THE DEPARTMENT OF ONCOLOGY-PATHOLOGY

Karolinska Institutet, Stockholm, Sweden

# RADIATION DOSE AND RELATED RISK IN INTERVENTIONAL CARDIOLOGY

Angeliki Karambatsakidou


Karolinska Institutet

Stockholm 2021

Published by Karolinska Institutet.
Printed by US-AB 2020

ISBN 978-91-8016-061-2

# RADIATION DOSE AND RELATED RISK IN INTERVENTIONAL CARDIOLOGY

## THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

**Angeliki Karambatsakidou**

*Principal Supervisor:*
Assoc Prof Annette Fransson
Karolinska Institutet
Department of Oncology-Pathology

*Co-supervisor:*
PhD Gavin Poludniowski
Karolinska Institutet
Department of Clinical Science, Intervention and Technology

*Opponent:*
PhD Claire-Louise Chapple
University of Newcastle upon Tyne, England

*Examination Board:*
Assoc Prof Michael Sandborg
Linköping University Hospital
Department of Medical Radiation Physics

Assoc Prof Anders Tingberg
Lund University
Department of Medical Radiation Physics

Assoc Prof Sven Nyrén
Karolinska Institutet
Department of Molecular Medicine and Surgery

*To my beloved sons Konstantinos and Leandros*

*"Γηράσκω δ' αεί πολλά διδασκόμενος"*

*As I grow older, I constantly learn more*

*Solon 630-560 BC*

**CONTENTS**

# ABSTRACT

Cardiac catheterization procedures are classified as high radiation dose procedures, European Directive 2013/59/Euratom, and may result in skin injuries (deterministic effects) and/or increased cancer risk (stochastic effects). The radiation-induced effects can be expressed differently depending on whether the patient is a child or an adult. In adults there is an increased risk for developing radiation-induced skin injuries while in children the risk for radiation-induced cancer is more prominent. The cancer risk associated with radiation should be communicated to patients [directive 2013/59/Euratom], and patients with increased risk for skin injuries should be included in a follow-up program [ICRP 85]. However, skin dose and cancer risk estimates from cardiac interventional procedures are complicated because the dose indicator on the X-ray equipment only provides information on the total amount of radiation (air kerma-area product, KAP and cumulative air kerma at patient entrance reference point) used, without taking into account different radiation geometries.
To facilitate monitoring of radiation induced effects, conversion coefficients that relate the radiation exposure as expressed by the air kerma-area product (KAP) to maximum entrance skin dose (MESD), equivalent organ dose ($H_T$), effective dose (E), risk for exposure-induced cancer death (REID) and organ-specific risks of exposure-induced cancer death ($REID_{HT}$) have been estimated in the current thesis. Based on such coefficients, simple tools are suggested that can be used in the clinical routine with the aim to assess radiation doses and related risks. Two commercial software were used for the estimation of dose and related risks, WinODS (version 1.0a; RADOS Technology Oy, Finland) and PCXMC (v.1.5 and v.2.0; Radiation and Nuclear Safety Authority, Helsinki, Finland). In addition, film dosimetry techniques were been used for skin dose determination.

The results from cohort studies on adult patients that underwent cardiac procedures showed that the skin dose (MESD) varies with both the type of cardiac procedure and with the skill of operator. On a patient-by-patient basis, the conversion coefficient relating KAP to skin dose can be used to identify patients with risk for radiation induced skin injury, to be included in follow up programs in accordance with ICRP 85.

The relationship between E and KAP and between $H_T$ and KAP demonstrated a need for age- dependent conversion coefficients (E / KAP; $H_T$ / KAP) within the paediatric age range. Estimation of these quantities are performed using radiation

exposure data retrieved from the patient radiation dose sheet as well as data from the complete radiation dose structured reports (RDSR); the latter contains detailed information on beam geometry and exposure data for the whole procedure. No significant difference between the two methodologies could be demonstrated for the population-averaged conversion coefficients (E / KAP; $H_T$ / KAP) except for $H_T$ (lung) in new-borns. The importance of this outcome is that hospitals that do not have access to the data retrieval and calculational methods used in this thesis (partly in-house development) can apply less detailed techniques without a significant effect on the estimated population dose, for a specific age group.

Furthermore, the relationship between risk for exposure-induced cancer death (REID) and KAP displayed both age- and gender-dependence for paediatric cardiac catheterization procedures. The conversion coefficient (REID / KAP) can be used to assess the population cancer risk. In clinical situations, the estimated population cancer risk for the procedure can guide the operator in communicating risks to the patient/parent. Additionally, it has been shown that the risk organs for adult patients undergoing cardiac catheterizations are lung and bone marrow (leukemia), as well as for children lung and breast.

The thesis introduces a novel concept based on age- and gender-specific risk reference values (RRV) that is related to a specific REID-level. By setting an "acceptable" level on the REID for a given patient group, the corresponding KAP value can be calculated and used for monitoring risk for late effects when performing cardiac intervention.

In conclusion, cardiac catheterizations are life-saving procedures and thus the benefit is always considered to outweigh the risk. However, the ALARA principle (as low as reasonably achievable) must still be applied, which means that the patient must not be exposed to a higher radiation dose than is required for the procedure. Conversion coefficients presented in this dissertation can be a support for applying both the ALARA principle in clinical practice as well as for the identification of patients to be included in follow-up programs addressing skin injury and for communicating population cancer risk to patients. An additional intent of this thesis work has been to shed further light on important parameters that affect the radiation dose and risk, such as beam geometry (related to operator skill) and patient age and gender.

# SUMMARY IN SWEDISH / SAMMANFATTNING PÅ SVENSKA

Hjärtkateteriseringar definieras som högdosingrepp i EU direktivet 2013/59/Euratom och bedöms kunna orsaka strålningsrelaterade skador. Effekterna kan se olika ut beroende på om patienten är ett barn eller en vuxen. Vuxna har en ökad risk för hudskador (akuta skador) medan barn som är mer strålkänsliga än vuxna har högre risk för strålningsinducerad cancer (sena skador). Internationella strålskyddsorgan har tagit fram direktiv och rekommendationer för att följa upp patienter med strålningsinducerade akuta skador (ICRP 85) och även göra patienterna medvetna om de sena skadorna från strålningen via information som de ska få från vårdgivaren (direktiv 2013/59/Euratom).

Hjärtkateterisering är ett ingrepp som utförs genom att föra in en kateter (tunn slang) i ett kärl via ljumsken eller armen samt spruta in kontrast samtidigt som man använder röntgenstrålning för att visualisera kärlen. Denna teknik används för att diagnostisera olika typer av hjärtfel och/eller behandla dem. Under senare tid har antalet ingrepp ökat pga att risken för medicinska komplikationer är mindre med denna teknik jämfört med öppen kirurgi. Huddos- och cancerriskuppskattningar från hjärtkateteriseringar är emellertid komplicerade eftersom dosindikatorn på röntgenutrustningen endast ger information om den totala mängden strålning (air kerma-area produkten, KAP och luftkerma i patientens referenspunkt) som använts, utan att ta hänsyn till olika bestrålningsgeometrier.

Fokus för denna avhandling var att analysera hur den totala strålningsmängden (KAP) förhåller sig till huddos (MESD, *maximum entrance skin dose*), ekvivalent organdos ($H_T$), effektiv dos (E), cancerrisk (REID, *risk for exposure-induced cancer death*) och organspecifik cancerrisk ($REID_{HT}$, *organ-specific risks of exposure-induced cancer death*) med syfte att tillhandahålla enkla verktyg att användas i den kliniska rutinen för att bedöma stråldoser och relaterade risker. De kommersiella mjukvaror som använts var WinODS (version 1.0a; RADOS Technology Oy, Finland) och PCXMC (v.1.5 och v.2.0; Radiation and Nuclear Safety Authority, Helsinki, Finland). Dessutom har filmdosimetriteknik använts för huddosbestämning.

Resultaten från kohortstudier på vuxna patienter som genomgått hjärtprocedurer visade att huddosen (MESD) varierar med såväl procedur som operatör. För den enskilda patienten kan omvandlingskoefficienten som relaterar KAP till huddos

användas inför beslut om uppföljning av eventuell hudskada i enlighet med ICRP 85.

Relationen mellan E och KAP och mellan $H_T$ och KAP har analyserats retrospektivt för patienter i olika åldersgrupper som genomgått hjärtprocedurer. Effekten av minskad strålkänslighet med stigande ålder kunde synliggöras genom omvandlingskoefficienterna (E/KAP; $H_T$/KAP) som tydligt minskade med stigande ålder för den pediatriska gruppen. Förståelse för sambandet mellan dos och risk och dess variation med ålder är av speciell vikt för barn; detta för att ej underskatta risken för sena effekter hos de yngre patienterna. I dessa studier användes dels strålningsrelaterade data från patientens stråldosrapport, dels uppgifter från den fullständiga RDSR-rapporten; den senare innehåller detaljerad information om strålgeometri och exponeringsbetingelser för hela proceduren. En viktig slutsats var att den mer exakta metoden baserad på RDSR-data inte signifikant påverkade omvandlingskoefficienterna och att enklare metoder för beräkning av sådana koefficienter därmed kan användas (undantag av $H_T$ lunga för nyfödda).

