**Background**—A better knowledge of patient x-ray dose and the associated radiation risk in pediatric interventional cardiology is warranted in view of the extensive use of x-rays and the higher radiosensitivity of children. In the present study, γ-H2AX foci were used as a biomarker for radiation-induced effects. Patient-specific dose was assessed and radiation risks were estimated according to the linear-no-threshold model, commonly used in radiation protection, and the γ-H2AX foci data.

**Methods and Results**—In 49 pediatric patients (median age, 0.75 years) with congenital heart disease who underwent cardiac catheterization procedures, blood samples were taken before and shortly after the procedure. γ-H2AX foci were determined in peripheral blood T lymphocytes. In each patient, a net increase in γ-H2AX foci, representing DNA double-strand breaks induced by interventional x-rays, was observed. In addition, a patient-specific Monte Carlo simulation of the procedure was performed, resulting in individual blood, organ, and tissue doses. Plotting of γ-H2AX foci versus blood dose indicated a low-dose hypersensitivity. Median effective doses calculated according to the International Commission on Radiological Protection 60 and 103 publications are 5.6 and 6.4 mSv, respectively. The lifetime-attributable risk of cancer mortality was calculated from the linear-no-threshold model and the γ-H2AX foci data. This resulted in lifetime-attributable risk values of 1 per thousand and 4 per thousand, respectively, for the patient population under study.

**Conclusions**—γ-H2AX foci as a biomarker for DNA damage indicate that radiation risk estimates according to the linear-no-threshold hypothesis are possibly underestimates. Great care should be taken to minimize and optimize patient radiation exposure. *(Circulation. 2009;120:1903-1909.)*

**Key Words:** catheterization ■ pediatrics ■ radiation risk

**C**atheterization procedures are increasingly being used to treat congenital heart disease. A limiting factor in interventional cardiology could be the x-ray dose, which can be high as a result of the extensive use of fluoroscopy and multiple cine runs because these procedures can be very complex. This is especially important in infants and children because they are at least 3 times more sensitive to radiation-induced malignancies compared with adults. Cardiac catheterization procedures need to be repeated several times in some patients; moreover, in infants, a large fraction of the body is irradiated by the x-ray beam. Several articles have dealt with patient x-ray doses and the associated risk in pediatric interventional cardiology.}

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**Editorial see p 1847**

**Clinical Perspective on p 1909**

In the typical patient dose range related to diagnostic and interventional use of x-rays (0 to 50 mSv), the associated cancer risk cannot be deduced from epidemiological data owing to a lack of statistical power. Until now, risk estimates for late effects in these patients have been based on a linear extrapolation of high-dose data as obtained in the lifespan study of atomic bomb survivors: the linear-no-threshold (LNT) model. An alternative approach to study the deleterious effects of low-dose x-ray exposure is the use of biomarkers, representing early steps in radiation carcinogenesis. The chromosomal aberrations and micronuclei in peripheral blood lymphocytes after exposure are validated biomarkers of somatic chromosomal damage and intermediate end points in carcinogenesis. However, the sensitivity of these cytogenetic techniques is not sufficient for individual biological dosimetry of patients receiving doses <50 mSv as in pediatric interventional cardiology. DNA double-strand breaks (DSBs)
are considered the most relevant lesions to the DNA for the deleterious effects of x-rays and other types of ionizing radiation. Ionizing radiation–induced DSBs activate histone H2AX within 3 minutes after DNA damage by phosphorylating a highly conserved serine, Ser 139. 18–20 The phosphorylated form of H2AX, γ-H2AX, is not homogeneously spread in the cell nucleus but forms foci. 20 These γ-H2AX foci seem to be essential for the recruitment of repair or signaling proteins to DNA damage sites. 18, 19, 21 One γ-H2AX focus is demonstrated to represent 1 DNA DSB. 21–23

In the present study, γ-H2AX foci in peripheral blood lymphocytes are used as a biomarker for the assessment of individual DNA radiation damage in pediatric patients undergoing cardiac catheterization. This biomarker approach highlights the dose response of x-ray effects in the low-dose range, for which until now a LNT model was adopted. To this end, a Monte Carlo simulation of the complete procedure for each patient was performed. Apart from blood dose, doses to other organs and tissues considered in the International Commission on Radiological Protection (ICRP) publication 103 were calculated, allowing determination of the effective dose. 24 Risks for x-ray–induced malignancies in the pediatric patient population under study based on the LNT model and the γ-H2AX focus data are discussed.

