Cumulative Patient Effective Dose and Acute Radiation-Induced Chromosomal DNA Damage in Children with Congenital Heart Disease

Lamia Ait-Ali, Maria Grazia Andreassi, Ilenia Foffa, et al.

Updated information and services can be found at:
http://heart.bmj.com/content/early/2009/08/16/hrt.2008.160309

These include:

P<P	Published online August 16, 2009 in advance of the print journal.
Email alerting service	Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

Advance online articles have been peer reviewed and accepted for publication but have not yet appeared in the paper journal (edited, typeset versions may be posted when available prior to final publication). Advance online articles are citable and establish publication priority; they are indexed by PubMed from initial publication. Citations to Advance online articles must include the digital object identifier (DOIs) and date of initial publication.

To order reprints of this article go to:
http://heart.bmj.com/cgi/reprintform

To subscribe to *Heart* go to:
http://heart.bmj.com/subscriptions

CUMULATIVE PATIENT EFFECTIVE DOSE AND ACUTE RADIATION-INDUCED CHROMOSOMAL DNA DAMAGE IN CHILDREN WITH CONGENITAL HEART DISEASE

Lamia Ait-Ali,[§][*] Maria Grazia Andreassi,[§][*] Ilenia Foffa,[§][*] Isabella Spadoni,[*] Eliseo Vano,[**] Eugenio Picano[§]

[§] CNR Institute of Clinical Physiology, Pisa, Italy

[*] G. Pasquinucci Hospital , G. Monasterio Foundation, Massa, Italy;

[**]Complutense University, Madrid, San Carlos University Hospital, Madrid, Spain

Address for correspondence:

Dr. Maria Grazia Andreassi, CNR Institute of Clinical Physiology,

G. Pasquinucci Hospital, Via Aurelia Sud-Montepepe, 54100 Massa, Italy

Fax +39 0585 493601; Tel +39 0585 493646;

Email: andreas@ifc.cnr.it

1

Abstract

BACKGROUND: The seventh Committee on "*Biological effects of Ionizing Radiation*" (BEIR VII, 2006) underlines "*the need of studies of infants who are exposed to diagnostic radiation because catheters have been placed in their hearts*".

OBJECTIVE: To determine the Lifetime Attributable Risk (LAR) of cancer associated with the estimated cumulative radiological dose in 59 children (42 males, age=2.8±3.2 years) with complex CHD, and to assess chromosomal DNA damage after cardiac catheterization procedures.

METHODS: In all patients, the cumulative exposure was estimated as effective dose in milliSievert (mSv), and LAR cancer was determined from BEIR VII report. In a subset of 18 patients (13 males, age: 5□2± 5.7 years) micronucleus (MN) as biomarker of DNA damage and long-term risk predictor of cancer was assayed before and 2 hours after catheterization procedures. Dose–area product (DAP; Gy cm2) was assessed as measure of patient dose.

RESULTS: The median life time cumulative effective dose was 7.7 mSv per patient (range 4.6-41.2 mSv). Cardiac catheterization procedures and computed tomography were responsible for 95% of the total effective dose. For a 1-year-old child, the LAR cancer was 1 in 382 (25th-75th percentiles 1 in 531-1 in 187) and 1 in 156 (25th-75th percentiles 1 in 239-1 in 83) for male and female patients, respectively. Median MN values increased significantly after procedure when compared to baseline (pre= 6 ‰ vs post= 9 ‰, p=0.02). The median of DAP values was 20 Gy cm^2 (range of 1-277 Gy cm^2).

CONCLUSION: CHD children are exposed to a significant cumulative dose. Both indirect cancer risk estimations and direct DNA data emphasize the need for strict radiation dose optimization in children.

2

INTRODUCTION

Radiation can be used to effectively diagnose and treat individuals, but it can also cause subsequent cancers and other conditions[1]. Trends indicate that worldwide population exposure from medical radiation is increasing[2,3] and the use of procedures with a high radiation dose continues to grow steadily[4-8], especially in cardiology[6,8]– and particularly in pediatric cardiology[9]. Children are at least four times more sensitive than adults to the induction of cancer, and the proliferation of appropriate and inappropriate examinations with high radiological dose in children has risen concern among the pediatric community[10] and regulatory bodies [11,12]. The National Academies ' Biological Effects of Ionizing Radiation 7th Report (BEIR VII Phase 2), presented to USA Congress in June 2005 and published in 2006, underlines "*the need of studies of infants who are exposed to diagnostic radiation because catheters have been placed in their hearts*" among priority research needs [12].

BEIR VII report develops risk estimates for cancer from exposure to low-level ionizing radiation using the most current data and epidemiological models available, providing a framework for estimating cancer risk associated with radiation exposure from medical exposure [12].