Vidare har förhållandet mellan risk för cancer (REID) och KAP analyserats retrospektivt för hjärtkateteriseringar. Resultaten visade att omvandlingskoefficienten för cancerrisk (REID/KAP) är både ålders- och könsberoende för den pediatriska gruppen. Denna omvandlingskoefficient kan användas vid bedömning av den populationscancerrisk som ingreppet innebär. I den kliniska situationen kan en skattad populationscancerrisk från användningen av strålning under ingreppet vara ett stöd för remittent/operatör när man ska informera om den risk som ingreppet innebär till patienten/föräldern. Information om strålningsrelaterade risker förutsätts vårdgivaren kunna ge enligt det europeiska direktivet 2013/59/Euratom. Studierna fastställde vidare att riskorganen för vuxna patienter som genomgår hjärtkateterisering är lunga och leukemi samt för barn lunga och bröst.

En relativ hög andel, 7%, av alla hjärtkateteriseringar utförs på barn. För att hjälpa operatören att bevaka dos-/risk-nivåer till patienter av olika ålder och kön som genomgår hjärtkateteriseringar har ett nytt koncept introducerats för dessa förfaranden. Det nya konceptet baseras på ålders- och könsspecifika riskreferensvärden (RRV) som relateras till populationscancerrisken. Genom att ansätta en ”acceptabel” nivå för den strålningsrelaterade risken för en given patientgrupp kan motsvarande KAP-värde beräknas och användas som ett monitoreringsverktyg i klinisk rutin.

Hjärtkateteriseringar är livräddande ingrepp och därmed bedöms nyttan alltid vara större än risken. ALARA-principen (as low as reasonably achievable) ska dock

fortfarande tillämpas vilket innebär att patienten inte ska utsättas för högre stråldos än vad som krävs för ingreppet. Omvandlingskoefficienter som presenteras i denna avhandling kan vara ett stöd för att tillämpa såväl ALARA-principen i den kliniska verksamheten som inför beslut om uppföljning av patienter med möjliga hudskador och för att kommunicera populationscancerrisk till patienter.

# LIST OF SCIENTIFIC PAPERS

I. **Skin dose alarm levels in cardiac angiography procedures: is a single DAP value sufficient?**
Karambatsakidou A, Tornvall P, Saleh N, Chouliaras T, Löfberg P-O, Fransson A.
Br J Radiol – 78:803-809 (2005)

II. **Effective dose conversion factors in paediatric interventional cardiology.**
Karambatsakidou A, Sahlgren B, Hansson B, Lidegran M, Fransson A.
Br J Radiol 82:748-755 (2009).

III. **Calculating organ and effective doses in paediatric interventional cardiac radiology based on DICOM structured reports – Is detailed examination data critical to dose estimates?**
Karambatsakidou A, Omar A, Fransson A, Poludniowski G.
Physica Medica 57:17–24 (2019)

IV. **Age-specific and gender-specific radiation risks in paediatric angiography and interventional cardiology: conversion coefficients and risk reference values.**
Karambatsakidou A, Steiner K, Fransson A, Poludniowski G.
Br J Radiol. 93(1110):20190869 (2020)

V. **Skin dose, effective dose and related risk in transcatheter aortic valve implantation (TAVI) procedures: is the cancer risk acceptable for younger patients?**
Karambatsakidou A, Omar A, Chehrazi B, Rück A, Scherp Nilsson J, Fransson A.
Radiat Prot Dosimetry 169(1-4):225-31 (2016)

# OTHER PUBLICATIONS AND PROFFERED PAPERS

I. **Plasma exudation in the skin measured by external detection of conversion electrons.**
Karambatsakidou A, Bergh G, Ahlgren L, Strand SE, Olsson O, Greiff L, Wollmer P.
Eur J Nucl Med. 1996 Mar;23(3):290-4

II. **Relationships between entrance skin dose, effective dose and dose area product for patients in diagnostic and interventional cardiac procedures.**
Hansson B, Karambatsakidou A.
Radiation Protection Dosimetry. Vol. 90, Nos 1-2, pp. 141-144 (2000)

III. **A new method using conversion electrons from In-113m transferrin to monitor plasma exudation in the skin.**
Strand S-E, Wollmer P, Karambatsakidou A, Olsson O, Bergh G, Greiff L. The Journal of Nuclear Medicine. 1994 May;35(5):176-177

IV. **Estimation of maximum skin dose and average lung dose in coronary angiography procedures.**
Karambatsakidou A, Tornvall P, Saleh N, Löfberg P-O, Fransson A.
European Radiology, 14 (Suppl 2), p. 520, 2004

V. **Automatic Monitoring of Accumulated Dose Indices From DICOM RDSR to Improve Radiation Safety in X-Ray Angiography.**
Omar A, Bujila R, Nowik P, Karambatsakidou A.
The 56th Annual Meeting & Exhibition of the American Association of Physicists in Medicine in Austin, TX from July 20 - 24, 2014 at the Austin Convention Center

VI. **New Challenges in Optimization of radiation-dose in infants hip examinations X-ray Procedures.**
Mobini S, Finnbogasson T, Östlund B-M, Chouliaras T, Karambatsakidou A, Lindström J.
8th European Conference on Medical Physics, Athens, Greece, 11-13 September, 2014

VII. **Dose and risk in paediatric interventional cardiology.**
Karambatsakidou A, Fransson A.
Röntgenveckan, Karlstad, Sverige, 8-12 September, 2014

/III. **Do we need action levels in paediatric interventional cardiology**.
Karambatsakidou A, Fransson A.
Nationellt möte om sjukhusfysik 2014, Vann, Sverige, 12-14 November, 2014

IX. **Skin dose, effective dose and related risk in TAVI procedures – Is the cancer risk acceptable for younger patients?**
Karambatsakidou A, Omar A, Chehrazi B, Rück A, Scherp Nilsson J, Fransson A.
Fourth Malmö Conference on Medical Imaging 2015, Gothenburg, Sweden, 28-30 May, 2015

X. **Radiation dose and risk-related observation levels in paeditric angiography and interventional cardiology.**
Karambatsakidou A, Omar A, Kvanta E, Fransson A.
4th Symposium of NACP, Oslo, Norge, 6-8 Feb, 2017

XI. **The dose to the lens of the eye for the heart team performing transcatheter aortic valve implementation (TAVI): Is there any concern for cataract?**
Karambatsakidou A, De Palma R.
Abstract from the 2nd European Congress of Medical Physics.
Physica Medica 52:84 (2018)

XII. **Cancer risk and associated conversion coefficients within paediatric angiography and interventional cardiology.**
Karambatsakidou A, Fransson-Andreo A, Kvanta E, Odenberg Storrank C, Poludniowski G. EuroSafe Imaging, 2020

# LIST OF ABBREVIATIONS

| | |
|---|---|
| ABM | Active bone marrow |
| ALARA | As low as reasonably achievable |
| BEIR | Biological Effects of Ionizing Radiation |
| CA | Coronary angiographies |
| CC | Conversion coefficient |
| CPE | Charge particle equilibrium |
| DDREF | Dose and dose rate effectiveness factor |
| DICOM | Digital Imaging and Communications in Medicine |
| E | Effective dose |
| EAR | Excess absolute risk |
| EC | European Commission |
| EPA | Environmental Protection Agency |
| ERR | Excess relative risk |
| Euratom | European Atomic Energy Community |
| FP | Flat panel detector |
| FR | Frontal |
| FSD | Focus-to-skin distance |
| HB | Homogeneous bone |
| HIS | Hospital information system |
| IAEA TRS | International Atomic Energy Agency Technical Reports Series |
| ICRP | International Commission on Radiological Protection |
| IEC | International Electrotechnical Commission |
| II | Image intensifier |
| IR | Interventional radiology |
| Kerma | Kinetic energy released in mater |
| KAP | Air kerma-area product |
| kVp | Peak tube kilovoltage |
| L | Linear dose-effect relationship |

| | |
|---|---|
| LAR | Lifetime attributable risk |
| LAT | Lateral |
| LQ | Linear-quadratic dose-effect relationship |
| MESD | Maximum entrance skin dose |
| NCRP | National Council on Radiation Protection and Measurements |
| $P_{KA}$ | Air kerma-area product |
| PCI | Percutaneous coronary intervention |
| PTCA | Percutaneous transluminal coronary angioplasty |
| Q | Quadratic dose-effect relationship |
| RDSR | Radiation dose structured reports |
| REID | Risk for exposure-induced cancer death |
| $REID_{HT}$ | Organ-specific risks of exposure-induced cancer death |
| RRV | Risk reference value |
| TAVI | Transcatheter aortic valve implantation |
| TLD | Thermoluminescent dosimeter |
| UNSCEAR | United Nations Scientific Committee on the Effects of Atomic Radiation |

# 1 INTRODUCTION

In the past three decades, both incidence of and mortality from acute myocardial infarction have decreased dramatically in Sweden (Swedish National Board of Health and Welfare) [1]. This general trend in high income countries is reflected on in a paper by Dagenais *et al* [2], in which cancer is presented as the most common cause of death in middle-aged patients in countries with a high living standard. The positive development within cardiovascular disease has been promoted by effective preventive measures and by the introduction of catheter-based x-ray interventional techniques allowing for improved treatment outcomes. However, on a global scale cardiovascular disease still ends up as the major cause of death.