Methods

Patients and Catheterization Procedure

The study population consisted of 49 children who underwent a cardiac catheterization for congenital heart disease (Table 1). The patient group comprised 23 male and 26 female patients with a median age of 0.75 years (range, neonatal to 11 years) and a median weight of 7.60 kg (range, 1.25 to 37 kg). Twenty-six patients were <1 year of age. Seventeen patients underwent cardiac catheterizations for diagnostic purposes. Thirty-two patients were referred for a therapeutic catheter procedure: 21 for balloon dilatation, 7 for atrial septal defect closure, 3 for patent ductus arteriosus occlusion, and 1 for embolization of a fistula. All examinations were carried out by the same experienced cardiologist. The parents of the children signed an informed consent, and the study was approved by the Ethics Committee of the University Hospital Ghent.

X-Ray System and Acquisition of Exposure Parameters

All studies were performed with an Integris BH5000 biplane x-ray system with automatic brightness control (Philips, Eindhoven, the Netherlands). Pulsed fluoroscopy (12.5 frames per second) and cineangiography (25 frames per second) were used. For both fluoroscopy and cineangiography, an x-ray beam filtration of 1.5 mm Al combined with 0.4 mm Cu was used. The dose-area product (DAP) was measured with transmission ionization chambers attached to frontal and lateral tubes (PTW, Freiburg, Germany). DAP meters were calibrated as described previously. 2

For each projection used in the cardiac intervention, the position of the x-ray tube (rotation and skew), source-to-image-intensifier distance, field size, tube potential, and fluoroscopy time were recorded for all patients. DAP data for each fluoroscopy and cine run were gathered by connecting the DAP readout units to a laptop and using software written in house as described earlier. 2 Table 1 summarizes the exposure data of the patients undergoing a diagnostic or therapeutic catheterization procedure.

Sample Collection and Lymphocyte Isolation

Two blood samples were collected from each patient, 1 before and 1 shortly after the procedure. The blood samples consisted of circulating blood obtained from the catheter (the catheter was flushed continuously), so an additional venipuncture was not necessary. The blood samples were kept for 15 minutes in a water bath at 37°C to allow some DNA repair. Afterward, DNA repair was arrested by cooling samples in ice water. T lymphocytes were isolated from blood with the RosetteSep blood separation technique (StemCell Technologies, Grenoble, France). Subsequently, cells were kept in 8 mL complete RPMI medium (84% RPMI-1640, 15% FCS, 1% L-glutamine, 50 U/mL penicillin, and 50 μg/mL streptomycin; Life Technologies, Merelbeke, Belgium).

Immunofluorescence Staining and Scoring of γ-H2AX

For immunofluorescence staining, 500 μL cells suspended in complete RPMI medium were centrifuged. The cells were fixed on polysine slides (VWR International, Leuven, Belgium) with 3% paraformaldehyde (Sigma-Aldrich, Bornem, Belgium) in PBS and afterward put in PBS. Permeabilization of the cells was carried out by placing the slides on ice and dripping Triton X-100 (0.2%; Sigma-Aldrich, Belgium) solution on each slide. Immunofluorescence staining of the cells was performed with anti–phospho-histone H2AX (1:300; BioLegend, Antwerp, Belgium) solution on each slide. Immunofluorescence staining of the cells was performed with anti–phospho-histone H2AX (1:300; BioLegend, Antwerp, Belgium) as primary antibody.
and RAM-TRITC (1:1000; DakoCytomation, Glostrup, Denmark) as secondary antibody. The slides were dried, and DAPI (2%) gel mount (Sigma-Aldrich, Belgium) was added to the cells before a cover glass was placed on the slides.

