Mutation Research 645 (2008) 39–43

Contents lists available at ScienceDirect

Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis

journal homepage: www.elsevier.com/locate/molmut
Community address: www.elsevier.com/locate/mutres

Is the genotoxic effect of magnetic resonance negligible? Low persistence of micronucleus frequency in lymphocytes of individuals after cardiac scan

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ARTICLE INFO

Article history:
Received 26 June 2008
Received in revised form 1 August 2008
Accepted 8 August 2008
Available online 30 August 2008

Keywords:
Genotoxic effect
Magnetic resonance
Micronuclei

ABSTRACT

Magnetic resonance imaging is a diagnostic technique widely used in medicine and showing a growing impact in cardiology. Biological effects associated to magnetic resonance electromagnetic fields have received far little attention, but it cannot be ruled out that these fields can alter DNA structure. The present study aimed at to identify possible DNA damage induced by magnetic resonance scan in humans.

Lymphocyte cultures from healthy subjects had been exposed into magnetic resonance device for different times and under different variable magnetic exposure in order to build dose-effect curves, using micronuclei induction as biological marker. Replicate cultures were also left for 24 h at room temperature before stimulation, to verify possible damage recovery.

Furthermore, micronuclei induction and recovery up to 120 h have been also evaluated in circulating lymphocytes of individuals after cardiac scan.

A dose-dependent increase of micronuclei frequency was observed in vitro. However after 24 h, the frequency returns to control value when the exposure is within diagnostic dosage. After in vivo scan, a significant increase in micronuclei is found till 24 h, after the frequencies slowly return to control value.

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1. Introduction

Recently, medicine has exploited advanced diagnostic technologies able to give detailed information about patients' anatomy and function, such as computed tomography, positron emission tomography, single photon emission tomography, and magnetic resonance imaging (MRI).

MRI is a diagnostic technique widely used in medicine and showing a growing impact in cardiology. During cardiac MRI patients experience some of the strongest and fastest switching electromagnetic gradient available in MRI implying the highest administration of energy accepted by the controlling authorities. The possibility that a biological risk could be associated with exposure to the electromagnetic fields (EMF) produced during a MRI scan raised concerns both for patients and medical staff.

A recent review of the literature on occupational exposure to static magnetic field (MF) used in MRI pinpointed the absence of any specific effects as a consequence of the exposure, while experimental studies on volunteers showed some acute effects such as vertigo, nausea, changes in blood pressure and reversible arrhythmia [1]. Also modest neurobehavioral effects have been reported in workers exposed to 1.5 Tesla MRI system [2]. Although a general agreement exists that long term effects to human health from exposure to strong MF are unlikely [3], nevertheless it is strongly suggested that new studies are necessary in order to fill the present gaps and to provide assurance that the new technological applications of MF (e.g. MRI) are really safe and will not cause any unwanted health side effects [4].

Special attention has also been paid to teratogenic effects, as MRI is considered an acceptable alternative to ionizing radiations for pregnant patients. Studies with animals in vivo [5–7] and in cell lines [8,9] gave contradictory results, and, again, far too few studies have been carried out to reach any firm conclusion.

Another major point of public awareness focused on the possible correlations between the exposure to the whole EMFs produced by electricity and cancer [10] including childhood leukaemia [11],

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doi:10.1016/j.mrfmmm.2008.08.011

although most papers reported absence of biological effects in humans/mammals [12].

To our knowledge, no data are available on genetic effects deriving from human exposure to electromagnetic field inside a clinical scanner. The present study aimed to identify possible DNA damage induced in human cells by a commercial MRI scanner and using the imaging procedures routinely adopted in standard cardiac MRI examination.

To assess DNA damage, the micronucleus (MN) test was carried out. MN represents a biomarker of somatic DNA damage reflecting genomic instability, whether inherent or acquired. The detection of MN in interphase cells, combined with the statistical power available from examining thousands cells, has made this test an accepted and widely used method to evaluate chromosome damage [13,14] and to assess cancer risk [15].

For this purpose, lymphocyte cultures from healthy subjects have been exposed to MRI for different periods and different variable magnetic fields in the radiofrequency domain in order to build dose-effect curves. After exposure, some vials were also left at room temperature for 24 h before stimulation, to verify the presence of possible damage recovery.

Furthermore, lymphocyte cultures were set up from individuals (both patients and volunteers) before and after cardiac MRI scan, and the extinction of the somatic damage up to 120 h was also evaluated.

