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Radiation Risk From Pediatric Cardiac Catheterization Friendly Fire on Children With Congenital Heart Disease

Maria Grazia Andreassi, BSc, PhD

Congenital heart disease (CHD) is the most prevalent and fatal of all birth defects, occurring in nearly 1 in 100 live births.¹ Before the advent of cardiac surgery for congenital cardiac malformations, less than one fifth of children born with such lesions reached adulthood. The progress of surgical management and, more recently, interventional catheterization has allowed an increasing number of congenital heart defects to be corrected surgically so that an increasing number of patients reach adolescence and adult life, even those with complex defects.^{2,3}

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Indeed, grown-up patients with surgically repaired CHD are a large and growing population, estimated to be 1 million in United States in the year 2000 compared with an estimated 300 000 in 1980, and 1.4 million cases are anticipated in 2020.² Numbers are likely to be similar in the European Union, although no hard figures are available.³

One worrisome social and medical problem in the management of patients with CHD is certainly the long-term effects of intensive medical exposure to ionizing radiation received during childhood, especially for interventional catheterization procedures.⁴⁻⁷ Pediatric cardiac catheterizations are undoubtedly an essential diagnostic and therapeutic tool for the diagnosis and the treatment of CHD; however, they also deliver one of the highest radiation doses to patients.⁴⁻⁷

Ionizing radiation exposure is a definite risk factor for cancer development. Children are especially vulnerable to the oncogenic effects of radiation. Tissues and organs that are growing and developing are more sensitive to radiation effects than those that are fully mature. Moreover, the oncogenic effects of radiation require a long latent period (decades) that varies with the type of malignancy. Thus, an infant or child patient has a longer lifetime risk for developing radiation-induced cancers than adult patients.⁸

In addition, catheterization procedures are also longer in children than adult procedures, especially in infants, because the vessels are smaller and more difficult to cannulate, many patients have undergone previous studies and have limited

access sites, and multiple angiograms in several cardiac chambers, with the use of different views, are often needed.⁹

Therefore, it is especially important to quantify the biological risk of pediatric cardiac catheterization, as strongly encouraged by the latest Biological Effects of Ionizing Radiation VII (BEIR VII) report, which recommends “the need of studies of infants who are exposed to diagnostic radiation because catheters have been placed in their hearts, as well as infants who receive multiple x-rays and CT scans” (research need 8) and also encourages “the determination of the level of various molecular markers of DNA damage as a function of low-dose ionizing radiation” (research need 1).⁸

In view of this, the study by Beels et al¹⁰ in the current issue of *Circulation* provides important scientific insight into the mechanisms of radiation-induced risk at low doses of ionizing radiation. The investigators not only demonstrated an increase in γ -H2AX foci, representing a biomarker of DNA double-strand breaks, in pediatric patients who had undergone cardiac catheterization procedures, but they also found that the in vivo dose response does not appear to be linear at all but is much higher than expected from the extrapolation of the high-dose behavior. These findings imply that radiation exposure risk may be even more harmful than that predicted by current estimates on the basis of the linear-no-threshold (LNT) model.

Beels and colleagues¹⁰ reported an estimated median effective dose of 6.4 mSv (range, 0.5 to 53.4 mSv) calculated with the Monte Carlo simulation by using the new tissue weighting factors of the International Commission on Radiological Protection 103 publication.¹¹

According to the estimates of the BEIR VII report,⁸ the lifetime attributable risk values of cancer incidence from a single cardiac catheterization were 2.1% (1 in 476) and 0.8% (1 in 1250) for female and male patients,¹⁰ respectively (Figure 1). However, risk estimates based on the γ -H2AX foci data were much higher than expected from the LNT model used in the BEIR VII: The median lifetime attributable risk of cancer mortality increased from 0.091% (1 in 1098) to 0.404% (1 in 248).