The aim of the present study was to determine the Lifetime Attributable Risk (LAR) of cancer (fatal and non-fatal) associated with the estimated lifetime cumulative radiological dose in children with complex congenital heart disease (CHD) by using the BEIR VII estimates.

Since these data provide only indirect population-based estimates, we also evaluated directly whether radiation exposure during cardiac catheterization procedures can induce chromosomal DNA damage. To this purpose, micronucleus assay (MN) was performed as a biomarker of chromosomal damage and intermediate endpoint of carcinogenesis[13,14] before and after radiation exposure.

METHODS

Patients

The patient population included 59 consecutive CHD in-patients (42 males, age=2.8±3.2 years) with complex CHD who were admitted in 2007 for cardiac hemodynamic procedures to the G. Pasquinucci Hospital in Massa, Italy. Exclusion criteria included the inability to obtain consent from the child's parents, and the impossibility to reconstruct an accurate history for both the type and number of radiological procedure.

Thirty-one interventional procedures were performed (10 atrioseptostomy according to Rashkind, 2 pulmonary branches balloon angioplasty, 7 pulmonary valvuloplasty, 2 aortic valvuloplasty, 3 patent ductus arteriosus closure, 1 ventricular septal defect closure, 6 aortic coarctation balloon angioplasty).

In all patients, a detailed radiological history has been also reconstructed. All available paper and electronic records of present and past hospital admissions were analyzed using- as the primary source of information - the electronic data bank of our Institute.

 All past examinations performed outside our Institute were recalled by interviewing the patients parents at the time of admission and by direct perusal of available medical records of the patient. Examinations without available record were not considered. Demographic and clinical characteristics of the studied patients are summarized in table 1. Legal representative of patients gave their informed consent at the time of admission to grant the use of hospital data for research purposes and specifically for the bioassay study, authorized by the local Ethical Research Committee.

Indirect estimation of cumulative dose and cancer risk for radiation exposure

For each exam the estimated effective dose in mSv was derived from average dose values reported by the peer-reviewed literature on effective dose for pediatric ionizing procedures[17-21].

Representative Values and Ranges of Effective for some diagnostic radiology procedures are presented in Table 2.

In order to calculate cumulative risk of cancer, we used estimates of cancer from Biological Effects of Ionising Radiation Committee VII (BEIR VII) released in 2006 [12]. According to these estimates, it is predicted that for 10 mSv effective dose in adult approximately one individual in 2000 would develop fatal cancer [11] and one in 1000 would develop fatal and non-fatal cancer [12]. The BEIR VII report estimates that the cancer risk in children is higher than for adults. For instance, the same radiation in the first years of life for boys produces three to four times the cancer risk as exposure between the ages of 20 and 50[12].

Direct Dose estimation and Micronucleus assay

The MN cytokinesis block assay in the human lymphocytes was performed on a randomly selected subset of 18 patients (13 males, age: 5.2± 5.7 years) without comorbidity, and who had undergone cardiac catheterization procedures for diagnostic purposes (n=13) and for therapeutic procedures (n=5).

All procedures were performed using the Philips Integris H5000C monoplane with the X Ray tube MRC 200 0508 ROT GS 1001. Dose-area product (DAP) was obtained from a transmission ionization chamber built into the collimator housing of the radiography tube. The DAP (Gy cm^2) is a quantity used to estimate patient doses in fluoroscopy guided procedures and represents the dose in air measured at a given distance from the X ray tube multiplied by the area of the X ray beam at that distance[15-17].

The cumulated DAP for a procedure is a surrogate measurement for the total amount of X-ray energy delivered to the patient, and is considered a valid indicator of a patient's dose and consequent risk for radiation-induced effects. Effective dose was also estimated by the use of a conversion factor (1.2 mSv Gy^{-1} cm^{-2}) derived from the literature [CF=effective dose/DAP (mSv Gycm^{-2})][19].

Venous blood samples were collected at baseline and two hours following the procedure. Two separate cultures from each sample were set up by mixing 0.3 ml of whole blood with 4.7 ml of RPMI 1640 medium; cultures were incubated at 37°C for 72 h. Cytochalasin B (6 μg/ml) was added

5

44 h after culture initiation. Cells were then harvested and fixed according to the standard method in use in our laboratory[14]. For each sample, 1000 binucleated cells were scored by use of an optical microscope (final magnification ×400) for MN analysis, following the criteria for micronucleus acceptance[22]. We quantified the micronucleated binucleated cell frequency as the number of micronucleated cells per 1000 cells. MN frequency was evaluated by the same three microscopists who had no information as to the identity of patients.