The most common type of cardiovascular disease is coronary artery disease causing blocked or narrowed heart arteries. This is today treated with catheter-based x-ray interventional techniques [3]. The era of catheter-based cardiac treatment, angioplasty, started in 1977 and since then the number of interventional procedures has increased significantly [4-6]. In Sweden, around 2 million (approximately 20% of the population) suffer from cardiovascular disease, and about 45 000 coronary angiographies (CA) and 25 000 percutaneous coronary interventions (PCI), also referred to as percutaneous transluminal coronary angioplasty (PTCA), are performed yearly (Swedeheart annual report, 2019) [7]. The less invasive nature of interventional techniques compared to surgery is manifested in shortened hospitalization and improved quality of life.

Cardiac interventional procedures are classified as high radiation dose procedures [8, 9] with the main radiation induced side effect being skin injury (deterministic effect/tissue reaction; of main concern in adult patients) and increased cancer risk (stochastic effect; of main concern in paediatric and young adult patients). International radiation protection bodies have addressed these concerns by providing directives and recommendations in areas such as dose monitoring [8], risk communication [9] and follow-up of patients with skin injuries [10]. However, maximum entrance skin dose (MESD; given by the equivalent dose to the skin in this thesis) and risk for exposure-induced cancer death (REID) is complex to estimate since the dose indicator easily obtainable from the catheterization equipment, the air kerma-area product (KAP), only reports the total amount of radiation used during the procedure without taking into account the different irradiation projections used. The conditions inherent to catheterization procedures

call for reliable, yet fast, methods to estimate MESD and REID in the clinical setting. Such methods have not been available.

This thesis addresses methods that can be applied to relate the KAP-value from an intervention to patient dose and related cancer risk with focus on cardiac treatments with catheter-based x-ray techniques. Both deterministic effects (here: skin dose, MESD) and stochastic effects (here: cancer risk, REID) have been investigated. The purpose has been to provide medical staff performing cardiac catheterizations with tools to address concerns related to the use of radiation on patient safety from such procedures. The work addresses specifically key factors that contribute to the uncertainty in the estimation of radiation dose and risk, such as patient age, gender, operator experience and irradiation geometry.

The main method to estimate MESD has been film dosimetry whereas equivalent organ dose ($H_T$), effective dose (E) and REID have been estimated through Monte Carlo (MC) simulations based on data from radiation dose structured reports (RDSR) and/or from patient radiation dose sheet.

Figure 1 summarizes the major events in the evolution of radiation protection relevant to interventional radiological techniques since the beginning of the interventional era. The contributions to the field from papers which are included in this thesis are presented in chronological order along this timeline.

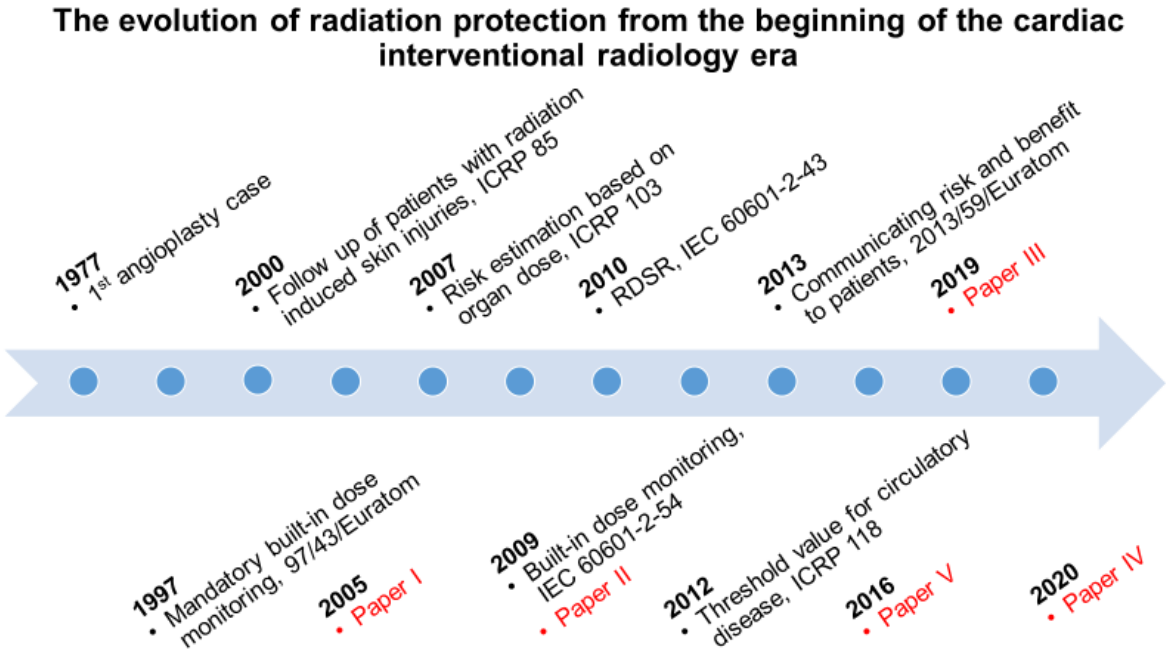



Figure 1 The evolution of radiation protection from the beginning of the cardiac interventional radiology era.
Paper I: Patient data (adults); conversion coefficients for maximum entrance skin dose (MESD) for different cardiology procedures and different operators
Paper II: Patient data (paediatric); age-dependent conversion coefficients for effective dose (E)
Paper III: Patient data (paediatric); age-dependent conversion coefficients for equivalent organ dose ($H_T$) and E
Paper IV: Patient data (paediatric); age- and gender-dependent conversion coefficients for risk for exposure-induced cancer death (REID), age- and gender-dependent conversion coefficients for organ-specific risks of exposure-induced cancer death ($REID_{HT}$) and age- and gender-dependent risk reference values (RRV)
Paper V: Patient data (adult); TAVI; conversion coefficients for MESD, E and REID

# 2 BACKGROUND

## 2.1 DOSE AND RISK IN INTERVENTIONAL RADIOLOGY– INTERNATIONAL PRACTICE WITHIN RADIOLOGICAL PROTECTION

Interventional radiology (IR) refers to minimally invasive techniques that are used to diagnose and/or treat deeply situated structures by introducing a catheter through a tiny opening in the body and visualize its movement inside the body using x-ray imaging. The use of radiation can involve side effects referred to as either deterministic (acute effects) and/or stochastic (long term) effects. Deterministic effects, sometimes referred to as *harmful tissue reactions* in this thesis, can appear if the radiation dose reaches certain threshold levels. Stochastic effects (*cancer*), on the other hand are believed not to have any threshold and with a risk that increases with dose. Another important factor that needs to be taken into account is that the radiation sensitivity for deterministic and stochastic effects in a specific organ can differ between children and adults [9].

### Deterministic effects

At the dose levels used in IR, deterministic effects could appear in the skin, brain, eye lens and the heart. In their 2013 report UNSCEAR concluded that the paediatric brain (cognitive defects), eye lens (cataract) and heart (circulatory disease) appeared to be more radiation sensitive compared to adults [9]. The skin seemed, on the other hand, to be more resistant in children which could reflect a faster skin repair process in children compared to in adults.

The most common type of harmful tissue reactions within IR are skin reactions [11] where the basal layer of the epidermis, being the second outermost layer of the epidermis, is at greatest risk [12]. Radiation skin reactions start with early transient erythema for skin doses >2 Gy (few hours after exposure) and is developed to main erythematous reactions for skin doses ~6 Gy (~10 days after exposure) and later, to dermal ischaemia for skin doses ~15 Gy (8-10 weeks after exposure). The threshold doses indicate the radiation required to cause a tissue reaction in 1% of the exposed individuals [13].

## Stochastic effects

Current risk models are based on epidemiological data from the Japanese atomic bomb survivors in Hiroshima and Nagasaki (1945) taking into account the site of cancer, gender, age at exposure and attained age. The dose-effect relationship for stochastic effects are considered as being either linear (L), linear-quadratic (LQ) or quadratic (Q), depending on the specific organ. The Japanese epidemiological data is continuously updated, and existing dose effect estimates include cancer incidence and mortality data from this population until 1998 and 1987 (cancer incidence: BEIR VII, UNSCEAR 2006, ICRP 103 (solid cancer), [14]; ICRP 103 (leukemia) [15]) and until 2000 (cancer mortality: BEIR VII, UNSCEAR 2006, [16]). One of the organizations (ICRP) has stopped using mortality data and now includes only data for cancer incidence [13]. This is motivated by a considerably decline in mortality due to improved cancer treatments.

While the dose effect at higher radiation doses can be modelled based on the outcome from the Japanese atomic bomb events, the relationship between low radiation dose and cancer induction continuous being a topic of much debate in the scientific community. More data will be needed to resolve this issue of great concern in a society that relies so heavily on medical diagnosis and treatments using radiation; interventional radiology included. As science progresses, updated models to determine the radiation induced cancer risk are being developed with the current ones published in BEIR VII [17], ICRP 103 [13], and UNSCEAR 2006 [18]. The general consensus is that children and young adults are more sensitive to stochastic effects of radiation than the elderly population. This is related to their larger proportion of dividing cells together with more years of post-exposure life (13, 17, 19). At the same time, some contradictory views on this issue related to specific cancer sites exists as e.g. UNSCEAR 2013 [19] states that 10% of the cancer types observed in children show less sensitivity to radiation (e.g. lung) than adults and only 25% of the cancer types in children show a higher sensitivity (leukemia, thyroid, skin, breast and brain).