An Olympus BX60 fluorescence microscope with an Olympus BX60 fluorescence microscope with an Olympus BX60 oil lens with an Olympus BX60 oil lens with an Olympus BX60 oil lens was used for the microscopic analysis. The slides were scanned for γ-H2AX foci with Cytovision software (Applied Imaging, San Jose, Calif) and z stack of 10. Different pictures (Applied Imaging camera) of 1 slide were stored, and on average, 280 cells were scored manually for foci by 2 independent scorers. The number of foci induced by interventional x-rays was calculated by subtracting the number of foci per cell in blood samples taken before and after the catheterization procedure.

In Vitro Irradiation
To compare the γ-H2AX foci dose response after in vivo and in vitro exposure, heparinized whole-blood samples from 3 healthy volunteers were irradiated in vitro at different dose levels with a radiation quality of 100-kVp x-rays and 2 mm Al filtration with a Philips MG420 x-ray generator coupled to a MCN420 tube. The irradiation was carried out in a 37°C water bath. Dosimetry was performed with an NE2571 Farmer ionization chamber (Thermo Electron, Altrincham, UK). The irradiated blood samples were kept for 15 minutes at 37°C, followed by 10 minutes in ice water to simulate the situation of patient blood samples after in vivo exposure. For assessment of γ-H2AX foci, the protocol described earlier was applied.

Monte Carlo Simulation Model
A Monte Carlo patient dose simulation was set up to correlate the number of foci induced by the catheterization procedure with the radiation dose received by the corresponding patient. First, a mathematical anthropomorphic phantom was generated that was based on gender, body length, and weight of the individual patient, as described earlier.² The phantom calculation was based on an interpolation between the revised ORNL pediatric phantoms (newborn and 1, 5, 10, and 15 years).²³ Subsequently, the recorded irradiation geometry of the x-ray beams, together with field size and x-ray spectral distribution used for a particular projection in a patient, was implemented within the computed phantom. The x-ray spectra were calculated with an analytical program.²⁶ Doses were calculated with the MCNP-X 2.5.0 Monte Carlo simulation code. The x-ray simulation was based on the assumption that the heart lies in the isocenter of the x-ray beams of the C arms.

Calculation of Blood Dose, Organ Doses, and Effective Dose
For every tube incidence and for each exposure mode within a catheterization procedure, equivalent organ and tissue doses per unit of DAP were simulated with the Monte Carlo code. By multiplying these values by the corresponding recorded DAP, we obtained the total equivalent organ and tissue doses of a complete procedure. The effective dose was calculated from the latter data and from tissue weighting factors of the ICRP 60 and 103 publications.²⁴,²⁷

In addition to organ and effective doses, the individual blood dose was calculated for the interpretation of the γ-H2AX foci data. Because of the heterogeneous patient dose distribution and the distribution of blood throughout the body (12.5% in lungs, 10% in heart, and 77.5% in the remainder of the body), the blood dose was calculated as the weighted sum of the doses to the lungs, the heart, and the remainder of the body, with the percentage of the blood pool in these compartments as a weighting factor.²⁸

Risk Estimation
Lifetime radiation risk caused by the catheterization procedure in our patient population was calculated according to the BEIR VII risk models for different cancer types, together with the age-dependent incidence and mortality rates within the Euro-American population.²⁹ Therefore, the lifetime-attributable risk (LAR) of cancer incidence and mortality related to leukemia, breast cancer, lung cancer, and all cancers combined was calculated, taking into account the simulated organ doses and the age of the individual patient. In a first set of LAR calculations, the LNT model was adopted with a dose and dose-rate effectiveness factor of 2.

In addition to this LNT risk estimation, a second set of LAR cancer mortality values was calculated on the basis of the in vivo γ-H2AX foci data obtained in the present work. In this analysis, the number of γ-H2AX foci was considered as a biomarker of DNA DSBs, initial lesions of late effects of ionizing radiation exposure. For this second risk estimation, the number of γ-H2AX foci per cell after 0.5 Gy in vitro irradiation (6.49 foci) was associated with LAR cancer mortality values calculated with BEIR VII for this dose. For this dose level (0.5 Gy), epidemiological data are available for LAR values. Subsequently, the γ-H2AX foci number, induced by x-rays for a particular patient, was converted to LAR cancer mortality values through the use of the foci-LAR relationship for 0.5 Gy.