Statistical analysis

Statistical analyses of the data were conducted with the Stat view statistical package, version 5.0.1 [Abacus Concepts, Berkeley, CA, USA]. The average dose values of individual examinations was expressed as median and 25-75° percentiles. Differences were evaluated by the Mann-Whitney U test. Because of the skewness of the distributions of MN values, analyses have been performed using the logarithmic transformation of data. Results are expressed as mean (±SD). Differences between the means of the 2 continuous variables were evaluated by the paired Student's t test. Regression analysis with Pearson's test was also used to evaluate the relationship between the 2 continuous variables. A p value <0.05 was considered significant.

RESULTS

In total, 1548 procedures with ionising radiation were performed during lifetime in the 59 pts.

On average, each patient underwent a mean of 26.2 ± 26.3 examinations (range=1-150, 25th-75th interquartile range: 12-27.7). The number of each type of examinations is given in table 3. The median life time cumulative effective dose was 7.7 mSv per patient (range 4.6-41.2 mSv, 25th-75th percentiles 5.5-12.3). The estimated median effective dose was not significantly different between male (7.1 mSv, 25th-75th percentiles 5.1-12.5 mSv) and female (9.4 mSv, 25th-75th percentiles 6.5-18.1 mSv) patients. A positive significant correlation was found between cumulative radiological effective dose and age (r=0.518, p<0.0001).

Figure 1 shows the contribution of various types of medical ionising procedures to the total collective dose. Conventional X-ray examinations represent 93% of total number of examinations

6

corresponding only to 5 % of collective effective dose. Three types of procedures were responsible for about 95% of the total collective effective dose: diagnostic catheterization, interventional catheterization and CT.

The corresponding estimated lifetime attributable risk of fatal cancer for all combinations of age (ranging from 0-15 years) was 1 in 1717 and 1 in 859, for male (receiving 7·1 mSv) and female (receving 9·4 mSv) patients, respectively.

The LAR (fatal and non-fatal cancer) was 1 in 804 for males, and 1 in 331 for females. However risks were 1·9-2 times higher for child of 1 year compared to 15 years old.

For a 1-year-old child, the median risk of (fatal and non-fatal) cancer was 1 in 382 (25th-75th percentiles 1 in 531-1 in 187) and 1 in 156 (25th-75th percentiles 1 in 239-1 in 83) for male and female patients, respectively.

Concerning direct dose estimation in the subset of 18 patients, the median fluoroscopy time during the cardiac catheterizations was 22.8 min (range, 3 to 34 min) without any significant difference between diagnostic and interventional procedures (p=0·6). The mean DAP values was 45.3±64.8 Gy cm^2 with a median of 20 Gy cm^2 with a 25th-75th interquartile range of 12-64 Gy cm^2.

Median effective DAP values were found to be significantly higher in therapeutic interventions compared with diagnostic procedures (93 Gy cm^2 vs 14 Gy cm^2, p=0·005). DAP values for all patients studied are presented in table 4. The highest values of DAP dose delivered was found for interventional procedure involving 1 aortic coarctation balloon angioplasty (277 Gy cm^2).

Median effective MN value was 6 ‰ (25th-75th interquartile range: 4-7 ‰) at baseline and showed a significant rise at 2 hrs with a median of 9 ‰ (25th-75th interquartile range: 8-11 ‰) after procedures (Figure 2). Median MN values were higher for both diagnostic (7 ‰ vs 11 ‰, p=0.02) and therapeutic cardiac catheterization procedures (5 ‰ vs 9 ‰, p=0.03) when compared to baseline values. However, we did not observe any relationship between DAP and % MN increase (r= 0·1, p = 0·74), also after taking into account the patient's weight (r=0·1, p=0.6).

DISCUSSION

The average contemporary child with CHD is exposed to a significant cumulative radiological effective dose. The new generation of patients with congenital heart disease benefits of the enormous advances in cardiac imaging and interventional cardiology, but also receives an unprecedented radiological exposure, associated with a significant long-term risk of cancer based on the latest risk estimates.

The rise of imaging testing in children

We are witnessing a spectacular rise in potential and versatility of cardiovascular imaging in children. The use of multi-slice CT is increasing even faster in children than in adults, presumably because of the big advantage of a short exposure time that allows for its use without a sedative[23]. It is estimated that there were at least 6·5 million CT in USA in the pediatric age band in the year 2006, corresponding to about 15% of all CT examinations[5]. Nuclear cardiology stress testing in children is performed in 30% of US institutions, according to a recent survey of the AHA-ACC[24]. The Spanish Society of Cardiology has published data on pediatric cardiology[25] showing increases in the number of fluoroscopic procedures over the years 2000-2004 of between 21% (for dilation) to 97% (for embolizations).

Catheterization procedures in children are typically more time consuming than adult procedures [20]. For several reasons, procedure are more longer in children, especially infants because many patients have had previous studies and have limited access site; in infants the vessels are smaller and more difficult to cannulate; multiple angiograms in several cardiac chambers , using different views, are often needed.