2. Materials and methods

2.1. Participants

Peripheral lymphocyte samples from 8 healthy volunteers (5 females and 3 males, age 43 ± 16 years (mean ± S.D., range between 27 and 65) were used for in vitro treatment. A total of 8 participants (4 females and 4 males, age 43 ± 17 years, range 28–66), either patients and volunteers, were enrolled on a voluntary basis for MRI cardiac scan.

All participant were non-smokers and none of them was under therapies. Informed written consent was obtained from all participants. The study was authorised by the Clinical Physiology Internal Ethical Committee.

2.2. Cell culture

Peripheral blood was collected into heparinised tubes. Lymphocyte cultures were set up by mixing 0.5 ml of whole blood samples, with 4.5 ml of RPMI-1640 medium containing 15% foetal calf serum, antibiotics (5 UI/ml penicillin and 5 mg/ml streptomycin), and phytohaemagglutinin (PHA, 1.5% of the final culture medium) (all reagents from Gibco, Life Technologies, Italy) according to standard techniques [16].

The in vitro-treated lymphocytes were stimulated in PHA-containing fresh medium immediately after irradiation and after the flasks with the treated blood were kept 24 h at room temperature to allow possible recovery.

Control flasks were placed in the console room, next to the scanner one. To verify the extent of magnetic fields outside the device, but within the scanner room, duplicate flasks were left in the MRI device room for the whole time of treatment and named "room" control. We measured a static field of 1 Gauss in the position of this flask room control (about 3 m from the scanner bore entrance), while the radiofrequency and gradient fields can be considered negligible at this position.

For biomonitoring, lymphocytes from peripheral blood of exposed persons were collected and cultured immediately before (Control) and immediately after ($T = 0$ h) MRI scan and also after 24, 48, 72, 96, 120 h from the scan.

Duplicate cultures were incubated at 37 °C in a humidified atmosphere with 5% CO_2 and maintained for 72 h.

2.3. MN test

For the MN test, cytochalasin B (6 μg/ml, Sigma Chemical Co., St. Louis, MO) was added after 44 h of culture to block cytokinesis, allowing identifying lymphocytes dividing in culture. Cells that have undergone the first mitosis are thus recognised as binucleated cells and are selectively screened for the presence of MN [17]. Cell harvesting, hypotonic treatment, fixation and slide preparation were performed according to standard procedures [14,16]. MN were blindly scored in 1000 binucleated cells, following standard criteria [17], and frequency was expressed as the number of binucleated cells presenting one or more MN per 1000 cells. In order to check the status of the cell culture and cell division, the nuclear division index (NDI) was verified according to the formula (NDI = [(Mn + 2Bn + 3Trn + 4Ten)/(Mn + Bn + Trn + Ten)], where MN, BN, TRN, and TEN indicate the number of mono, bi, tri, and tetranucleated cells.

2.4. Exposure system and field characteristics

MRI technique employs three different electromagnetic fields: one strong static field, which aligns all the hydrogen atomic nuclei in the same direction, a radiofrequency field for the protons energisation and three gradient fields, whose amplitudes change both in spatial and temporal domains, useful for spatial localisation. For the image generation, temporal successions of radiofrequency and gradient pulses, namely "pulse sequences", are applied to the sample to be imaged [18].

A commercially available scanner (GE 1.5 T, CVi HD release, equipped with a maximum gradients strength of 50 mT/m, and a maximum gradients speed of 150 mT/m s^{-1}, General Electric, USA) was employed. Standard pulse sequences were utilised to generate images: gradient echo, steady state free precession, triple inversion recovery, FastSE, EPI derived perfusion sequences [19].

For in vitro treatment, four vials with whole blood from the same volunteer, diluted in medium without PHA, were exposed to an increasing number of pulse sequences (from Exposure 1 to Exposure 4).

For biomonitoring, participants were exposed to the pulse sequences routinely used in a standard cardiac examination. No contrast agents were used during the MRI examination.

2.5. Evaluation of the absorbed energy

The absorbed energy on our biological sample was calculated according to Bottomley algorithm [20] for specific absorption rate (SAR) estimation. For this purpose we modeled our flask like a cylinder (1.15 cm radius, 12 cm length) containing the same volume of the flask (30 ml). The sample conductivity was calculated using a method for liquid sample dielectric properties measurement [21].

The absorbed energy values corresponding to Exposure 1 to Exposure 4, were estimated as a sum of the SAR values for each sequence weighted by the relative sequence length, multiplied by the mass of the blood sample (0.03 kg).

Accordingly, the total energy absorbed by the human subject was evaluated as a sum of the SAR values for each sequence weighted by the relative sequence repetition time, multiplied by the human subject mass.

