Cardiac MR Imaging and the Specter of Double-Strand Breaks[1]

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A wide range of imaging modalities are available for the assessment of cardiovascular disease, including echocardiography, computed tomography (CT), nuclear imaging (single photon emission CT [SPECT]/positron emission tomography), and magnetic resonance (MR) imaging (1). The advantages and disadvantages of the various tests include certain considerations, such as the performance characteristics and appropriateness of each to detect a specific condition, availability, cost, exposure to ionizing radiation, and use of contrast agent. MR imaging, a powerful diagnostic imaging modality, utilizes electromagnetic fields of three different frequency bands: static magnetic field, time-varying gradient magnetic fields, and pulsed radiofrequency fields (2). Unlike ionizing radiation, which is an established carcinogen, the magnetic and radiofrequency fields used in MR imaging have not been clearly linked to subsequent cancer risks (3,4). Concern about potential cancer risks after cardiac MR imaging has been raised, however, by a few small studies, including a study (with 20 patients) by Fiechter et al (5) that reported increased double-strand breaks (DSBs). The finding was surprising because of the lack of evidence or mechanism for cancer risks and the small sample size, but warranted further exploration. In this edition of the journal, Brand et al (6) report results from a replication study. In their study of 45 patients who underwent cardiac MR imaging, Brand et al did not find evidence of increased DSBs in the lymphocytes of patients immediately after the procedure.

The two studies used broadly similar methods (5,6). Blood was drawn before and after MR imaging, and DSBs were quantified in isolated blood lymphocytes by using immunofluorescence microscopy after staining against the phosphorylated histone variant γ-H2AX. The patients were of similar age (mean ages, 50 years vs 53 years), they were undergoing procedures for similar conditions, and all examinations were performed with a 1.5-T MR imager. Brand et al (6) found that the mean number of DSBs at baseline was 0.116 per cell before MR imaging and 0.117 per cell 5 minutes after MR imaging ($P = .71$). Fiechter et al (5) reported that the mean number of DSBs before MR imaging was 0.143 per cell and this increased to 0.270 per cell after MR imaging. There are some differences in study design that could have affected the results, including clear exclusion criteria by Brand et al of patients who had history of lymphoma or leukemia and those who had undergone recent radiographic examination, radiation therapy, or systemic chemotherapy. Differences in timing of blood draw could also be a factor, although increased DSBs have also been reported immediately after CT scans (7,8). Brand et al also noted a surprisingly wide range of DSBs in the study by Fiechter et al in the levels both before and after MR imaging. In Brand et al, the baseline values ranged from 0.092 to 0.169 DSB per cell, whereas in Fiechter et al they were 0–0.661 DSB per cell before and 0–1.065 DSB per cell after MR imaging. The very low readings are unusual for this age range because most people accumulate damage from a variety of sources, and levels of 1 DSB per cell or more would usually be seen after ionizing radiation doses of 50 mGy or more (9). Small sample size and low power to detect small effects is likely a limitation of both studies. Small underpowered studies with positive findings are most likely to be from chance, and the effect size is likely to be exaggerated (10). Small null studies may just be underpowered (10).

The International Agency for Research on Cancer has classified both extremely low frequency (ELF) magnetic

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fields (3) and more recently radiofrequency fields (4) as class 2B or "possibly carcinogenic to humans" based on possible increased risk of acute lymphoblastic leukemia (for ELF), or glioma and vestibular schwannoma (for radiofrequency) in a few epidemiologic studies. However, the majority of experimental and mechanistic evidence to date has not been able to confirm this association. In vitro data obtained with static magnetic fields use varying exposure conditions, and biologic end points are difficult to interpret, particularly regarding high-strength MR imaging fields. Cellular studies of ELF and radiofrequency remain similarly inconclusive because of the huge variety of exposure conditions and biologic end points (11). It thus remains unclear whether ELF or radiofrequency is associated with risk of cancer in humans. A comprehensive multicenter study with standardized MR imaging exposure protocols and several genetic and epigenetic damage end points at multiple time-points after exposure in a large number of individuals could help reduce uncertainties. Nonetheless, large risks can probably be ruled out even with existing data.