LNT Model and Risk Prediction: From Population Risk to Individual Risk

Although ionizing radiation is a recognized human carcinogen, considerable uncertainty remains about the clinical risk at low doses. The effects of exposure to low-level ionizing radiation on human health are reviewed at regular intervals by international regulatory bodies that consider scientific progress worldwide to arrive at a balanced view of the risks involved and provide the best estimates. The cancer risk estimates are based primarily on epidemiological studies of

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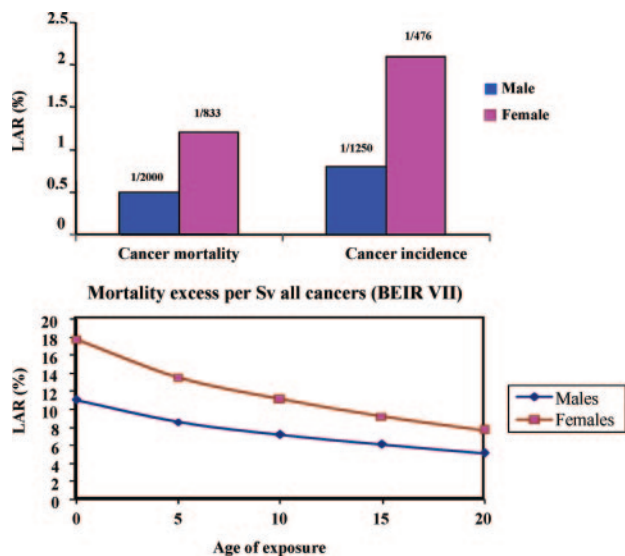


Figure 1. The estimated lifetime attributable risk of cancer mortality and incidence by a single cardiac catheterization in the study by Beels et al¹⁰ calculated with the use of BEIR VII and the LNT model. Female patients have double the risk of male patients. LAR indicates lifetime attributable risk.

exposed human populations, incorporating data from atomic bomb survivor studies, as well as medical and occupational radiation studies.

The current consensus, recently reconfirmed and endorsed by the BEIR VII report⁸ and the International Commission on Radiological Protection 2007 recommendations,¹¹ is that the LNT approach remains the most appropriate risk model at low doses. The model indicates that the risk of cancer proceeds in a linear fashion and that no radiation doses, no matter how small, can be considered completely safe.

The biological findings observed in the study by Beels and colleagues¹⁰ are notable because the hypersensitivity observed at low doses in γ -H2AX foci induction challenges the LNT concept, suggesting that damage occurs not only to the cell that was exposed to radiation but also to surrounding cells (Figure 2).

For years, radiation biologists have thought that the DNA damage is the main initiating event in radiation-associated cancer risk. In the last 2 decades, this view has been challenged by findings that show the occurrence of nontargeted effects in unexposed “bystander cells” that are in close proximity to directly irradiated cells.¹² Bystander effects have been described mainly in vitro cell culture systems, but the mechanisms underlying the bystander phenomenon are largely unknown. It has been suggested that cell-to-cell communication or soluble factors released by irradiated cells may be involved.¹² Radiation-induced bystander effects include increases in reactive oxygen species, cell death or cell proliferation, induction of mutations, and chromosome aberrations.¹² Interestingly, a recent experimental mouse study provided the first demonstration that bystander radiation responses (as measured by γ -H2AX foci formation) can initiate tumorigenesis in unexposed tissues in vivo.¹³ These observations suggest that bystander effects may potentially have important implications on the estimates of risk from low-dose exposures to ionizing radiation.^{12,13}

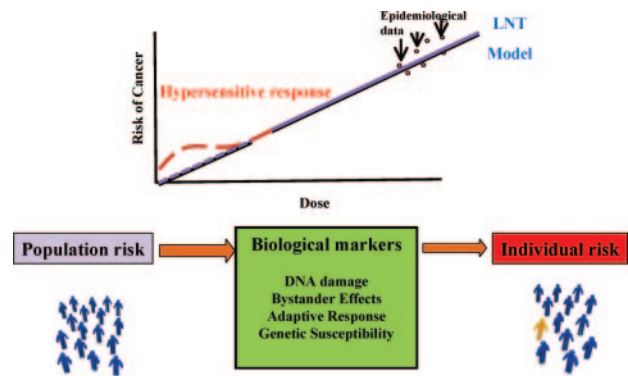


Figure 2. Diagrammatic representation of low-dose risk extrapolation from epidemiological data and hypersensitive response from γ -H2AX foci data. The evaluation of biological markers may provide a more reliable risk estimate in the low-dose range, allowing identification of high-risk susceptible subpopulations.