2.6. Temperature control

During the in vitro treatments the temperature was continuously monitored by means of a fiber optic temperature sensor (FOT-M/4M, FISO, Canada) inserted in a duplicate flask placed in the exposure area.

2.7. Statistical analysis

A general linear mixed (GLM) model approach was used to analyse the repeated measures data. In this model, MN was the response variable; the patient effects were fitted as random; dose was fitted as a fixed effect to describe the mean profile of the response variable over the time.

Patient age was included in the model (fixed effect) as categorical variable (age < 40 and age > 41 years). Dunnett's test was used to analyse differences between each time point and the baseline level. Paired Student's test was used to evaluate the statistical difference in the MN frequency between the control groups. Because the sample did not follow a Gaussian distribution, the raw data (micronuclei frequency) were subjected to square-root transformation prior to the analysis [22,23].

All data were presented in a form of mean ± standard deviation.

A difference at $p < 0.05$ was considered statistically significant. All statistical calculations were carried out using the Statgraphics Plus version 5.1 (Statistical Graphics Corporation, 2001, Rockville, USA) software package.

3. Results

Table 1 shows the energy absorbed by the blood samples during the different exposures, while Table 2 shows the energy absorbed by each volunteer participant. Although the range between Exposure 1 and Exposure 2 represents the routine procedures of MRI image acquisition, the different values of absorbed energy are due

Table 1
Energy absorbed by the in vitro-treated blood samples

	Energy (J)	t exposure (s)
Exposure 1	1.014×10^{-3}	686
Exposure 2	4.330×10^{-3}	1186
Exposure 3	8.738×10^{-3}	1618
Exposure 4	11.190×10^{-3}	2188

Table 2
Energy absorbed by human subjects

	Energy (J)
Subject 1	34.67
Subject 2	306.14
Subject 3	23.04
Subject 4	18.51
Subject 5	81.00
Subject 6	148.00
Subject 7	101.00
Subject 8	41.07

to one being a 100 ml flask containing 30 ml medium/blood and the other a whole human body.

3.1. In vitro treatment

Table 3 shows the MN induction in peripheral lymphocytes of 8 donors under four different exposure times/intensities, and at the two setting times of the cultures (0 and 24 h after treatment).

A dose-dependent increase of MN frequency was observed at $t = 0$ h. GLM statistical analysis showed that this increase is significant for each exposure ($p < 0.001$) also taking into account the donors age ($p < 0.001$). A doubling of MN frequency is evident at Exposure 3 with respect to the controls, and a further increase is present at Exposure 4 (mean 28.7 ± 4.9 versus 11.4 ± 4.2).

The temperature of the samples, which was influenced by the administered radio waves, by the temperature of the room and by the ventilator system of the scanner, resulted in a significant increase of $0.13 \pm 0.46\,^{\circ}C$ ($p < 0.001$) which however remained within the limits of biological effect.

To evaluate the possible effects of repair mechanisms on genomic damage, five replicate cultures (from participants 2, 3, 4, 6, 7), previously left at room temperature for 24 h, were also set up. The data show that, after 24 h, MN frequency returns to control value for the first two lowest exposures, suggesting that DNA damage can be completely recovered when repair mechanisms are allowed to work. On the contrary, the DNA damage was incompletely repaired in cells exposed to the two highest exposures: the MN induction remains statistically significant but at a very lower extent with respect to the equivalent cultures without recovery.

The NDI (Table 4) shows a significant decrease at the two highest exposures, at both times of culture, while the NDI of the first two exposures does not differ from the control value, with the 24 h values slightly higher, although not significant, than the 0 h ones.

The cytogenetic analysis of "room" control flasks to verify whether fields were also present and able to modulate the somatic damage in the MRI device room, showed no statistical difference although it is worth to note a weak increase in all the cases (data not shown).

3.2. Biomonitoring

As the results of in vitro-treated lymphocytes not necessarily reflect the in vivo response, MN frequency was also estimated in peripheral blood lymphocytes of subjects before and after a cardiac MRI scan. Table 5 shows the results, together with the demographic characteristic of the population studied. All the participants present a significant increase of MN frequency, in some cases more than a doubling. To evaluate the persistence of the genetic damage, cultures were set up from the same 8 participants 24, 48, 72, 96 and 120 h after the MRI scan. A significant increase in MN frequency is found also 24 h after MRI scan (Fig. 1).