Deoxyribonucleic acid (DNA) DSBs occur in cells in response to many exposures, including ionizing radiation, chemical agents, and drugs. Many of these breaks, however, will be transient because efficient cellular mechanisms repair the damage, and levels have been shown to decline within a few hours of exposure to ionizing radiation because of these efficient repair mechanisms. These repair mechanisms are essential to avoid chromosome aberrations. It is these chromosome aberrations, rather than DSBs, that are the reference standard of biomarkers of radiation exposure (12). Chromosomal aberration frequency was linked directly to subsequent cancer risk most convincingly in a large pooled analysis of epidemiologic studies including 22 358 participants from 11 countries (13), whereas DSBs have not (14). Unfortunately, it is challenging to use tests of chromosomal aberrations for low-dose radiation typical of that received from diagnostic radiation exposures. Therefore, γ-H2AX was developed as a relatively simple, precise, and sensitive cellular biomarker to detect the presence of DNA DSBs and their repair after low doses of ionizing radiation (15). It has been widely used to study many types of diagnostic radiation exposures, but the assay can still have problems with quantification of staining and lack of an experimental standard, and there are gaps in knowledge about the effect of underlying diseases (14).

In a recent editorial (16), we reviewed studies that reported increased DSBs from radiation doses attributable to the addition of iodinated contrast media to chest CT scans. In those studies, the investigators used γ-H2AX to compare DSBs in patients who were and were not administered contrast agent before and after CT (7,8,17). One of the features that distinguish the current study by Brand et al (6) from those studies, aside from the modality, is the type of contrast medium used. Gadolinium, rather than iodine, was used in the Brand study and all patients underwent MR imaging with contrast agent, so there was no comparison group without contrast agent. Even in the absence of a control group, the lack of increase in level of DSBs above background after MR imaging with gadolinium-based contrast agents may be reassuring.

Efforts have been made to reduce radiation exposure from cardiac CT angiography, which can be clinically meaningful because of the need to compensate for cardiac motion. Two large international studies, Protector 1 and 2 (18,19), surveyed cardiac CT angiography practices and reported wide variation in the use of these procedures and a wide range of doses to which patients were exposed. One of the approaches used to estimate the radiation dose was to measure the number of DSBs per cell in patients in relation to dose after several different cardiac CT angiography procedures to identify procedures that induced the fewest breaks by using γ-H2AX (20–22). The number of DSBs per cell was significantly reduced after sequential and high-pitch CT examinations compared with the frequency per cell in patients who had low-pitch scans even with the dose-length product normalized to the scan length (19 and 36 patients, respectively, in references 20 and 21) and lower frequencies in sequential versus helical scans (34 patients) (22). A recent study of 67 patients who underwent cardiac CT angiography reported that patients exposed to greater than 7.5 mSv had evidence of DNA damage associated with DSBs along with activation of genes related to programmed cell death (ie, apoptosis) and DNA repair (23). These studies and many others that investigate CT, though also relatively small, demonstrate that DSBs can be detected consistently after ionizing radiation exposure after relatively low doses, and that DSBs can be reduced by dose-reduction methods.

Use of cardiac MR imaging has been rapidly increasing in the United States. A recent report based on Medicare data found that while MR imaging use overall has been stable since 2008, the use of cardiac MR imaging had increased 10-fold over a decade (24). Cardiac MR imaging has a number of advantages over other tests, including that it is less time consuming than SPECT and more accurate, as shown in the Clinical Evaluation of MR Imaging in Coronary Heart Disease, or CE-MARC, trial (25). There are, however, other established safety concerns, including serious reactions to contrast agents and potential risks from exposure of ferromagnetic material or implants to MR imaging. The appropriateness criteria do not distinguish currently between imaging modalities or suggest any sequence in which tests should be performed, and for many indications multiple modalities, particularly cardiac CT angiography, SPECT, and cardiac MR imaging,

Published online
10.1148/radiol.2015151943 **Content code:** CA

Radiology 2015; 277:329–331

Abbreviations:
DNA = deoxyribonucleic acid
DSB = double-strand break
ELF = extremely low frequency

Conflicts of interest are listed at the end of this article.

See also the article by Brand et al in this issue.

are all considered appropriate (1). The study by Brand et al (6), though small and possibly underpowered (6), is in line with the majority of the existing data, which does not support an association between nonionizing radiation exposures and cancer risk. Therefore, the use of nonionizing, rather than ionizing, radiation should still be considered one of the advantages of MR imaging for cardiovascular disease assessment.

Disclosures of Conflicts of Interest: A.B.d.G. disclosed no relevant relationships. R.**A.K.** disclosed no relevant relationships. **D.M.** disclosed no relevant relationships. **P.R.** disclosed no relevant relationships.

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