Special problems of medical radiation in children

The growing use of interventional and non-invasive imaging with ionizing radiation in children represents a tremendous benefit for the diagnosis and treatment of small patients. However, there are special problems in children that one may wish to consider. First, for any given dose children

8

are three-to-four times more sensitive than adults to the induction of cancer as they have more rapidly dividing cells than adults and have longer life expectancy[1,3,11,12]. Second, for a given procedure, the effective dose is larger in a small infant than in an adult: organs are closer together in small children, resulting in more radiation dose to nearby organs when the volume of interest is being imaged[1,11,12]. Third, in pediatric cardiology, radiological procedures are practiced and/ or prescribed by cardiologists, who may sometimes have suboptimal awareness of doses and risks[26] due to lack of adequate formal radiation training[27]- although it is also true that even radiologists may substantially underestimate of radiation doses and risks[28]. Fourth, cardiological examinations deliver the highest organ dose from CT and interventions[29,30] to lung and breast. In particular, during a cardiac CT the breast dose is about 10-times higher than with cardiac interventional procedures. Recent ICRP 2007 documents[31] left virtually unchanged the whole body risk estimates, but raised the breast risk factor (i.e., the excess probability of fatal cancer) by 210%, from 40 in 1·000·000 per mSv in ICRP 1991 to 124 in 1,000,000 per mSv in ICRP 2007[31]. The same document also raised, albeit less markedly, the lung risk factor by 33%, from 85 to 113 in 1,000,000 per mSv. Although these estimates are clouded by a certain degree of uncertainty in the low dose range, the epidemiological data[32] in children exposed to medical radiation corroborate the assumption of all major organizations that even low doses can harm the patient, and no safe dose exists[12].

Comparison with previous radiological and biodosimetric studies

In our patients the main contribution to dose was from interventional procedures and CT (84% and 11% of the average dose, respectively). This picture is broadly consistent with recent data on sources of irradiation for the "average" (non-cardiological) patient[5] and on adult cardiological patient[33]. The present data are also in agreement with the preliminary data presented by the European Heart Survey, reporting an annual effective dose of 0·46 mSv/year in the follow-up of these patients, with about 80% of the dose coming from CT and angiography[34].

Chromosome aberrations in circulating lymphocytes are an intermediate end-point of carcinogenesis and a long-term predictor of cancer[13,14], and increase a few hours after a

9

fluoroscopic cardiac procedure in children was reported, in a pioneering study conducted in 1978 by Adams et al.[35] Young adolescents with repaired congenital heart disease who were exposed to low dose diagnostic ionizing radiation at age <1 year, have an up to three-fold increase in chromosomal aberrations in circulating lymphocytes decades after the exposure[14]. In the present study, the indirect population based estimates of cumulative dose and cancer risk were corroborated by direct measurements of MN increase in a subset of patients. The increase was obvious and consistent, although with substantial variability probably due to genetic differences in polymorphisms of genes involved in DNA damage and/ or repair and environmental oxidant-antooxidant milieu[36]. This approach provides a direct documentation of radiation genotoxicity and may clear the pathway to individually tailored radiation-sparing or chemopreventive strategies.

Study limitations

The number of patients is relatively small, but they are consecutive and representative of the spectrum of clinical situations met in a contemporary pediatric cardiology and cardiac surgery. An undoubted limitation of our study is that the lifetime radiological history was derived from hospital records, when available, and from patient history. This leads unavoidably to an approximation, and possibly to an underestimation, of the total radiological burden .

Another limitation is that there is in the real world a marked variability in the dose of each exam[37]. This variability is highest for interventional procedures. For instance, a percutaneous procedure of closure of patent ductus arteriosus is associated with an average effective dose corresponding to 7·6 mSv, but the individual procedure value may range anywhere in between 2·1 and 36 mSv[4,38,39] Both these aspects – the recall bias and the adoption of typical dose values from the literature rather than true measured values – might have affected the precision of individual patient dose estimation, but are unlikely to substantially affect the order of magnitude of observed values. In addition, we integrated the history-based approach, based upon indirect assessment of doses and population-based estimates of risks, with a direct, patient based, individual assessment of patient dose and of acute radiation damage through direct bio-dosimetry with micronucleus assay and faithful radiation

1

dose measurement with DAP. The 2 approaches are conceptually complementary and seem to point in the same direction, that a potentially oncogenic radiation induced damage is not negligible in these children.