In order not to overestimate the cancer risk at low dose and low dose-rate (< 100 mSv, < 0.1 mGy/min, [20]) a dose and dose rate effectiveness factor (DDREF) was introduced in ICRP 60 [21]. Table 1 summarizes the variations on DDREF used by the different organizations. The variation reflects how the DDREF was derived, where UNSCEAR [18] base DDREF on life span study data, BEIR [17] on life span study and animal-data and ICRP [13] on human epidemiological studies (including life span study) and animal studies.

Yet another concern relates to the risk models, excess absolute risk (EAR) and excess relative risk (ERR), used to estimate radiation induced cancers across populations with different baseline cancer rates. To offset this transfer error, BEIR [17] and ICRP [13] use a weighted average of the EAR- and ERR-based risk estimates for each cancer site. UNSCEAR [18] have instead chosen to present the result from each model separately and at the same time expresses concern for the uncertainty involved with transferring risk across populations.

The lifetime attributable risk (LAR) and the REID have been used to express the risk to a reference population (Euro-Americans in this thesis) over a lifetime to develop or die from radiation related cancer. The difference between these risk descriptors is the implementation of the survival function, where LAR refers to the survival function in an unexposed population and REID refers to the survival function in a population following exposure to radiation. At low dose, such as in diagnostic radiology, LAR and REID can be regarded as equal [22]. It should be noted that while ICRP [13] and BEIR [17] use LAR to express population risk, UNSCEAR [18] has chosen to use REID.

The current recommendations of the different international organizations discussed here (UNSCEAR, ICRP, BEIR) on which model should be applied together with their respective data sources are summarized in table 1. Other models exist, such as the EPA from the U.S [23]. It uses the same basic model as BEIR VII [17] with some modifications.

The radiation risk estimates presented in the papers included in this thesis are all based on the BEIR risk models [17].

Tabell 1 Comparison of the three cancer risk models, BEIR VII, UNSCEAR 2006 and ICRP 103

| | BEIR VII | UNSCEAR 2006 | ICRP 103 |
|---|---|---|---|
| Epidemiological data | Epidemiological data from the Japanese atomic bomb survivors | | |
| Dose-risk relationship | Leukemia: LQ[1]<br>Solid cancer[6]: L[2] | Leukemia: LQ[1,2]<br>Solid cancer[7]: LQ[1], L[2] with exception of skin and bone cancer | Leukemia: LQ[2]<br>Solid cancer[8]: L[2] |
| Risk transfer model for lung and breast | Lung: ERR/EAR - 30%/70%<br>Breast: EAR - 100% | Doesn't uses a hybrid ERR/EAR-model. Uses each model separately | Lung: ERR/EAR - 30%/70%<br>Breast: EAR - 100% |
| Reference population. | American | [China, Japan, Puerto Rico, UK, USA][3] | Euro-American[4] and Asian[5] |
| DDREF | 1.5 | 2 | 2 |

L, linear; LQ, linear-quadratic; ERR, excess relative risk; EAR, excess absolute risk; DDREF, dose and dose rate effectiveness factor

[1]mortality; [2]morbidity; [3]five populations separately; [4]averaged over Sweden, UK and USA; [5]averaged over Shanghai, Osaka, Hiroshima, Nagasaki; [6]include stomach, colon, liver, lung, breast, prostate, ovary, bladder, thyroid, and others; [7]not specified; [8]include thyroid, breast, esophagus, stomach, colon, liver, lung, ovary, bladder, and others.

## 2.2 DOSE AND RISK DESCRIPTORS

Estimation of risk from the use of radiation relies on a reasonably accurate dose estimate. While patient dose estimation in radiation therapy based on high energy external beam or brachytherapy techniques involves advanced and individualized dose planning since many years, diagnostic and interventional procedures have had to rely on much more crude and rudimentary approaches to estimate dose. Today, the access to detailed information on each irradiation event that forms part of a patient diagnostic/interventional procedure is slowly changing this and more sophisticated approaches to estimate dose can be attempted.

The main dose and risk descriptors of interest in interventional radiology are described below.

## Dose descriptors

A key quantity is the dose index $P_{KA}$ (also referred to as KAP). KAP has been used to obtain coefficients to convert a radiation exposure to dose or to risk for adverse radiation effects in groups of patients.

The $P_{KA}$ is expressed as the product of air kerma free-in-air ($K_a$) and beam area (A=x*y) in a plane perpendicular to the beam axis [24]:

$$P_{\mathrm{KA}} = \int_A K_{\mathrm{a}}\ (x, y)\ dx\ dy \quad (1)$$

Harmful tissue reactions can appear following exposures exceeding a dose of 2 Gy to the skin [10]. The absorbed dose to the skin on the beam entrance side (D) is estimated according to equation 2 (IAEA TRS-457 [25]; Benmakhlouf *et al* [26]).

$$D = K_{a,i} * B_a(Q, FS) * (\mu_{en}(Q, FS)/\rho)_{w,a} \quad (2)$$

where $B_a(Q, FS)$ = backscatter factor in air for beam quality Q and field size FS
$K_{a,i}$ = incident air kerma
$(\mu_{en}(Q, FS)/\rho)_{w,a}$ = mass-energy absorption ratio, water to air, for beam quality Q and field size FS

## Risk descriptors

Estimating the risk of cancer induction in an exposed population relies on access to estimates of dose to the different organs of the body. The relation between $H_T$ (used to estimate stochastic effects of radiation) and mean absorbed dose is defined as [13]:

$$H_T = \sum_R \left(D_{T,R} w_R\right) \quad (3)$$

where $D_{T,R}$= mean absorbed dose in organ T from radiation of quality R
$w_R$ = radiation weighting factor ($w_R$=1 for x-rays)

The radiation weighting factor accounts for variation in biological (detrimental) effect from different types of radiation.

The effective dose (E) is a quantity that has been applied to provide gross risk estimates from the use of radiation for radiation protection purposes. Although it is not aimed for risk estimations in patients, it has been applied in communicating the risk from the use of radiation in health care for many years. It is calculated from the $H_T$ [13]:

$$E = \sum_T (H_T w_T) \quad (4)$$

where $H_T$ = equivalent organ dose (organ T) for an adult reference person
$w_T$ = tissue weighting factor (averaged over age- and gender)

The tissue $w_T$ accounts for variation in radiation sensitivity between different tissues/organs.

The lifetime risk quantity REID is used for population cancer risk estimations in this thesis, and is defined as the difference in mortality rate for exposed and unexposed populations of a given gender and a given age of exposure [27]:

$$\text{REID}(e, H_T) = \int_{e+L}^{\infty} [\lambda(a \mid e, H_T) - \lambda(a)]\, S(a \mid e, H_T)\, da \quad (5)$$

where L= latency time; L=5 years for solid cancers and L=2 years for leukemia
a = attained age (years)
e = age at exposure (years)
$H_T$ = equivalent organ dose in organ T
$\lambda(a \mid e, H_T) = \lambda(a)\,[1+\text{ERR}(a, e, H_T)]$ or/and
$\lambda(a \mid e, H_T) = \lambda(a) + \text{EAR}(a, e, H_T)$

The $\lambda(a \mid e, H_T)$ is the cancer mortality rate at age *a* given that the person was exposed at the age e, the $\lambda$ (a) is the background/baseline cancer mortality rate without radiation exposure. The survival function $S(a \mid e, H_T)$ denotes the probability that the person is alive at age *a*, given an equivalent organ dose $H_T$ at the age *e*.

The lifetime risk quantity REID [27] has been slightly modified by the BEIR VII [17] committee through replacing the survival function $S(a \mid e, H_T)$ in equation 5 with the $S(a \mid e)$, the probability of an unexposed person to survive to age a, and renamed the REID to LAR. For x-ray diagnostic radiation doses, the REID and LAR can be considered almost identical [22]. LAR is also used in ICRP 103 [13].

Epidemiological data from exposed atomic bomb survivors in Hiroshima and Nagasaki (1945) is used to derive the two risk models, ERR and EAR. Each risk model is determined for solid cancer and leukemia and for cancer incidence and/or cancer mortality. Moreover, ERR and EAR are used to transfer the risk estimates from the Japanese atomic bomb survivors to a reference population (Euro-Americans in this thesis) in terms of lifetime risk.
The basic formula of the risk models (equation 6) is expressed as the product of the dose-response function $F_1(D)$ being linear (solid cancer), linear-quadratic (leukemia) or quadratic, and the modifier function $F_2(X)$ being an exponential function

including age at exposure, attained age and gender as variables. Equation 6 applies for risk models (ERR, EAR) used in BEIR VII [17], ICRP 103 [13] and UNSCEAR 2006 [18].

$$\text{ERR or EAR} = F_1(D) \times F_2(X) \quad (6)$$

where $$F_1(D) = \begin{cases} \alpha D & \text{Linear} \\ \alpha D + \beta D^2 & \text{Linear-quadratic} \\ \beta D^2 & \text{Quadratic} \end{cases}$$

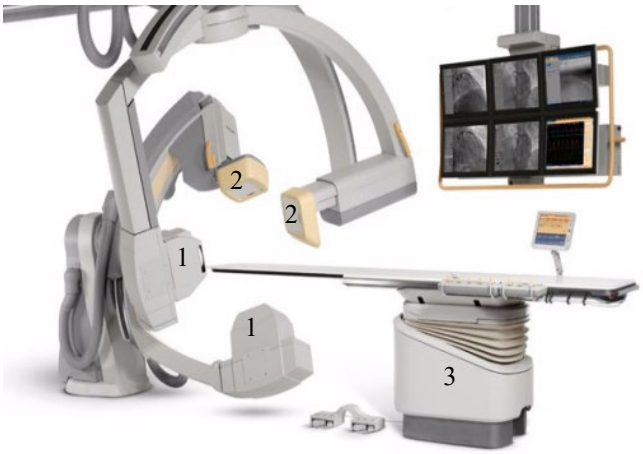
$$F_2(X) = e^{\theta X}$$

α, β, θ = fitting parameters, determined using epidemiological data from an exposed population.