Table 3
MN frequency after in vitro exposure to different times and intensities from MRI device

MN ‰										
Individual	Control		Exposure 1		Exposure 2		Exposure 3		Exposure 4	
	$t = 0$ h	$t = 24$ h	$t = 0$ h	$t = 24$ h	$t = 0$ h	$t = 24$ h	$t = 0$ h	$t = 24$ h	$t = 0$ h	$t = 24$ h
1	9	n.a.	15	n.a.	16	n.a.	19	n.a.	n.a.	n.a.
2	12	13	16	14	18	16	28	18	30	23
3	7	7	12	8	17	10	24	19	26	22
4	9	9	10	8	15	12	18	12	23	17
5	19	n.a.	19	n.a.	21	n.a.	25	n.a.	35	n.a.
6	11	10	18	14	22	17	27	21	30	23
7	16	15	19	15	21	16	24	20	34	27
8	8	n.a.	12	n.a.	17	n.a.	20	n.a.	23	n.a.
Mean ± S.D.	11.4 ± 4.2	10.8 ± 3.2	$15.1 \pm 3.5^{**}$	11.8 ± 3.5	$18.4 \pm 2.6^{**}$	14.2 ± 3.0	$23.1 \pm 3.7^{**}$	$18 \pm 3.5^{**}$	$28.7 \pm 4.9^{**}$	$22.4 \pm 3.6^{**}$

**Statistically different from control at $p < 0.01$ level, with Dunnett's test. n.a.: not available.

Table 4
NDI after in vitro exposure to different times and intensities from MRI device

MN ‰										
Individual	Control		Exposure 1		Exposure 2		Exposure 3		Exposure 4	
	$t = 0$ h	$t = 24$ h	$t = 0$ h	$t = 24$ h	$t = 0$ h	$t = 24$ h	$t = 0$ h	$t = 24$ h	$t = 2$ h	$t = 24$ h
1	1.9	n.a	1.9	n.a	1.7	n.a	2.0	n.a	n.a	n.a
2	1.9	1.7	1.7	1.8	1.8	1.8	1.7	1.5	1.7	1.5
3	1.8	1.7	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.4
4	1.7	1.7	1.5	1.7	1.5	1.7	1.4	1.5	1.4	1.4
5	1.3	n.a	1.3	n.a	1.3	n.a	1.3	n.a	1.3	n.a
6	1.9	1.9	2.0	1.9	1.9	1.9	1.6	1.7	1.6	1.7
7	2.0	1.8	2.0	1.8	2.0	1.9	1.8	1.6	1.8	1.6
8	2.0	n.a	2.0	n.a	2.0	n.a	1.8	n.a	1.8	n.a
Mean ± S.D.	1.8 ± 0.2	1.8 ± 0.1	1.7 ± 0.3	1.8 ± 0.1	1.7 ± 0.2	1.8 ± 0.1	$1.6 \pm 0.2^{**}$	$1.6 \pm 0.1^{**}$	$1.6 \pm 1.9^{**}$	$1.5 \pm 0.1^{**}$

**Statistically different from control at $p < 0.01$ level; with Dunnett's test. n.a.: not available.

Table 5
Demographic characteristics and MN frequency of the participants before and after the MRI scan

MN ‰				
Individual	Gender	Age (years)	Pre-MRI	Post-MRI
1[a]	F	30	12	21
2[a]	F	41	7	15
3[a]	M	66	17	29
4[b]	M	30	10	21
5[b]	F	28	15	22
6[b]	F	59	7.5	18.5
7[b]	M	61	6.5	15.5
8[b]	M	28	2.5	13
Mean ± S.D.		42.9 ± 16.5	9.7 ± 4.8	19.4 ± 5.1*

*Statistically different from control at $p < 0.01$ level, with Dunnett's test.
[a] Patients.
[b] Volunteers.

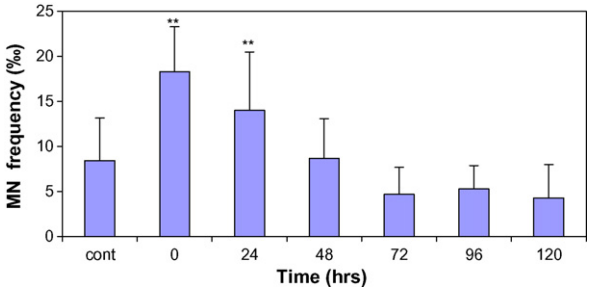

Fig. 1. Time-course of MN induction after cardiac MRI scan. Each time represents the means (±S.D.) of 8 independent experiments. **Statistically different from control at $p < 0.001$ level, with Dunnett's test.

Successively, MN frequencies slowly return to control value. The apparent lower frequency found at 72, 94 and 120 h is due to experimental variability, the statistical analysis also confirming they are not different from the control value.