Clinical implications: justify and optimize

Although the benefits of imaging are immense, it is also possible that not all these examinations are entirely appropriate and that there is a suboptimal management of radiological doses (and long-term cancer risks) in everyday clinical practice of pediatric cardiology. The radiation concern is particularly important in our patients with congenital heart disease for three reasons. First, adult grown-up patients with surgically repaired congenital heart disease are a large and growing population, estimated to be one million in US in the year 2000, compared to an estimated 300,000 in 1980, and 1·4 million are anticipated in 2020[40]. Second, the long-term outcome of the underlying cardiac disease has been dramatically improved by interventions in the last decade, and now their excellent long-term survival is the rule, rather that the exception[9,10]. Third and most importantly, children are several times more sensitive to radiation than middle –aged adults[1,3,11,12]. Therefore, when managing today a serious condition such as a complex congenital heart disease, we have also to protect the patient from risks that may become clinically manifest after years and even decades. We should justify the indication and optimize the dose delivery, adjusting doses, reducing multiple scans with contrast material, and eliminating inappropriate referrals.

For instance, the application of currently available dose-reduction techniques for heart scan and invasive cardiology could be strongly applied in daily practice in order to allow a reduction of patient doses whilst maintaining the image quality[41,42]. These practice patterns were recommended by the FDA, the European Union referral guidelines for imaging, and by the recent White Paper of the American College of Radiology[43]. In Europe the justification, optimization and responsibility principles are also reinforced by the EURATOM law[44]. The challenge ahead is to implement these recommendations in universal clinical practice.

1

Exclusive licence

The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of

all authors, an exclusive licence (or non-exclusive for government employees) on a worldwide basis

to the BMJ Publishing Group Ltd and its Licensees to permit this article (if accepted) to be

published in Heart and any other BMJPGL products to exploit all subsidiary rights, as set out in our

licence .

1

REFERENCES

1) **United Nations Scientific Committee** on the sources and effects of Ionising radiation. Report on the effects of atomic radiation to the general Assembly, 2000. Medical radiation exposures. United Nations, New York, 2001.

2) **Picano E**. Sustainability of medical imaging. *BMJ* 2004; 328: 578-80.

3) **Hall EJ.** Lessons we have learned from our children: cancer risks from diagnostic radiology. *Pediatr Radiol* 2002; 3: 700-6.

4) **Vano E**, Faulkner K. ICRP special radiation protection issues in interventional radiology, digital and cardiac imaging. *Radiat Prot Dosimetry* 2005; 117: 13-17.

5) **Brenner DJ**, Hall EJ . Computed tomography--an increasing source of radiation exposure. *N Engl J Med* 2007; 357: 2277-84.

6) **Togni M**, Balmer F, Pfiffner D, Maier W, Zeiher AM, Meier B. Percutaneous coronary intervention in Europe 1992-2001. *Eur Heart J* 2004; 25: 1208-1213.

7) **Lucas FL**, DeLorenzo MA, Sievers AE, Wennberg DE. Temporal trends in the utilization of diagnostic testing and treatments for cardiovascular disease in the United States, 1993-2001. *Circulation* 2006; 113: 374-379.

8) **Ayanian JZ**. Rising rates of cardiac procedures in the United States and Canada. Too much of a good thing? *Circulation* 2006; 113: 333-335.

9) **Patel HT**, Hijazi ZM. Pediatric catheter interventions: a year in review 2004-2005. *Curr Opin Pediatr* 2005;17: 568-73.

10) **Justino H**. The ALARA concept in pediatric cardiac catheterization: techniques and tactics for managing radiation dose. *Pediatr Radiol* 2006; 36: 146-153.

11) **International Commission on Radiation Protection**: Radiation and your patient: a guide for medical practitioners. A web module produced by Committee 3 of the International Commission on Radiological Protection 2001. Available at: www.icrp.org/docs/Rad_for_GP_for_web.pdf. (accessed July 27, 2008).

12) **Committee to Assess Health Risks from Exposure to Low Levels of Ionizing Radiation**; Nuclear and Radiation Studies Board, Division on Earth and Life Studies, National Research Council of the National Academies. *Health Risks From Exposure to Low Levels of Ionizing Radiation: BEIR VII Phase 2*. Washington, DC: The National Academies Press; 2006.

13) **Bonassi S**, Znaor A, Ceppi M, Lando C, Chang WP, Holland N, Kirsch-Volders M, Zeiger E, Ban S, Barale R, Bigatti MP, Bolognesi C, Cebulska-Wasilewska A, Fabianova E, Fucic A, Hagmar L, Joksic G, Martelli A, Migliore L, Mirkova E, Scarfi MR, Zijno A, Norppa H, Fenech M. An increased micronucleus frequency in peripheral blood lymphocytes predicts the risk of cancer in humans. *Carcinogenesis* 2007; 28: 625-631.