To obtain the best possible cancer risk transfer between epidemiological data and a reference population (Euro-Americans in this thesis), a weighted mean of ERR and EAR is adopted in BEIR VII. The weightings are 0.7/0.3 (ERR/EAR) for most solid cancers. For lung cancer the weightings are reversed and for breast- and thyroid cancers the EAR- and ERR-model are applied, respectively.

For low dose and/or dose rate exposures, BEIR VII corrects the estimated risks for solid cancers by dividing the risk value obtained with a DDREF of 1.5.

## 2.3 INTERVENTIONAL TECHNIQUES IN CARDIAC PROCEDURES




1. X-ray tube
2. Image receptor
3. Patient couch

Figure 2 Schematic image of a biplane angiography and interventional system (reproduced courtesy of Philips).

Cardiac catheter-based angiography and interventional procedures are performed with dedicated x-ray systems which can be either monoplane (adult patients) or biplane (paediatric patients, fig. 2). The system uses predefined programs that allow for varying settings of parameters such as frame rate, air kerma rate, total tube filtration, and automatic dose rate control; the latter adjusts the beam quality to patient size and type of examination. Furthermore, different magnification modes can be chosen manually by the operator. Since 2010, all angiography and interventional x-ray systems produce DICOM Radiation Dose Structured Reports (RDSR) [28] that contain information on parameter settings from each irradiation event during the complete intervention. In addition, it is mandatory that the system provides information on the cumulative air kerma-area product, KAP, from the entire examination [8].

Interventional procedures are dynamic in that they use varying irradiation beam geometries and projections, beam qualities and dose rates. A single KAP-value is therefore not sufficient to determine whether the dose to a specific organ is high or not. Due to the complex nature of these examinations the KAP-value must therefore be accompanied with information on the type of catheter-based procedure. For patient risk estimations, information on the patient's age and gender are essential.

Cardiac catheterization procedures are minimally invasive and are performed by an interventionist (operator) who uses a catheter (thin, plastic tube) that is inserted into the blood vessel via the groin or arm and is then guided into the heart during radioscopy. In the next step, contrast dye is injected while radiation is used to visualize and detect blocked/narrowed heart arteries, a narrowed aortic valve and/or other cardiac pathologies. Blocked arteries are treated with angioplasty/percutaneous coronary intervention (PCI) procedures and consists of placing a stent to widen the artery. A calcified aortic valve is treated using the transcatheter aortic valve implant (TAVI) technique which involves replacing the valve with an implant taken from an animal (cow/pig). In paediatric patients with congenital cardiac disease, catheter-based techniques are used to repair defects such as holes or narrowed arteries/valves.

In children the use of magnification modes and higher frame rates is common due to the thinner vessels and higher heart rates observed in these patients.

## 2.4 RADIATION RELATED RISKS IN INTERVENTIONAL CARDIOLOGY

Since the introduction of catheter-based techniques to diagnose and treat heart conditions, radiation induced effects such as skin burns in adult patients and increased cancer risk in younger patients have been of concern. Figure 3 illustrates

how the two types of adverse radiation effects i.e. harmful skin reactions (deterministic) and radiation induced cancer (stochastic) vary with dose.

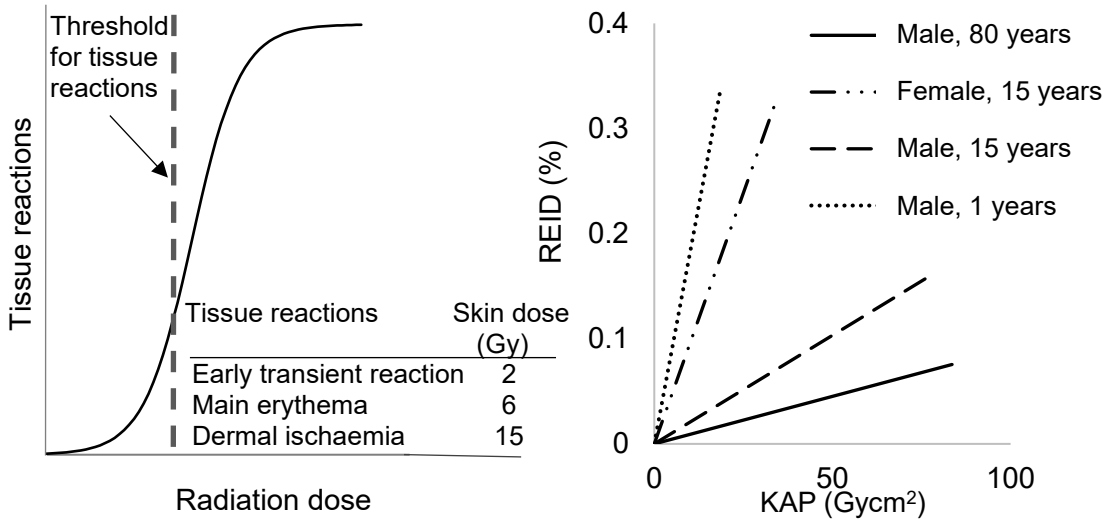



Figure 3 Deterministic effects with threshold values for some skin reactions (left panel; modified from ICRP 103) and stochastic effects in patients undergoing cardiac interventions; the latter illustrating the dependence on age and gender (right panel, data from paper IV and V).

### 2.4.1 Deterministic effects in cardiac interventions

Skin reactions occur when the radiation dose exceeds a specific threshold dose value (fig. 3, left panel). The severity of the skin reactions varies with dose in a typical s-shaped manner [13]. High skin doses from interventional procedures could be expected after repeated or very complex procedures. In very rare situations dose levels like those given in fractionated radiotherapy have been reported [10]. In interventional cardiology the problem of high skin dose is reduced to adult patients. This is related to the relatively higher radiation exposure that is required to perform an intervention on the adult trunk compared to a much thinner paediatric patient. In addition, the skin of children is believed to be more resistant to radiation [19]. Thus, skin injuries from cardiac interventions are not a concern for this latter patient group [29-31].

Tissue reactions from heart procedures have been documented in the literature since the 1990s [32-38]. Despite the fast development and increased use of such techniques the reported occurrence of skin injuries or inflammatory skin reactions from such procedures continues to be rather low (1:10000-1:100000; [39]). This may to some extent be due to that the medical staff is not always aware of the risk for such injuries and will therefore not communicate this to the patient either.

However, all patients undergoing IR procedures should be counselled on radiation related risks, before and after the IR procedure, and those with increased risk of radiation induced skin injuries should be followed up in accordance with the recommendations by ICRP 85 [10]. In addition, notes should be included in the patient record if MESD ≥ 1 Sv (equals 1 Gy in absorbed dose from x-rays) for procedures which might be repeated or if the cumulative MESD ≥ 3 Sv (or 3 Gy in absorbed dose from x-rays). The care-provider should provide a follow-up program for patients having reached a cumulative MESD of 3 Sv (or 3 Gy in absorbed dose) or higher.

### 2.4.2 Stochastic effects in cardiac interventions

Interventional radiology plays an important role in children suffering from congenital cardiac disease and, in recent years, the frequency of such procedures has increased [40]. Congenital heart disorders affect around 0.8% of the new-borns [41] and many of these children require complex medical treatment involving radiation. There are indications that E >50 mSv are associated with increased cancer risk [13, 17]; such dose levels are not unusual in this patient group. Figure 3 (right panel) illustrates the dose-risk pattern for patients undergoing interventional cardiac procedures i.e. that the radiation related cancer risk at a given KAP-level is higher in younger patients than in elderly, and also higher in female compared to male patients.

Children with congenital heart defects often undergo multiple examinations involving radiation [42-44], especially the very young ones [45]. This contributes to high cumulative organ doses and thus increased risk for cancer. Taking this into consideration, paediatric cardiac radiological interventions are still justified compared to alternative treatments using surgical intervention as the latter in general involves other, more severe, risks for the individual patient [9]. At the same time and due to a longer life expectancy in children compared to adults, it is of utmost importance to consider and, if possible, reduce any extra risk for adverse health effects in these patients. In order to achieve this, staff need to be well informed of the possible risks associated with paediatric interventions and also be acquainted and feel comfortable with how to communicate risks associated with radiation exposure to the patients and/or their parents.

# 3 METHODOLOGY TO ESTIMATE DOSE AND RISK FROM CARDIOLOGY INTERVENTIONS

The Karolinska University Hospital is specialized in paediatric cardiac catheterization procedures and also performs a substantial number of catheterizations on adult patients. From a clinical perspective, there is a need to understand how the measured/estimated KAP-value from a cardiac catheterization procedure relates to risk for deterministic and stochastic effects for a given type of procedure and patient age/gender group. This requires estimates of the radiation dose delivered to different organs.