Statistics
Correlations in scatterplots were investigated by calculating the Pearson correlation (r). Differences between 2 (not normally distributed) populations were tested for significance with the 2-tailed Mann–Whitney and Wilcoxon signed-rank tests for unpaired and paired data sets, respectively (95% confidence level). All statistical calculations were performed with the SPSS 16.0.2 program (SPSS Inc, Chicago, Ill).

Results
In Figure 1, the average number of γ-H2AX foci per cell induced by the in vivo x-ray exposure in lymphocytes during the catheterization procedure for the individual patients is plotted versus the Monte Carlo–simulated blood dose. It is surprising that every procedure, even with a low blood dose, results in an increase of foci. Moreover, the in vivo dose response appears not to be linear at all. An analysis of the increase in foci by interventional x-rays among age groups and between both genders did not show statistically significant differences.

The number of foci induced by in vitro irradiation, averaged over 3 donors, is also presented versus dose in Figure 1. The in vitro dose response (full line) has a biphasic behavior: a steep increase in the very low dose range up to 6 mGy, followed by a flatter dose dependence at higher doses. To guide the eye, a quadratic fit was performed for the low-dose range (0 to 6 mGy) and a linear fit for the high-dose range (6 to 500 mGy). Both in vivo and in vitro data show a more or less similar behavior of dose response, but foci numbers induced in vivo by x-rays of the procedure are generally lower than those obtained after in vitro irradiation. The dashed line in Figure 1 represents a linear extrapolation to 0 dose of the high-dose number of γ-H2AX foci induced in vitro at 0.5 Gy following the LNT hypothesis. In vivo foci numbers in the low-dose range are without a doubt much higher than expected from the extrapolation of the high-dose behavior, pointing to a low-dose hyperradiosensitivity.

Based on the Monte Carlo–calculated organ and tissue doses, the effective dose in the individual patient was determined with the methodology of both ICRP publications 60 and 103. Compared with ICRP publication 60,²⁷ tissue weighting factors (wT) for a number of organs and tissues in the calculation of the effective dose were changed in ICRP 103 (eg, wT for breasts is increased from 0.05 to 0.12). Median effective dose values of 6.4 mSv (range, 0.5 to 53.4 mSv) and 5.6 mSv (range, 0.4 to 44.5 mSv) were found when ICRP 103 and ICRP 60 methodology, respectively, was
applied \((P<0.001)\). The new protocol for calculation of the effective dose following ICRP 103 results in an average increase of 21\% (SD, 11\%) compared with ICRP 60. The effective doses calculated according to ICRP 103 equal the blood doses within 8\%. In Figure 2, the measured total DAP values are presented as a function of effective doses, calculated according to the ICRP 60 and 103 publications. Both effective dose calculations are correlated with DAP \((r=0.64\) and \(r=0.66, P<0.01)\). The relatively poor correlation in the present study is due to the large variation in age and biometry data of the population under study (Table 1).

Based on the simulated organ doses, median LAR values of cancer incidence and mortality for the group of male and female patients were calculated for all cancers, lung cancer, breast cancer, and leukemia following the BEIR VII report. These data are summarized in Table 2. For the group of patients <1 year of age, the median LAR values of cancer incidence and mortality were 0.9 per thousand and 0.6 per thousand for male and 2.5 per thousand and 1.3 per thousand for female patients. In Figure 3, the correlation between the LAR of cancer mortality and effective dose (ICRP 103) for the total group of male and female patients is illustrated \((r=0.98\) and \(r=0.97, P<0.01)\). For the male and female populations of the present study, an LAR of cancer mortality of 9.1%/Sv and 18.1%/Sv, respectively, was found.

In addition to the risk estimations based on the LNT hypothesis, risk estimates using the in vivo γ-H2AX foci results obtained in the present work (Figure 1) were calculated. For the patient population of the present study, the median LAR of cancer mortality increased from the original value of 0.091\% to a value of 0.404\% (range, 0.128\% to 1.626\%). Risk estimates based on the γ-H2AX foci as a biomarker for DNA radiation damage are much higher than expected from the LNT model as used in radiation protection until now.