14) **Andreassi MG**, Ait-Ali L, Botto N, Manfredi S, Mottola G, Picano E. Cardiac catheterization and long-term chromosomal damage in children with congenital heart disease. *Eur Heart J* 2006; 27: 2703-8.

15) **Betsou S**, Efstathopoulos EP, Katritsis D, Faulkner K, Panayiotakis G. Patient radiation doses during cardiac catheterisation procedures. *Br J Radiol* 1998; 71: 634–639.

16) **Hirshfeld JW** Jr, Balter S, Brinker JA, Kern MJ, Klein LW, Lindsay BD, Tommaso CL, Tracy CM, Wagner LK, Creager MA, Elnicki M, Lorell BH, Rodgers GP, Weitz HH American College of Cardiology Foundation; American Heart Association/; HRS; SCAI American College of Physicians Task Force on Clinical Competence, Training. ACCF/AHA/HRS/SCAI clinical competence statement on physician knowledge to optimize patient safety and image quality in fluoroscopically guided invasive cardiovascular procedures: a report of the American College of Cardiology Foundation/ American Heart Association/American College. *Circulation* 2005; 111: 511–532.

17) **Boothroyd A**, McDonald E, Moores BM, Sluming V, Carty H. Radiation exposure to children during cardiac catheterization. *Br J Radiol* 1997; 70: 180 –185.

18) **Moore JD**, Shim D; Sweet J, Arheart KL, Beekman RH. Radiation exposure to children during coil occlusion of the patent ductus arteriosus. *Catheter Cardiovasc Interv* 1999; 47: 449-54.

19) **Bacher K**, Bogaert E, Lapere R, De Wolf D, Thierens H. Patient-specific dose and radiation risk estimation in pediatric cardiac catheterization. *Circulation* 2005; 111: 83–89.

20) **Martinez LC**, Vano E, Gutierrez F, Rodriguez C, Gilarranz R, Manzanas MJ. Patient doses from fluoroscopically guided cardiac procedures in pediatrics. *Phys Med Biol* 2007; 52: 4749-59.

21) **Brody AS**, Frush DP, Huda W, Brent RL; American Academy of Pediatrics Section on Radiology. Radiation risk to children from computed tomography. *Pediatrics* 2007; 120: 677-82.

22) **Fenech M**. Optimisation of micronucleus assays for biological dosimetry. In: Gledhill BL, Mauro F, eds. New Horizons in Biological Dosimetry. New York: Wiley; 1981. p373–376.

23) **Hall EJ**. Lessons we have learned from our children: cancer risks from diagnostic radiology. *Pediatr Radiol* 2002; 32: 700-6.

24) **Rodgers GP**, Ayanian JZ, Balady G, Beasley JW, Brown KA, Gervino EV, Paridon S, Quinones M, Schlant RC, Winters WL Jr, Achord JL, Boone AW, Hirshfeld JW Jr, Lorell BH, Rodgers GP, Tracy CM, Weitz HH. Rodgers, American College of Cardiology/American Heart Association Clinical Competence Statement on Stress Testing. A Report of the American College of Cardiology/American Heart Association/American College of Physicians-American Society of Internal Medicine Task Force on Clinical. *Circulation*. 2000; 102: 1726.

25) **López-Palop R**, Moreu J, Fernández-Vázquez F, Hernández R; Sección de Hemodinámica y Cardiología Spanish Cardiac Catheterization and Coronary Intervention Registry. 14th official report of the Spanish Society of Cardiology Working Group on Cardiac

Catheterization and Interventional Cardiology (1990-2004)]. *Rev Esp Cardiol* 2005; 58: 1318-34.

26) **Correia MJ**, Hellies A, Andreassi MG, Ghelarducci B, Picano E. Lack of radiological awareness among physicians working in a tertiary-care cardiological centre. *Int J Cardiol* 2005; 103: 307– 311.

27) **Vano E**, Gonzalez L, Fernandez JM, Alfonso F, Macaya C. Occupational radiation doses in interventional cardiology: a 15-year follow-up. *Br J Radiol* 2006; 79: 383-8.

28) **Lee CI**, Haims AH, Monico EP, Brink JA, Forman HP. Diagnostic CT scans: assessment of patient, physician, and radiologist awareness of radiation dose and possible risks. *Radiology*. 2004; 231: 393-8.

29) **Zanzonico P**, Rothenberg LN, Strauss HW. Radiation exposure of computed tomography and direct intracoronary angiography: risk has its reward. *J Am Coll Cardiol* 2006; 47: 1846-9.

30) **Einstein AJ**, Henzlova MJ, Rajagopalan S. Estimating risk of Cancer associated with radiation exposure from 64-slice Computed Tomography Coronary Angiography. *JAMA* 2007; 298 : 317- 323.

31) **International Commission on Radiation Protection**. Recommendations of the International Commission on Radiological Protection. ICRP publication 103. Ann ICRP 2007; 37: 1-332.