The current work focuses on the estimation of the MESD, $H_T$, E, REID, $REID_{HT}$ and the associated conversion coefficients based on KAP from cardiac catheterization procedures in adult and paediatric patients.

## 3.1 SKIN DOSE MONITORING

Maximum entrance skin dose is not directly available from the DICOM/RDSR data pertaining to a specific patient procedure. The dose monitoring from the catheterization equipment instead only reports the total amount of radiation used during the complete procedure (KAP) and the cumulative air kerma at patient entrance reference point (15 cm from the isocenter in direction towards the x-ray tube [46]). A pragmatic approach to address this problem was suggested by the NCRP [47] and consists of implementing an overall action level for patient follow-up of 500 $Gycm^2$ (KAP), or 5 Gy in cumulative air kerma at the patient entrance reference point.

In order to decrease the large uncertainties involved with the NCRP approach, several publications have reported alternative techniques for skin dose estimations. They include techniques based on measurements, such as using thermoluminescent dosimeters (TLD), films, real-time patient dosimeters, or on theoretical models [48-58]. Common to all these techniques is, however, that they cannot easily be implemented in a clinical setting due to either complexity and/or cost.

The last 7-8 years, dose mapping systems have become available: Dose Tracking System (Toshiba/Canon Medical Systems Corporation) [59], Dose Map (General Electric, Fairfiled, USA) [60], em.dose (esprimed SAS, Villejuif, France) [61]. They provide a skin dose map and a value of the maximum skin dose, either in real-time

(Dose Tracking System, Dose Map) or retrospectively (em.dose). A disadvantage is that these systems normally are restricted to be used with one specific manufacturer's equipment (em.dose is system independent). A common method to validate dose mapping software is radiochromic film, which is also considered as the gold standard for entrance skin dose estimations.

The question is what a film placed on the beam entrance side actually measures and how it relates to the dose to the skin? Looking at the different layers of the epidermis, its outermost layer is composed of dead skin and thereby not sensitive to radiation induced damage. The second layer, on the other hand, is indeed radiation sensitive and therefore of interest here. Given that the build-up region encountered in the energy range of diagnostic x-rays [62] can be equated with the thickness of the dead skin layer [63], the maximum dose is consequently deposited in the second outermost layer of the epidermis where the condition of charged particle equilibrium (CPE) exists. The effective point of measurement of the Gafchromic film XR-RV3 (116.5 μm) used in this work is only slightly larger than the thickness of to the dead skin layer (~80 μm). We can therefore assume that CPE exists at the point of measurement and thereby the film dose equates the dose to the sensitive part of the epidermis.

The MESD from film measurements is estimated using a calibration curve which converts the pixel values/optical density into absorbed dose (or entrance surface kerma) to air. This is followed by a calculation of the dose to water by applying the mass-energy absorption coefficient ratio $(\mu_{en}/\rho)_{w,air}$. It should be noted that in this thesis the calibration curves included the effect of backscatter that exists in the clinical situation with a patient being exposed. The (skin) dose for a specific beam quality based on the incident air kerma ($K_{a,i}$) at the film entrance level can be estimated using equation 2 [26].

In this work, Gafchromic film, slow radiographic films (EDR2, Kodak) and diode dosimeters (Unfors Patient Skin Dosemeter (PSD); Unfors Instruments, Billdal, Sweden) have been used to estimate skin dose.

Based on estimated maximum skin doses, conversion coefficients correlating MESD with KAP for different types of cardiac procedures are presented. The impact of operator experience is addressed for the first time in paper I. The use of such coefficients as triggers for follow-up of patients at risk for radiation-induced skin injuries is suggested.

Other groups have reported conversion coefficients for MESD/KAP with results showing both good correlation between MESD and KAP [51, 64, 65], and poor correlation [66-68].

## 3.2 ESTIMATION OF ORGAN DOSE AND EFFECTIVE DOSE

Effective dose is a convenient tool for simple relative cancer risk comparisons between different procedures and x-ray modalities. When more detailed cancer risk assessments are attempted, ICRP 103 [13] recommends the use of equivalent organ doses. A few papers have reported organ doses from paediatric cardiology procedures [31, 69-72].

Commonly applied methods for the estimation of organ- and effective dose in diagnostic radiology include the PCXMC v.2.0 software [73] (Radiation and Nuclear Safety Authority, Helsinki, Finland) or measurements using anthropomorphic phantoms with inserted dosimeters.

One of the first programs to calculate organ dose from diagnostic radiology examinations was WinODS [74] (version 1.0a; RADOS Technology Oy, Finland). It was based on a size- and gender-adjustable phantom model and pre-calculated depth-dose distributions in a homogeneous water phantom. The program, a kind of pioneer in this field, was used in paper I and is a precursor to the software PCXMC.

Dose calculations with PCXMC v.1.5 and v.2.0 [75, 73] are performed using the Monte Carlo (MC) technique to simulate radiation transport. It has been applied in this thesis to estimate dose and radiation risk from cardiac catheterizations in papers II-V. The mechanisms of interaction included in the MC simulations are photo-electric absorption and Rayleigh- and Compton scattering. For beam energies used in interventional radiology, the secondary electrons in soft tissue are of such low energy that they can be treated as being absorbed at the site of the photon interaction, the only exception being in the bone marrow.
In, PCXMC the dose to the active bone marrow (ABM) is assessed using a three-factor technique by Lee C [76]. In this method, the ABM and the rest of the skeletal bone are treated as homogeneous bone tissue (HBT). The absorbed dose to the ABM is determined from the energy deposited in the HBT and applying correction factors that take into account 1) the fraction of ABM in the HBT area 2) the higher energy absorption in hard bone at low photon energies and 3) the increased absorbed dose by the photoelectrons as they enter the ABM from trabeculae.

To calculate $H_T$ and E in PCXMC v.2.0, mathematical hermaphrodite phantom models of Cristy and Eckerman [77] are used with small modifications [73]. The phantoms model humans of different age and gender (newborn, 1- , 5- , 10- , 15-

years old and adult). Data on peak tube kilovoltage (kVp), thickness of beam total filtration, KAP-value, collimated beam size, beam position, focus-to-skin distance (FSD), irradiation geometry are used together with patient height, weight and age as input to the organ dose calculations. The program reports the mean absorbed dose averaged over the organ volume.

As interventional procedures include multitudes of radiation events, detailed exposure data from RDSR can be used as input to the calculations in order to reduce the uncertainties of the organ dose estimates. In case RDSR data is not easily available, the patient radiation dose sheet that can be obtained from the x-ray system at the end of the procedure can be used.

In this thesis work, E and/or $H_T$ have been estimated using three different approaches to account for the variation of beam geometry and radiation quality during the procedure:

1. Using precalculated conversion coefficients for E ($CC_{E:KAP}$=E/KAP) derived by Schmidt *et al* [78], combined with correction factors to adjust for different tube voltages and filtrations. With this approach, the main simplifications are related to the irradiation geometry (fixed field sizes for each age group, fixed focus-skin distance) and to exposure-related data from the radioscopy part of the intervention (all radioscopy performed using only the frontal plane; anterior-posterior projection). These assumptions were needed as detailed information on the variation of these parameters during the intervention could not be retrieved from the patient radiation dose sheet.
2. Using the dose calculation software PCXMC v.1.5 and v.2.0 [75, 73] /WinODS [74] together with exposure related data from patient radiation dose sheet. The same assumptions on the irradiation geometry as above are adopted. Further, due to lack of data in the patient radiation dose sheet, the KAP from all radioscopy irradiation is assumed to be delivered either from the anterior-posterior projection (study V) or equally distributed over the complete set of radiography images (study III).
3. Using the software PCXMC v.2.0 [73] incorporated into an inhouse developed framework that perform automated dose calculations based on detailed patient beam data from RDSR files and data from the hospital information system (HIS) on patient height and weight [79]. This approach consists of three steps, where the first is to define the correlation between the patient's anatomy and the projected x-ray beam. This is done using a so-called target-centric approach that is based on locating body anatomies using information on which position is most irradiated, i.e. the target. Next step

takes into account the absorption properties of the patient table in order to calculate a $K_{a,i}$ on the location of the phantom model. The final step is to convert the $K_{a,i}$ at beam entrance to $H_T$ using PCXMC v.2.0 [73].

## 3.3 ESTIMATION OF RISK FOR RADIATION INDUCED CANCER

The effective dose, E, has long been used as an indicator of cancer risk [29, 40, 43, 80, 81]. However, as this dose quantity (equation 4) is based on a "reference adult person", the cancer incidence in patient groups with higher risk, such as children and female patients, is underestimated using this concept. In addition, the use of E in risk estimations is sensitive to changes in tissue weighting factors, $w_T$s. To assess the radiation-induced cancer risk in different patient cohorts, the ICRP [13] commission instead suggests the use of the mean equivalent organ dose, $H_T$ (or mean absorbed (organ) dose).

The E, $H_T$, REID and $REID_{HT}$ reported in this thesis are estimated using the software PCXMC v.1.5 and v.2.0 [75, 73]. All REID calculations were performed using version 2.0 of the software. The underlying risk module of PCXMC v.2.0 [73] is based on the risk models (ERR and EAR) from BEIR VII [17] and takes into account cancer site, gender, ethnicity, age at exposure and attained age. The lifetime risk quantity used in PCXMC v.2.0 [73] is the REID and not the simplified form of the lifetime risk LAR used by the BEIR VII [17] commission. For lifetime risk estimations, age-dependent mortality and cancer incidence rates for a Euro-American population [13] were used in this work.