The study by Beels and colleagues¹⁰ supports this hypothesis, showing a hypersensitive response mirrored by an excess number of γ -H2AX foci in vivo after pediatric cardiac catheterization.¹⁰ γ -H2AX foci analysis is considered a sensitive approach to assess the formation of DNA double-strand breaks, which are the most dangerous alterations of ionizing radiation exposure. DNA double-strand breaks are considered biologically important because their repair is intrinsically more difficult than that of other types of DNA damage, and, if unrepaired or repaired incorrectly, they can lead to chromosome aberrations.

Accordingly, recent data showed that pediatric cardiac catheterization can induce, both acutely⁷ and in the long term,⁶ increased chromosomal DNA damage in circulating lymphocytes, which represents an intermediate end point of cancer.¹⁴ Altogether, these studies clearly support the concept that biological markers of DNA damage can greatly enhance our ability to detect radiation-induced health risk. In fact, the detection and quantification of cancer risk at low doses (\approx 10 to 50 mSv) remains difficult through the traditional epidemiological approach, which requires millions of people to be followed up for several decades.

In addition, numerous inherent environmental, dietary, and biological variables cannot be accounted for in the epidemiological studies. Consequently, risk estimates at the population level can be highly inaccurate at the individual level. Epidemiological studies are extremely valuable, but their contribution can be supported and integrated by studies with biomarkers of exposure effects (γ -H2AX foci), disease risk (chromosome aberrations and epigenetic effects), and susceptibility (genetic functional polymorphisms). Research is needed to identify interindividual differences that could modulate radiation risks in order to obtain better estimates of the extent of the differences in sensitive subjects and in average population groups (Figure 2). Such biomarkers may be useful for identifying a subset of more vulnerable individuals who might be a target for preventive measurements (by pharmacological or dietary radioprotection).

Clinical Implications and Perspectives

On the basis of this study¹⁰ and previous evidence,^{6,7} there are reasonable grounds to believe that the burden of medical

radiation in CHD may result in an increased incidence of radiation-related cancer. Pediatric ionizing procedures have effective dose estimates in the range of 5 to 20 mSv, and there is often a need to perform multiple examinations. With cumulative radiation exposure, patients acquire increasing risks of developing cancer during their lifetime. Overall, the lifetime exposure of a contemporary young adolescent with CHD is ≈ 20 mSv.⁶

The main contribution to dose derives from computed tomographic and catheterization procedures, accounting for 95% of the cumulative effective dose in our contemporary pediatric cardiology.⁷ These procedures often provide essential life-saving information, but great care must be taken relative to the possible long-term health consequences.

The social concern is even higher if we include potential noncancer risks among the detrimental effects of low-dose radiation exposure. Although currently the major component of radiation health risk is considered to be cancer, recent epidemiological evidence suggests that low-dose ionizing radiation exposure, at moderate and lower doses (0 to 4 Sv), may increase the risk of other illnesses, particularly circulatory diseases (ie, heart disease and stroke), and may have effects on cognitive function after radiation exposure in infancy.^{15,16}

Considerable efforts should be made to mitigate radiation-induced cell damage. Because radiation-induced cellular damage is attributed primarily to the harmful effects of free radicals, the efficacy of nontoxic radioprotectors with radical scavenging properties should be investigated in the clinical setting. These agents may inhibit or reduce free radical toxicity, thus offering protection against radiation.¹⁷

Finally, it is obvious that every effort should be made to justify the indications and to optimize the doses during ionizing testing,^{18–20} and the alternative use of magnetic resonance or echocardiography should be considered.

The culture of safety is critically important in the catheterization laboratory, where cardiac catheter-based fluoroscopic procedures currently expose not only the patient but also interventional cardiologists and personnel staff to significant radiation health risks.²¹ Of course, physicians have the greatest responsibility for protecting their patients and themselves from the “friendly fire” of inappropriate imaging.

Disclosures

None.

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