C
ongenital heart disease (CHD) is the most prevalent and fatal of all birth defects, occurring in nearly 1 in 100 live births. 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.

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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

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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...
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 report and the International Commission on Radiological Protection 2007 recommendations, 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 colleagues 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. 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. Radiation-induced bystander effects include increases in reactive oxygen species, cell death or cell proliferation, induction of mutations, and chromosome aberrations.

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. These observations suggest that bystander effects may potentially have important implications on the estimates of risk from low-dose exposures to ionizing radiation.

The study by Beels and colleagues supports this hypothesis, showing a hypersensitive response mirrored by an excess number of γ-H2AX foci in vivo after pediatric cardiac catheterization. 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 acutely and in the long term, increased chromosomal DNA damage in circulating lymphocytes, which represents an intermediate end point of cancer. 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 (∼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 study and previous evidence, 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 \( \approx 20 \) mSv.

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 circular 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.

References


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