Discussion

Interventional cardiology plays a crucial role in the diagnosis and treatment of congenital heart disease.\(^1\),\(^2\) The justification of these interventional procedures is evident because complicated invasive surgery can be avoided. However, patient exposures to x-rays used in these complicated procedures can be high.\(^2\),\(^9\) Furthermore, x-ray doses in pediatric cardiac catheterizations are especially critical in view of the enhanced radiosensitivity of children compared with adults.\(^3\),\(^7\) One should also take into account that in children with congenital heart disease, there is often a need to perform multiple

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**Figure 1.** γ-H2AX foci per cell induced by the in vivo x-ray exposure vs blood dose in pediatric patients (○). The dose-response curve of γ-H2AX foci after in vitro irradiation of blood samples to x-rays is also shown (●). The dashed line represents a linear extrapolation to 0 dose of the high-dose number of γ-H2AX foci induced in vitro at 0.5 Gy following the LNT hypothesis. The whiskers for the in vitro work represent SDs for the interindividual variability among the 3 healthy donors. The whiskers on the in vivo data are based on SDs of the number of γ-H2AX foci per cell.

**Figure 2.** Effective doses calculated according to ICRP 60 (○) and ICRP 103 (●) publications as a function of DAP. The solid line represents a linear regression of the ICRP 103 effective doses–DAP data; dashed line, a fit similar to the ICRP 60 data.
examinations, resulting in an increase in the radiation risk.\textsuperscript{2,8} These considerations point to the importance of dose-reducing measures, the follow-up of the x-ray doses given to pediatric patients, and the associated radiation risks in this patient population.

The consensus of regulatory radiation protection organizations for the calculation of the radiation-induced cancer risk is currently based on the LNT model, without a threshold safe dose as discussed by Brenner et al.\textsuperscript{30} The BEIR VII report\textsuperscript{29} and ICRP publication 103\textsuperscript{24} confirmed that the LNT model is the best model to estimate radiation risks, continuing to support the concept that no radiation doses, no matter how small, can be considered completely safe. In the present work, organ and effective doses were calculated by Monte Carlo simulation of the individual procedure for each patient on the basis of patient exposure data in the present study. Cancer incidence and mortality risks from interventional x-rays of a congenital heart disease procedure according to BEIR VII are typically 2.1 per thousand and 1.2 per thousand for a female patient and 0.8 per thousand and 0.5 per thousand for a male patient, respectively. We want to emphasize that every procedure produces a corresponding increase in cancer risk. For some patients, cardiac catheterization procedures need to be repeated several times, leading to significant cumulative effective doses and cancer risks.

The LNT model assumes that the DNA damage is proportional to the dose and that cellular responses operate equally efficient at low and high radiation doses. The validity of the extrapolation from high to low doses is questioned by some radiobiological phenomena such as the bystander effect, low-dose hypersensitivity, delayed genomic instability, and induced DNA repair.\textsuperscript{13,14} To obtain a more reliable risk estimate in the low-dose range, the use of a biomarker of the biological effects of x-rays reflecting the dose-effect response for x-ray doses received by patients in interventional cardiology is warranted. It is generally accepted that DNA DSBs are the most relevant type of DNA lesions responsible for late effects of ionizing radiation such as cancer.\textsuperscript{33} Because the number of phosphorylated histone H2AX proteins forming γ-H2AX foci is closely related to the estimated number of DSBs, it is generally believed that γ-H2AX foci represent DSBs.\textsuperscript{21–23} The number of γ-H2AX foci per cell nucleus can thus be considered a reliable biomarker of the initial DNA lesions leading to the deleterious effects of x-rays. In the present study, we used γ-H2AX foci in peripheral blood T lymphocytes as a biomarker for the effects induced by x-rays in pediatric patients undergoing cardiac catheterization. An increase in γ-H2AX foci by interventional x-rays was observed for every patient. Hence, every patient acquired DNA damage, even at low doses. This DNA damage triggers the repair machinery of a cell.\textsuperscript{20} A misrepair event can be the result of DSB repair, which can lead to carcinogenesis.\textsuperscript{34} When the number of γ-H2AX foci is plotted versus the blood dose (Figure 1), calculated carefully for each patient by a Monte Carlo simulation, the data point to a hypersensitivity at low x-ray doses; an increase in γ-H2AX foci for a dose-length product as low as 1 mGy. Löbrich et al\textsuperscript{14} studied the excess γ-H2AX foci in lymphocytes induced by computed tomography examinations in adult patients. They observed an increase in foci for a dose-length product as low as 150 mGy · cm, corresponding to an estimated blood dose of 3 mGy.