In PCXMC v.2.0 the upper limit in the REID (infinity; equation 5) is replaced by 120 years. PCXMC v.2.0 has by default a DDREF factor of 1.5 in solid cancers and 1 for leukemia. For high organ doses (several tens or hundreds of mSv) PCXMC v.2.0 recommends a DDREF factor of 1 also for solid cancers, which must be corrected manually.

To correlate the KAP-value to organ dose or cancer risk is not a trivial task in interventional cardiology due to the large variations in patient size and various types of cardiac procedures encountered. In addition, gender plays an important role in risk estimation and needs to be taken into account.

In this thesis, conversion coefficients for equivalent organ dose ($CC_{HT:KAP}=H_T/KAP$), effective dose ($CC_{E:KAP}=E/KAP$) and cancer risk ($CC_{REIDHT:KAP}=REID_{HT}/KAP$; $CC_{REID:KAP}=REID/KAP$) are presented for different patient age and gender.

It is to our knowledge the first-time methods are presented that relate KAP with organ dose and cancer risk in paediatric interventional cardiology. It is also the first time an automated approach based on complete patient RDSR data linked to a commercial dose/risk estimation software have been attempted for this purpose.

# 4 SCIENTIFIC QUESTIONS, STUDY DESIGN AND RESULTS

The aim of this thesis has been to estimate radiation dose and associated risks from interventional cardiac radiology procedures performed on paediatric and adult patients using modern angiographic equipment. Such equipment provides the user with information on two dose-related metrics, the cumulative air kerma at patient entrance reference point [46] and/or the total KAP from the procedure. While the cumulative air kerma at patient entrance reference point can only be used in rough estimates of skin dose, the KAP provides a measure of the total amount of radiation used during the procedure and holds information that can be used to estimate dose to different organs and the risk for inducing cancer. In this thesis, the KAP-value plays a key role as the conversion coefficients for MESD, $H_T$, E, REID and $REID_{HT}$ are all expressed as a function of KAP. Access to such conversion coefficients allows for a direct estimation of levels of skin and organ doses to patients/group of patients undergoing this kind of procedures and thereby provide a link to risks for radiation induced deterministic and stochastic effects. They can be easily implemented in clinical routine work and used to trigger actions in areas such as follow-up of patient skin dose and operator training.

The thesis includes 4 scientific questions related to dose and risk in interventional cardiology. A summary of these together with the intended clinical use of the results is presented in figure 4. Where tests of significance are applied, a significance level of $\alpha=0.05$ was selected. For some statistics, non-overlapping 95% confidence intervals have been used as a criterion for significance. Note that this criterion is simple to apply, but conservative (non-overlapping CIs unequivocally indicate significance at $\alpha=0.05$ but marginally overlapping CIs may still be significant at that level).

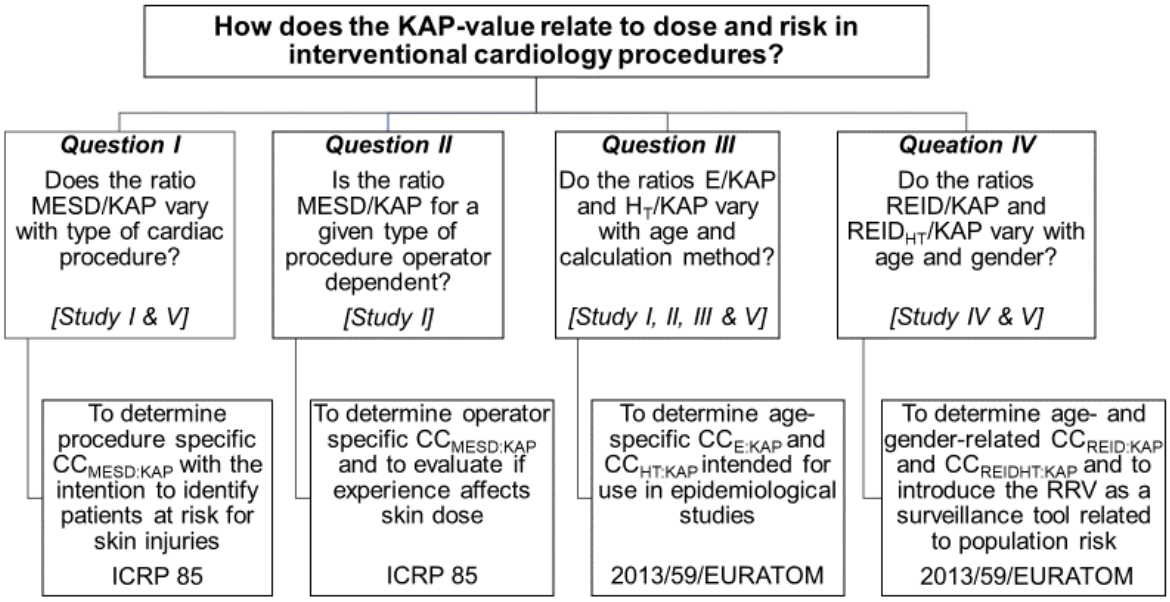



Figure 4 Overview of the scientific questions and clinical use of the conversion coefficients: $CC_{MESD:KAP}$ = MESD/KAP, $CC_{E:KAP}$ = E/KAP, $CC_{HT:KAP}$ = $H_T$/KAP, $CC_{REID:KAP}$ = REID/KAP, $CC_{REIDHT:KAP}$ = $REID_{HT/KAP}$.

## 4.1 DETERMINISTIC EFFECTS IN CARDIAC PROCEDURES

### 4.1.1 Outcome from question I [Studies I and V]

#### Scientific question I

Does the relation between patient skin dose (MESD) and total radiation exposure (KAP) vary with the type of cardiac procedure?

#### Study design

Study I was designed based on results from a pioneering work in the field performed at the Karolinska Hospital [58]. In the publication by Hansson [58], conversion coefficients (MESD/KAP) for different types of cardiac procedures (coronary angiography (CA), percutaneous coronary intervention (PCI)) were reported for the first-time. The work was based on measurements in anthropomorphic phantoms and the results indicated that the conversion coefficient for skin dose varied with the type of procedure. In studies I and V, the skin dose conversion coefficient and its dependence on procedure type is evaluated on patients undergoing CA, PTCA/PCI and TAVI. In both studies (I and V), the variation of patient skin dose and its

relationship to the amount of radiation used during the procedure, MESD/KAP, for different types of cardiac procedures (CA, PTCA/PCI, TAVI) are evaluated. All patient procedures were performed at the Karolinska University Hospital.

The skin dose distribution and MESD were estimated using radiographic slow film combined with direct reading diode dosimeters (EDR2, Eastman Kodak Co., Rochester, NY; Unfors Patient Skin Dosimeter (PSD), Unfors Instruments, Billdal, Sweden; paper I) and self-developed radiochromic films (XR-RV3 Gafchromic film, International Specialty Products, Wayne, NJ, USA; paper V). The film calibrations in the two studies were based on the detector R100B (RTI Electronics AB, Mölndal, Sweden; calibrated in terms of air kerma) traceable through PTW (Germany) and diode dosemeters (Unfors Patient Skin Dosemeter (PSD); Unfors Instruments, Billdal, Sweden; calibrated for air kerma) for Gafchromic and EDR2 films, respectively.

## Results

### *MESD and KAP for different types of cardiac procedures*

The MESD, KAP and corresponding conversion coefficient for skin dose ($CC_{MESD:KAP}$= MESD/KAP) for CA, PTCA and TAVI procedures are presented in Table 2 (film measurements). The linear correlations of MESD versus KAP were regarded as acceptable (r = 0.8-0.97).

Table 2 KAP (mean, range), MESD (mean, range), $CC_{MESD:KAP}$ (mean±1SD, 95% CI provided in square brackets) for patients undergoing CA (20 patients), PTCA (10 patients) and TAVI (15 patients).

| Procedure type | KAP ($Gycm^2$) | MESD (mSv) | $CC_{MESD:KAP}$ ($mSv/Gycm^2$) |
|---|---|---|---|
| CA | 49 (18-110) | 410 (150-1300) | 3.9±1.2 [3.3, 4.5] |
| PTCA | 40 (16-120) | 410 (150-1300) | 9.7±2.7 [7.8, 11.6] |
| TAVI | 29 (11-72) | 290 (100-870) | 9.7±1.5 [8.9, 10.5] |

KAP, air kerma-area product from the complete examination; MESD, maximum entrance skin dose; $CC_{MESD:KAP}$, conversion coefficient for maximum entrance skin dose; SD, standard deviation; CI, confidence interval (calculated using the t-distribution); CA, coronary angiography (diagnostic procedure); PTCA, percutaneous transluminal coronary angiography; TAVI, transcatheter aortic valve implantation.

The results based on diodes placed in the regions where the MESD was expected to be located showed a high failure rate with only 4 out of 20 (CA) and 1 out of 10 (PTCA) successful measurements using this technique.