32) **Kleinerman RA**. Cancer risks following diagnostic and therapeutic radiation exposure in children. *Pediatr Radiol* 2006; 36: 121-5.

33) **Bedetti G**, Botto N, Andreassi MG, Traino C, Vano E, Picano E. Cumulative Patient Effective Dose in Cardiology. *Br J Radiol* 2008.

34) **Hoffmann A**, Engelfriet P, Mulder B. Radiation exposure during follow-up of adults with congenital heart disease. *Int J Cardiol* 2007; 118: 151-3.

1

35) **Adams FH**, Norman A, Bass D, Oku G. Chromosome damage in infants and children after cardiac catheterization and angiocardiography. *Pediatrics* 1978; 2: 312–316.

36) **Au WW**. Heritable susceptibility factors for the development of cancer. *J Radiat Res* 2006; 47 Suppl B: 13-17.

37) **Einstein A.** Radiation risk from coronary artery disease imaging: how do different diagnostic tests compare? *Heart* 2008; 94: 1519 – 1521.

38) **Kocinaj D**, Cioppa A, Ambrosini G, et al. Radiation dose exposure during cardiac and peripheral arteries catheterisation. *Int J Cardiol* 2006; 113: 283-4.

39) **Neofotistou V**, Vano E, Padovani R, et al. Preliminary reference levels in interventional cardiology. *Eur Radiol* 2003; 13: 2259-63.

40) **Brickner ME**, Hillis LD, Lange RA. Congenital heart disease in adults. First of two parts. *N Engl J Med* 2000; 342: 256-63.

41) **Kuon E.** Radiation exposure in invasive cardiology. *Heart* 2008; 94: 667 - 674.

42) **Rixe J**, Conradi G, Rolf A, Schmermund A, Magedanz A, Erkapic D, Deetjen A, Hamm C, Dill T. Radiation Dose Exposure of Computed Tomography Coronary Angiography - Comparison of Dual Source-, 16 –slice and 64–slice – CT. Heart 2009; doi:10.1136/hrt.2008.161018

43) **Amis ES** Jr, Butler PF, Applegate KE, Birnbaum SB, Brateman LF, Hevezi JM, Mettler FA, Morin RL, Pentecost MJ, Smith GG, Strauss KJ, Zeman RK,. American College of Radiology. American College of Radiology white paper on radiation dose in medicine. *J Am Coll Radiol* 2007; 4 :272-84.

44) **Council Directive 97/43/Euratom of 30 June 1997** on health protection of individual against the dangers of ionizing radiation in relation to medical exposure, and repealing Directive 84/466/Euratom. Official Journal of the European Communities L 180 1997: 0022-7.

FIGURES LEGEND

Figure 1. The most frequent examinations and total collective dose in CHD : relative contribution of conventional radiographs, computed tomography, diagnostic catheterization and interventional radiology to (A) the frequency and (B) the total collective effective dose.

Figure 2:. Box-and-whiskers plot of micronuclei number before and 2-hours after radiation exposure in the overall population. Median and 25-75 percentiles are shown for each group. Values above the 90th percentile and below the 10th percentile (outliers) have been separately plotted (as circles).

Table 1: Demographic and clinical characteristics of the study population

Variable	Value
Age, mean ±SD, years	2.8±3.2
(range)	(1 month-16 years)
Gender, n	
Male/female	42/17
BMI, kg/m^2	11.5±15
(range)	(2.1-75)
Diagnosis, n	
Transposition of the great arteries (± ventricular septal defect)	12
Coarctation of the aorta (±ventricular septal defect)	8
Tetralogy of Fallot	7
Pulmonary stenosis	6
Functionally univentricular heart	5
Pulmonary atresia (± ventricular septal defect)	4
Patent ductus arteriosus	3
Other complex CHD	14

1

Table 2. Representative effective radiation dose, range and equivalent number of plain chest radiographs for pediatric cardiac procedures