To interpret the in vivo data, the dose response of γ-H2AX foci induced by in vitro irradiation of blood samples of 3 donors with 100-kV x-rays was determined. In this study, special attention was paid to the low-dose range in view of the

### Table 2. LAR of Cancer Incidence and Mortality Associated With X-Ray Exposure From a Cardiac Catheterization Procedure for Pediatric Male and Female Patients Following the BEIR VII Report

<table>
<thead>
<tr>
<th></th>
<th>LAR\textsubscript{incidence}, %</th>
<th>LAR\textsubscript{mortality}, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male (n = 23)</td>
<td>Female (n = 26)</td>
</tr>
<tr>
<td></td>
<td></td>
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</tr>
<tr>
<td>Lung cancer</td>
<td>0.041 (0.015–0.407)</td>
<td>0.086 (0.003–0.368)</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>...</td>
<td>0.095 (0.005–0.569)</td>
</tr>
<tr>
<td>Leukemia</td>
<td>0.004 (0.001–0.034)</td>
<td>0.002 (0.000–0.013)</td>
</tr>
<tr>
<td>All</td>
<td>0.076 (0.023–0.713)</td>
<td>0.205 (0.022–1.113)</td>
</tr>
</tbody>
</table>

Values are median (range).

Figure 3. The LAR of cancer mortality of the female (○) and male (●) populations calculated from the BEIR VII and the LNT model vs effective dose calculated according to the ICRP 103 publication. The solid and dashed lines represent linear regression fits for male and female patients, respectively.
results obtained for the patients. The in vitro dose-response curve shows a biphasic behavior with a steep increase up to 6 mGy, followed by a flatter linear increase at higher doses. This in vitro behavior conforms to the in vivo foci data, although the in vivo γ-H2AX foci yields are somewhat less than expected from the in vitro curve, taking into account the average blood dose (Figure 1). The effect of differences in dose rate between the in vivo and in vitro exposure of blood on the number of γ-H2AX foci was investigated by in vitro irradiation of blood samples at dose rates representative of cineangiography (10 mGy/min), fluorescence (0.1 mGy/min), and in vitro irradiation for dose-response assessment (30 mGy/min). No dose-rate effect on the number of γ-H2AX foci was observed, so dose-rate differences cannot account for the lower number of foci observed in the patient samples compared with the in vitro dose response (data not shown). A possible explanation for the in vivo–in vitro differences is offered by the relatively fast disappearance of foci with time \((T_{1/2}=3 \text{ hours})^{35}\) and the time between the in vivo x-ray exposure during the catheterization procedure and putting the blood samples taken after the procedure on ice, ranging from 30 minutes to 2 hours. This explanation is further supported by the data of Löbrich et al\(^{44}\) showing that the excess foci from blood samples taken 60 minutes after computed tomography exposure are only 70% of foci yields from blood samples taken 30 minutes after exposure.

In vitro dose-response curves of γ-H2AX foci in other cellular systems such as fibroblasts are reported in the literature to be linear, but a detailed analysis in the low-dose range as performed in present study is not available.\(^{14,16,36,37}\) Data are also lacking relative to the dose-response curve of γ-H2AX foci in lymphocytes based on in vitro irradiation of whole-blood samples, simulating the in vivo x-ray exposure. To elucidate the effect of the cell environment on foci formation in lymphocytes, we also determined the dose response after in vitro irradiation of isolated lymphocytes; the biphasic behavior and low-dose hypersensitivity observed after whole-blood irradiation were much less pronounced for isolated lymphocytes (data not shown). This finding points to the importance of extracellular factors as diffusible signaling molecules on foci formation at low x-ray doses, a bystander effect.

The scientific basis of the LNT theory is that the energy deposition to the cell nucleus and the resulting DNA damage are solely responsible for the biological effects and the associated detrimental health risks. Nontargeted effects such as associated reactive oxygen species formation. It is interesting that different studies,\(^{1,4,2}\) including one as early as 1978,\(^{41}\) have reported x-ray induction of chromosomal aberrations and micronuclei in circulating lymphocytes of children after cardiac catheterization. These cytogenetic end points are recognized internationally as intermediate end points of carcinogenesis.

