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EDITORIAL

Is cardiac magnetic resonance imaging causing DNA damage?

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This editorial refers to 'Impact of magnetic resonance imaging on human lymphocyte DNA integrity,' by M. Fiechter *et al.*, doi:10.1093/eurheartj/eht184

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Cardiac imaging is increasingly used to detect heart diseases and to guide therapy. Along with the increased use of cardiac imaging at clinics there is increased attention to the potential risks related to the methods used. Currently imaging tests using ultrasound or magnetic fields have been regarded safer alternatives compared with the tests utilizing ionizing radiation such as X-rays, computed tomography (CT), and nuclear imaging.[1]

However, various sources of risks related to, for example, exercise testing, pharmacological stressors, contrast agents, the imaging procedures themselves, invasive procedures, and cumulative ionizing radiation should all be taken into account collectively and ultimately weighed against the risks related to undetected disease or delayed diagnosis.

Magnetic resonance (MR) imaging relies on three different types of low-frequency electromagnetic waves: a static magnetic field, radiofrequency (RF) pulses, and gradient magnetic fields. Potential risks associated with MR may derive from the effects of each component on biological tissues and mainly on ferromagnetic objects. The latter is a well-known limitation of MR that can be avoided by appropriate patient selection, i.e. exclusion of patients with any metal object in their body. A strong static magnetic field as such is unlikely to cause significant adverse biological effects, although sporadic and transient sensations of nausea and dizziness have been reported. The RF energy delivered to the body may cause heating of tissues.[2] The amount of RF energy delivered is defined as the specific absorption rate (SAR). To avoid significant heating, clinical scanners are set to operate within defined SAR ranges. A gradient magnetic field can stimulate nerves and muscles, occasionally causing discomfort,[3] but current MR systems typically operate below nerve stimulation levels. However, cardiac MR imaging requires some of the strongest and fastest switching electromagnetic gradients available in MR, exposing the patients to the highest accepted energy levels.[4,5]

DNA double-strand breaks (DSBs) *in vivo* have been used as a marker of biological damage and genotoxic effects induced by medical procedures especially in studying the effects of ionizing radiation. There are several approaches to measure the induction and repair of DSBs. A number of methods such as the Comet assay[6,7] and measurement of gamma-H2AX phosphorylation (pH2AX)[8,9] allow detection of low levels of DNA damage. The classical Comet assay is a simple and sensitive gel electrophoresis-based technique that can be used, with modifications, to measure DNA single-strand breaks (SSBs) and DSBs, as well as cross-links and apoptotic nuclei in individual eukaryotic cells. The pH2AX assay is methodologically more versatile as the phosphorylation event occurring on DNA DSBs can be measured using immunofluorescence microscopy, flow cytometry, and western blotting. Induction of pH2AX occurs within seconds, and maximal accumulation is reached ~ 30 min after irradiation, followed by decay (epitope dephosphorylation), depending on the success of the repair processes.[8] Both methods are also suitable for assessing the level of induced DNA damage in peripheral blood cells, but the high linearity of pH2AX signals with the radiation dose makes this biomarker the method of choice for indicating the exposure and monitoring the repair. No significant differences in the amount of pH2AX foci between lymphocyte subsets have been detected. However, the observed large interindividual variation *in vitro*[10] and *in vivo* limits the usefulness of the pH2AX assay for radiation biodosimetry. Moreover, it should be noted that while microscope-based analysis of pH2AX foci allows detection of even a single DNA DSB in a cell, the accurate signal quantification by flow cytometric methods typically requires the presence of several foci per cell.

Fiechter *et al.*[11] have now investigated the impact of cardiac MR on lymphocyte DNA. They analysed DSBs in blood lymphocytes before and after routine 1.5T cardiac MR examination using immunofluorescence microscopy and flow cytometric analysis for measurement of pH2AX signals. They found a significant increase in median numbers of DSBs in lymphocytes after cardiac MR examination. The authors concluded that cardiac MR should be used with caution, and restrictions may apply similar to those of other X-ray-based imaging techniques in order to avoid unnecessary damage of DNA integrity with a potential carcinogenic effect.