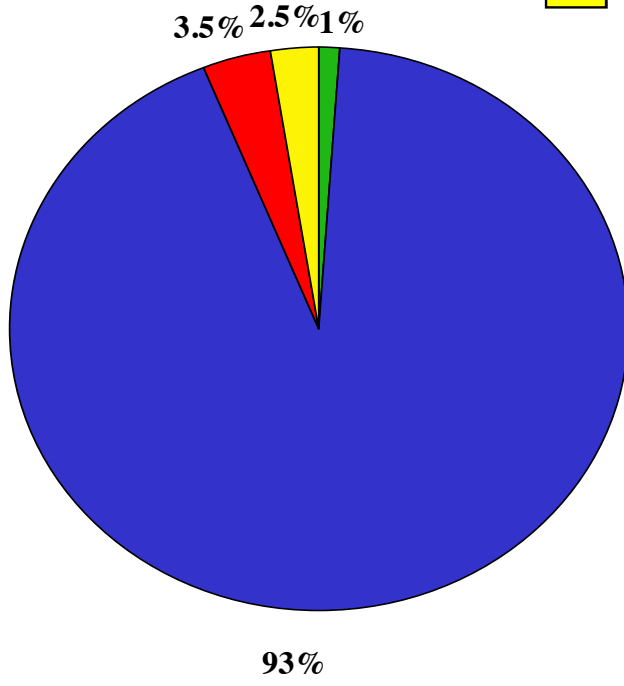| Examination	Effective dose, mSv (range)	Chest X-rays (range)
Conventional Radiology		
Chest x ray (single postero-anterior)	0.02	1
Computer Tomography		
Head CT	4 (1-6)	200 (50-300)
Chest CT	3 (5-12)	150 (250-600)
Abdomen CT	5 (4-20)	250 (200-1000)
Interventional Cardiology		
Diagnostic catheterization	4.6 (0-6-23)	230 (30-1150)
Therapeutic catheterization	6 (1-37)	300 (50-1850)

Table 3. Typical effective dose from pediatric and cardiology procedures

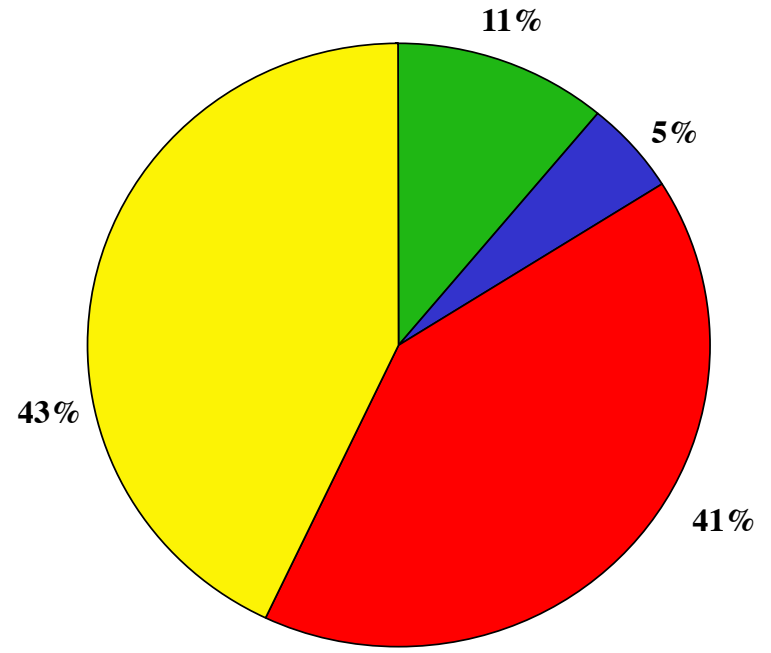| Examination	Total Number	Number per patient, mean (range)
Conventional Radiology		
Chest x ray	1432	25.1 ± 25.7 (1-144)
Computer Tomography		
Head CT	7	1.0 ± 0.6 (0-2)
Chest CT	7	1.2 ± 0.4 (1-2)
Interventional Cardiology		
Diagnostic catheterization	55	1.3 ± 0.6 (1-3)
Therapeutic catheterization	40	1.2 ± 0.6 (1-4)

Table 4. Patient dose for diagnostic and therapeutic catheterization procedures

Type of Procedure	Gender	Age, months	Weight, kg	Fluoroscopy time, min	DAP Gy cm²
Diagnostic	M	5	4.9	30	7
Stent implantation	M	168	57.0	25	277
Diagnostic	F	36	12.4	26	20
Diagnostic	F	1	2.9	23	6
Diagnostic	M	6	9.4	3	1
Balloon valvuloplasty	M	4	4.2	24	12
Diagnostic	M	8	6.7	34	14
Stent implantation	F	168	58.0	19	64
Stent implantation	F	192	75.0	13	99
Diagnostic	M	96	23.8	17	20
Diagnostic	M	132	37.0	30	65
Diagnostic	M	24	12.5	20	14
Diagnostic	M	6	5.0	27	12
Stent implantation	M	120	27.7	26	93
Diagnostic	F	48	29.0	19	35
Diagnostic	M	8	7.0	25	14
Diagnostic	M	96	25.2	28	35
Diagnostic	M	5	6.0	21	28

A) Frequency of examinations

B) Total collective dose

Legend:
- X-rays
- Computed Tomography
- Diagnostic cath
- Interventional cath

A) 93%, 3.5%, 2.5%, 1%

B) 11%, 5%, 41%, 43%