As could be expected from the observed hypersensitivity at low doses, risk estimates based on the γ-H2AX foci are much higher than expected from the LNT model. For the patient population studied, the average cancer mortality risk is increased from 1 per thousand (LNT) to 4 per thousand (γ-H2AX) with the use of a foci-LAR cancer mortality conversion factor deduced at 0.5 Gy. Our results point to the importance of follow-up studies of children subjected to cardiac catheterization. So far, data in the literature relative to excess cancer risk in these patients resulting from interventional x-rays are inconsistent.\(^{42,43}\) An early study\(^{42}\) did not demonstrate an increase of leukemia during a follow-up period of 13 years, but a more recent study\(^{43}\) reported a 2.3 excess cancer risk in a mean follow-up period of 28 years. As stated in the BEIR VII report, there is a need for large-scale follow-up studies of populations exposed during childhood to intervention-intensity x-rays.\(^{29}\)

**Conclusions**

Our study of γ-H2AX foci as a biomarker for DNA damage in pediatric cardiac catheterization has shown that risk estimates calculated according to the LNT hypothesis, the main paradigm of classic radiation protection, are possibly underestimates. In view of the high effective doses and the excess number of foci induced by the interventional x-rays, great care should be taken to minimize and optimize patient radiation exposure. This is of special importance in the hybrid approach, which combines surgical and interventional techniques in the management of various congenital cardiac defects. Radiological awareness among interventional cardiologists can help the most to minimize the long-term oncogenic effects of x-rays in this patient group.

**Acknowledgments**

We wish to thank all the children and their parents who participated in the study. Furthermore, we want to express our thanks to the volunteers and to Virginie de Gelder for her help with sample collection and laboratory work.

**Disclosures**

None.

**References**

Interventional cardiologists should be aware that x-ray doses to patients can be high, especially in cases of complex procedures involving extensive use of fluoroscopy and multiple cine runs. With respect to the x-ray–induced oncogenic risk, children undergoing a catheterization procedure, eg, for treatment of congenital heart disease, require special attention in view of their higher radiosensitivity and the fraction of the body irradiated. For some patients, cardiac catheterization procedures involving extensive use of fluoroscopy and multiple cine runs. With respect to the x-ray–induced oncogenic risk estimates seriously higher than those obtained from the linear-no-threshold hypothesis, generally used in radiation protection: reference values: a report of age- and gender-related differences in the anatomical and physiological characteristics of reference individuals. ICRP Publication 89. Ann ICRP. 2002;32:5–265.

Beers et al. Radiation Risk in Pediatric Cardiac Catheterization.

CLINICAL PERSPECTIVE

Interventional cardiologists should be aware that x-ray doses to patients can be high, especially in cases of complex procedures involving extensive use of fluoroscopy and multiple cine runs. With respect to the x-ray–induced oncogenic risk, children undergoing a catheterization procedure, eg, for treatment of congenital heart disease, require special attention in view of their higher radiosensitivity and the fraction of the body irradiated. For some patients, cardiac catheterization procedures need to be repeated several times, leading to significant cumulative effective doses and cancer risks. In the present study, a biomarker approach (analysis of γ-H2AX foci in lymphocytes) was used to assess DNA damage induced by interventional x-rays in a pediatric patient group. These patient data point to a low-dose hypersensitivity, resulting in risk estimates seriously higher than those obtained from the linear-no-threshold hypothesis, generally used in radiation protection until now. Present data emphasize the importance of all measures, technical and procedural, for reducing and optimizing patient x-ray exposure. This applies also to the hybrid approach, which combines surgery and interventional techniques. The direct link between x-ray exposure and effects in patients observed in the present work should trigger the radiological awareness of interventional cardiologists.
γ-H2AX Foci as a Biomarker for Patient X-Ray Exposure in Pediatric Cardiac Catheterization: Are We Underestimating Radiation Risks?
Laurence Beels, Klaus Bacher, Daniël De Wolf, Joke Werbrouck and Hubert Thierens

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