4. Discussion

In the present paper we evaluate the effects of exposures to MRI generated electromagnetic fields. To our knowledge this is the first study on the genetic effects of the whole radiations generated during MRI diagnostic scan. The overall data indicate that MRI is not inert from a biological/genetic point of view.

The data of the in vitro treatments show a dose-dependent effect in all samples and at all exposure times, clearly indicating that, in our experimental conditions, MRI has genotoxic effects. The continuous monitoring of the temperature allowed to exclude thermal effects: in fact, it is accepted that a temperature increase up to 1 °C is absolutely free of health risks [3] and ineffective in changes of MN frequency [24].

NDI was analysed in all the experiments, and the whole data showed the cell cycle was only slightly affected (never dropped below 70% of the control value), suggesting that high toxicity levels were absent. In particular, NDI was significantly lower at the two higher exposures in vitro, while a similar result – opposite trend between MN frequency and cell cycle kinetics – was not found at both times of the two first exposures, indicating that cell proliferation was not affected when used relatively low exposures to electromagnetic fields and that 24 h of recovery are enough to modulate MN frequency but not NDI.

24 h of recovery seem to allow a certain degree of repair, at least to heal the damage produced by diagnostic level of electromagnetic radiations. Repair mechanisms after ELF-MF have been reported in human cell lines [25].

The in vivo results also indicate genotoxicity induction after MRI scan. The data are quite consistent, despite the small population analysed. The absence of contrast media administration, that it is reported to induce chromosomal damage [26], is a further confirm of our data consistency. These results also pinpoint that, after 48 h, the MN number is turned into control values, suggesting that two cell divisions are enough to eliminate all MN from the lymphocytes population.

The persistence of induced DNA damage is a key issue when assessing genetic risk, since it can accumulate in the target cells and initiate DNA instability processes that can trigger tumorigenic events. MN, and chromosome aberrations as well, can be found long after irradiation. In mouse splenocytes MN were found up to 112 days after 2 Gy whole body irradiation [27]. In our case, the low persistence of MN could be ascribed to lethality of micronucleated cells, unable to survive for genomic imbalance, or to their dilution in the pool of unaffected dividing cells. Similar data have been reported in cultured human cell lines after gamma irradiation [28].

Our results allows further considerations at level of (sub)chronical exposure: the increased, although not statistically significant, MN frequency in "room" control samples suggests a need of awareness to assure occupational protection. Also in daily life the population is exposed to a variety of environmental insults which may be not genotoxic "per se", but they may enhance the negative effects induced by other biological, chemical and/or physical agents. It has been reported that EMF can promote vinblastine-induced aneuploidy in murine oocytes [29] and that co-exposure of human lymphocytes to ELF-EMF and benzo(*a*)pyrene led to significant increase in MN and sister chromatid frequencies [30]. ELF-EMF are also able to increase the mutagenic capacity of gamma irradiation by a 2.6 factor [31]. Similar correlation have been found in animals: foetal growth and postnatal development of mice are found affected after gestational exposure to high fields MRI conditions when in association with ultrasounds [32]. Furthermore, lymphocytes from workers occupationally exposed to low doses of ionising radiations and treated *ex vivo* with ELF-MF show a slight but significant increase in MN frequency when compared with the respective controls [33]. The overall data, and the fact that lymphocytes from Turner's syndrome individuals show significantly higher MN frequency after ELF-MF exposure [34], suggest the possibility that human population subgroups characterised by pathological status, genetic predisposition or environmental conditions present different sensibilities to EMF with different implications for their risk assessment.

Although preliminary evidence suggests that increased MN frequency is associated with early events in carcinogenesis [35], our data, showing a modest increased MN frequency (roughly doubled) and a return to normal frequency within a few days, cannot confirm a conclusion of risk. A possible resolution could result from future studies also aimed to distinguish whether MRI-induced MN are generated through aneuploidogen or clastogenic events using centromeric probes.

However, until a more exhaustive monitoring of the potential risk of diagnostic MRI is available, a prudent attention should be kept in order to avoid unnecessary examinations. Similar care has been recently recalled for diagnostic cardiac ultrasounds [36]. Although ultrasounds and MRI seems to have a substantial different effect in the long term with respect to ionizing radiations [37], it is never too much to draw attention on this, since doctors are insufficiently aware of the risks associated with clinical tests [38]. Better auditing prescriptions will reduce the number of inappropriate examinations thus avoiding detrimental effects both for public health and the environment.

Conflict of interest

None.

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