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Table 1 Amount of excess DNA double strand breaks per lymphocyte induced by different diagnostic procedures

	Early measurements		Later measurements		Reference
	DSB foci/ lymphocyte[a]	Time of measurement	DSB foci/ lymphocyte	Time of measurement	
[^{18F}]FDG injection (5 mSv)	0.11	30 min post-injection	0.16	30 min post-PET/CT	May *et al.* (2012)[15]
CTA (~2 mSv)	0.04	30 min post scan	–		Kuefner *et al.* (2010)[13]
CTA (~8 mSv)	0.24	30 min post-scan	0.092 and 0.014	2 and 5 h post-scan	Grudzenski *et al.* (2009)[14]
CTA (~17 mSv)	0.39	30 min post-scan	–		Kuefner *et al.* (2010)[13]
Invasive angiography	0.13[b]	15 min post-procedure	–		Kuefner *et al.* (2009)[12]
1.5T CMR	0.12	At the end of the scan	–		Fiechter *et al.* (2013)[11]

CMR, cardiac magnetic resonance; CTA, computed tomography angiography; DSB, doule-strand break; FDG, fluorodeoxyglucose; PET, positron emission tomography.
[a]Baseline level of DSBs is ~0.06–0.08 DSB foci/lymphocyte.
[b]Median of different non-cardiac dignostic and interventional procedures.

The results may sound surprising but are actually not completely new. In previous studies, *in vitro* and *in vivo* DNA damage in lymphocytes after cardiac MR has been demonstrated.[4] Interestingly, previous studies with low-dose coronary CT angiography,[12–14] nuclear imaging,[15] and invasive X-ray angiography[12] have documented DSBs with levels quite comparable with those detected after cardiac MR by Fiechter *et al.*,[11] while the values have been somewhat higher after CT angiography performed with a higher radiation dose (*Table 1*). In addition, the studies have demonstrated a strong relationship between the amount of DSBs and the amount of ionizing irradiation *in vitro*.[12,13] Based on serial measurements, repair of DSBs seems to be rapid as their number returns close to baseline in a few hours, but very limited data are available for the longer term existence of DSBs after scans. In the study by Simi *et al.*,[4] DNA damage was detected up to 24 h after cardiac MR.

The long-term biological and clinical significance of DNA DSBs induced by MRI remains unknown. Mammalian cells respond rapidly to DNA damage caused by external agents such as ionizing radiation by rapidly activating the molecular machinery which aims at maintaining genomic integrity and thus preventing carcinogenic mutations. Repair of DSBs involves a complex series of finely orchestrated protein interactions which reverse the changes in the nucleotides in an extremely efficient way both qualitatively and quantitatively.[16] The main mechanisms of DSB repair include non-homologous end-joining and homologous recombination. While they sometimes fail to restore genomic stability, the key question in the case of permanent DNA damage is the likelihood of a hazardous effect on the host.[17] Of note, the risk from radiation-induced carcinogenesis is considered as a stochastic event. In other words, even an extremely low level of damage may result in a harmful effect since no threshold for mutational changes exists.

Some limitations in the study of Fiechter *et al.*[11] need to be taken into account. The study population was small and the measured increase in DSBs relatively minute. Although the results are in agreement with an earlier comparable study,[4] it is important to confirm the findings in a larger population. Fiechter *et al.*[11] measured only one time point at the end of the MR scan. Temporal data about the dynamics of the DSB repair are needed. The effect of MR field strength (1.5T vs. 3T vs. 7T) needs to be studied, as well as the role of contrast agents which may enhance the biological effects of magnetic fields. It would also be important to determine if similar findings can be detected after MR imaging of other tissues such as the brain and abdominal organs. It is also pivotal to collect more data about DSBs for comparison of different imaging modalities including ultrasound or even sham imaging to better understand the usability of DSBs as a biomarker of cellular stress after various clinical procedures.

Assuming that DNA damage indeed occurs after cardiac MR imaging, what does that mean clinically? Unfortunately that information is not available, and will probably be very difficult to acquire. In the case of ionizing radiation, only extrapolation from larger radiation doses in population cohorts (e.g. atomic bomb survivors) has been able to document the increased risk of cancer after low-dose radiation. The Food and Drug Administration (FDA) has estimated that after 10 mSv of ionizing radiation, the excess incidence of fatal cancer would be 0.05%[18] and, since the current population incidence of cancer is high (one in three women and one in two men in Western countries will develop cancer in his or her lifetime), the minute increase in cancer due to radiation is extremely difficult to detect. Thus, also in the case of cardiac MR one could anticipate that the potential risk is too low to be confirmed in clinical population studies. The cellular mechanism of how cardiac MR induces DNA damage is not known and may be different from that of radiation. The distribution of exposure locally and to the whole body is also different. Due to numerous open issues, it is obvious that further larger studies are warranted before any restrictions on the use of cardiac MR should be imposed.

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