0.23	10 ± 0.25	*20 ± 0.5
	20 ± 0.9	4 ± 0.74	4 ± 0.5	6 ± 0.65	*20 ± 0.65

* Non significant change ($p > 0.05$)

Scanning electron microscope (SEM) was used to follow the morphological modification of erythrocytes during MRI. Figs. 1 and 2 show SEM micrographs of erythrocytes during MRI (after 18 minutes) and post MRI (after 30 minutes) respectively. Table 4 summarizes all data describing erythrocyte morphology. The red cell shape is encoded in the mechanical properties of the membrane; plasma membrane contributes bending and rigidity while the protein based membrane skeleton contributes stretch and shear elasticity [15]. Therefore the membrane mechanics can reproduce in detail the full stomatocyte- discocyte- echinocyte sequence [21].

Echinocytes are morphologically altered red blood cells that appear to have numerous, fine, uniform spicules throughout the cell membrane [7]. Some hematologists hypothesize that echinocyte formation is an anti-hemolytic tactic with an increase in plasma membrane surface area relative to cellular volume [27].

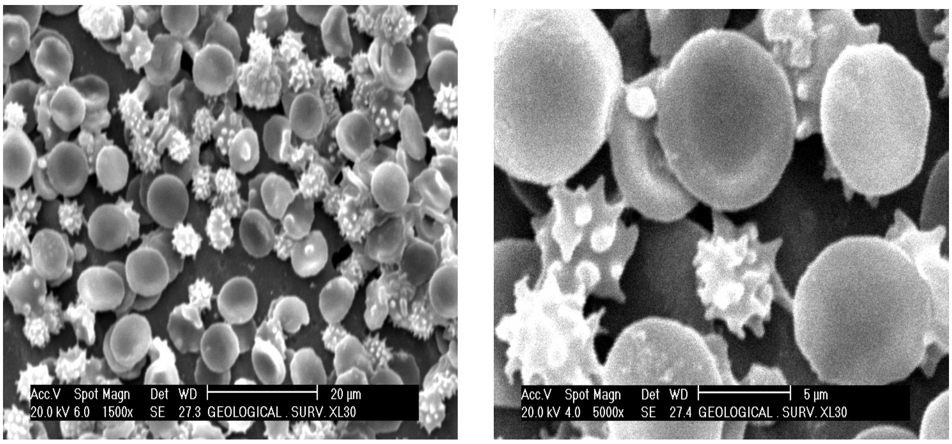
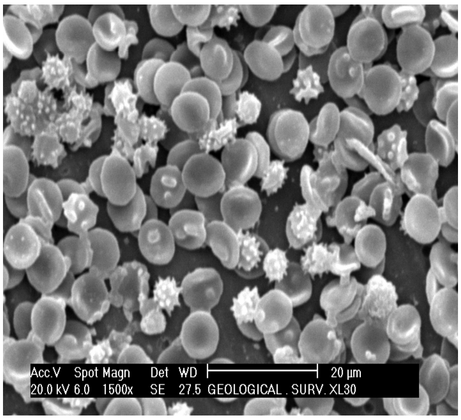


Fig. 1. Scanning electron micrographs of erythrocytes after 18 minutes during the MRI period.



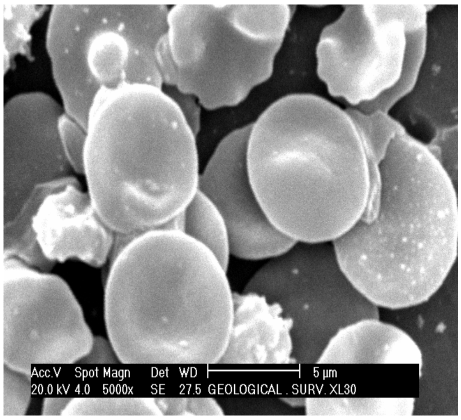


Fig. 2. Scanning electron micrographs of erythrocytes after 30 minutes post MRI period.

Table 4

Morphological shapes (%) and index values of erythrocyte (during and post MRI). All their statistical values (using Student's t-test) are significant ($p < 0.05$). M±SD calculated in 500 red blood cells distributed in 5 fields ($n = 500$)

RBC Morphology	0	I	II	III	IV	Morphological index
During MRI (after 18 min)	50 ± 1	12 ± 2	13 ± 1	9 ± 2	16 ± 3	1.29 ± 0.52
Post MRI (after 30 min)	48 ± 3	7 ± 2	6 ± 1	10 ± 3	29 ± 1	1.58 ± 0.72

Type I echinocytes (echinodiscocytes) are described as irregularly shaped erythrocytes without defined spicules. Type II echinocytes have cellular projections that vary in length; however, these erythrocytes maintain a disc-shaped appearance. Type III echinocytes are more spherical erythrocytes with high speculation. Spherocytes are spherical small erythrocytes (they have approximately two-thirds the diameter of normal RBC) with blunted spicules. Moreover, they have a decreased surface area to volume ratio in comparison to normal erythrocytes [26].

During MRI, large number of RBC affected by the magnetic field (stress) that converts its shape from the normal discoid biconcave to spherical shape (spherocytes). As shown in Figs. 2 and 3 the morphological alteration is great ($p < 0.01$) and also the morphological index is high (Table 4) during than post MRI. The presence of iron atoms in hemoglobin makes the red blood cells slightly less diamagnetic than plasma; as a result, RBCs have a tendency to move relative to the plasma toward regions of strong magnetic fields. This may give a second reason for the formation of echinocytes.

All the above changes may also be explained according to the solid and liquid behavior of the erythrocyte membrane [8]. A relatively large force (high magnet and RF) causes the membrane to undergo a continuous deformation. Removal of the force results in the cessation of deformation of the RBC membrane.

This is in agreement with Schenck [19] who showed that in the absence of ferromagnetic foreign bodies, there is no health hazard associated with magnetic field exposure and no evidence for hazards associated with cumulative exposure to these fields. The absence of direct harmful effects of strong static magnetic fields on human health can be attributed to the absence of ferromagnetic components in human tissues and to the extremely small value for the magnetic susceptibility of these tissues.

CONCLUSION

The interaction between RBC and MRI apparatus is very complex and involves several stress sources. This results in alteration in blood rheological properties, RBC morphology and membrane properties. The significance changes of these properties during the MRI period followed by non significance changes at the end of MRI period revealed that these changes are transient ones and confirm the safety of MRI. Also, this study explores the advantages of biophysical methods for evaluation of the changes which occur in erythrocytes during MRI period. However, there is a need for additional studies to support the belief that extended exposure to magnetic fields during interventional MRI and related activities is not harmful. Although there is no evidence for a cumulative effect of magnetic field exposure on health, further studies of the exposed populations will be helpful in establishing rational guidelines for occupational exposure to magnetic fields.

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