### *Variation in irradiation technique used for different procedures*

Figure 5 (left panel) shows a typical skin dose distribution from a diagnostic procedure (CA), displaying the characteristic pattern with many projections and relatively few beam overlapping areas. As most CA procedures follow a standard irradiation technique, the skin dose distribution does not vary considerably between patients and in 90% of the patients included in this study, the MESD was positioned on the right-hand side of the patient's back. Unlike CA, PTCA procedures are typically performed using fewer irradiation projections with more overlap of irradiated areas as can be seen in figure 5 (middle panel). In interventional procedures as PTCA, the dose distribution can differ significantly from patient to patient and will depend on the complexity of the procedure. The higher skin doses observed from such procedures are mostly located in regions of beam overlap between projections.
The right panel in figure 5 shows a typical dose distribution map from TAVI procedures with few projections and frequent beam overlap. The skin dose distribution pattern for PTCA and TAVI results in similar $CC_{MESD:KAP}$ but from completely different dose distributions.

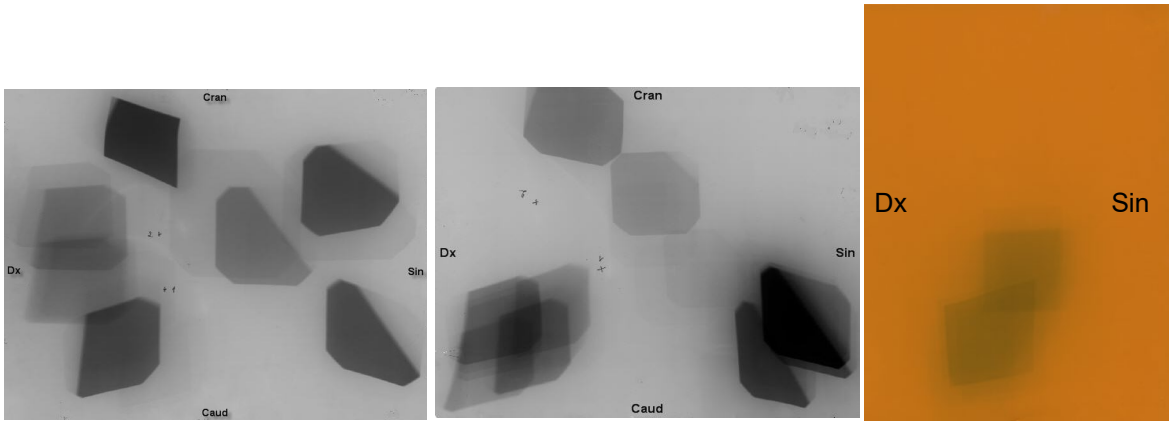



Figure 5 Skin exposure mapping using film for a coronary angiography (CA; left panel; EDR2 Kodak), a percutaneous transluminal coronary angiography (PTCA; middle panel; EDR2 Kodak) and a transcatheter aortic valve implantation (TAVI; right panel; Gafchromic XR-RV3) procedure, respectively. Maximum entrance skin dose (MESD) was located on the right shoulder (Dx) for CA, on the left (Sin) side of the patient's back for PTCA and on the middle of the patient's back for TAVI. The diodes in the images (left and middle panel) are marked with crosses.

*Outcome and clinical implementation of the results*

The results verified that MESD and KAP vary with the type of cardiac procedure. The difference was pronounced when comparing diagnostic (CA) with interventional techniques (PTCA, TAVI) as the confidence intervals (table 2) do no overlap between them and this therefore calls for procedure-specific skin dose conversion coefficients, MESD/KAP. For patient follow-up of possible skin injury, alarm levels for transient skin erythema were estimated from the mean values of $CC_{MESD:KAP}$ in table 2 and for each procedure type. The defined alarm levels for 2 Sv in equivalent skin dose (or 2 Gy in absorbed dose) was set to 500 $Gycm^2$ for CA and 210 $Gycm^2$ for PTCA and TAVI.

### 4.1.2 Outcome from question II [Study I]

#### Scientific question II

Is the relation between patient skin dose (MESD) and total radiation exposure (KAP) for a given type of procedure operator dependent?

#### Study design

As demonstrated in figure 5 (in the previous section), cardiac angiography and interventional procedures do not follow the same irradiation pattern. This will influence the location of the MESD on the skin. In large university clinics having many operators there may be additional and significant variation in irradiation technique – *for the same type of procedure* - between the more experienced operator and those undergoing training. With experience comes skill and in the case of interventions, experienced operators are generally more aware of dose reduction techniques and the importance of irradiation geometry and may therefore, to a greater extent, avoid irradiation of the same skin area for a prolonged period of time.

In study I the impact of operator experience on the patient skin dose was evaluated. The conversion coefficients for MESD were estimated for two operators, one with relatively short experience (2 years) while the second person was a senior operator with about 10 years of experience in performing this kind of procedures. The skin dose mapping was performed using slow radiographic films (EDR2, Eastman Kodak Co., Rochester, NY) combined with direct reading diode dosimeters (Unfors Patient Skin Dosimeter (PSD), Unfors Instruments, Billdal, Sweden) on patients undergoing CA procedures.

## Results

*Variation in beam projections between operators*

Figure 6 shows the result from film measurements of CAs procedures, performed by two operators with experience of 2 years (operator A, left panel) and 10 years (operator B, right panel), respectively. The skin dose maps between the two operators differ, and the operator with less experience tended to use more beam projections and less variation in projection angles between patients.

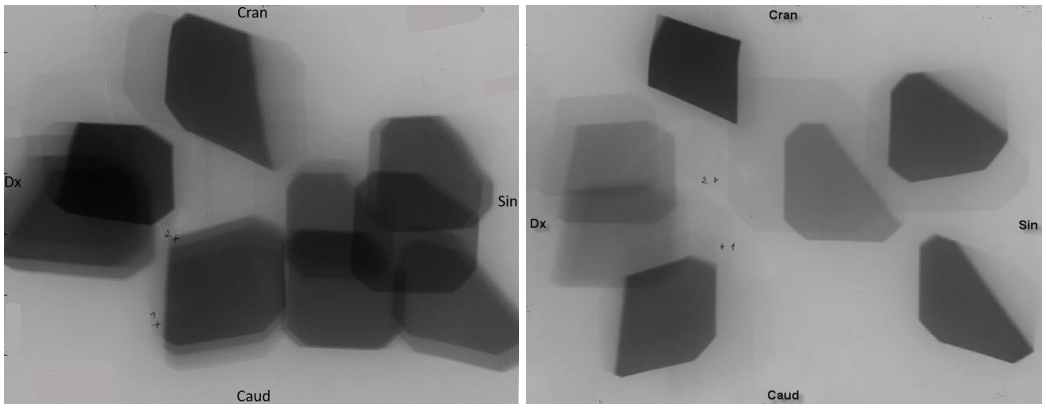



Figure 6 Skin exposure maps (radiographic films) from two patients that underwent coronary angiography procedures, performed by two different operators (left panel, operator A, 2 years of experience; right panel, operator B, 10 years of experience).

### *Variation in MESD/KAP between operators*

The relation between MESD and KAP for the two operators, which performed 10 CA procedures each, are shown in figure 7.

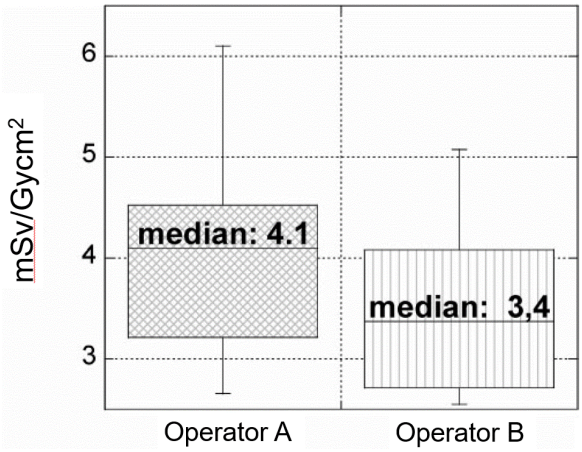



Figure 7 The median conversion coefficients ($CC_{MESD:KAP}$) for the two operators was 4.1 mSv/Gycm$^2$ (operator A: 2 years of experience) and 3.4 mSv/Gycm$^2$ (operator B: 10 years of experience), respectively. The boxes for each operator enclose 50% of the conversion coefficients for the 10 CA studies each operator performed. The maximum and minimum of the conversion coefficients corresponds to the endpoints of the bars.

### *Outcome and clinical implementation of the results*

The results showed that MESD/KAP varies with operator experience, being 20% higher for the less experienced operator (operator A, fig. 7). Based on the results, alarm levels corresponding to 2 Sv in equivalent skin dose (or 2 Gy in absorbed dose) for CA and for each operator would correspond to 470 Gycm$^2$ (CA; operator A) and 570 Gycm$^2$ (CA, operator B). No test of statistical significance of the results was attempted before publication. However, the analysis was reconsidered when this thesis was written. Statistical significance between operators was tested for both $CC_{MESD:KAP}$ and MESD using the Mann Whitney U-test. A clear difference between operators could be shown with regard to MESD, while the $CC_{MESD:KAP}$ did not display such difference. This demonstrates that the less experienced operator exposed the patients to higher KAP and thereby higher MESD, which is expected, but is not conclusive that there is a difference in the ratio MESD/KAP.

Based on this outcome, a single conversion coefficient per procedure type is recommended to be used in the clinic.

## 4.2 STOCHASTIC EFFECTS IN CARDIAC PROCEDURES

### 4.2.1 Outcome from question III [Studies I, II, III and V]

#### Scientific question III

Does the relation between effective dose (E) and air kerma-area product (KAP), and between equivalent organ dose ($H_T$) and (KAP) vary with age and calculation method?

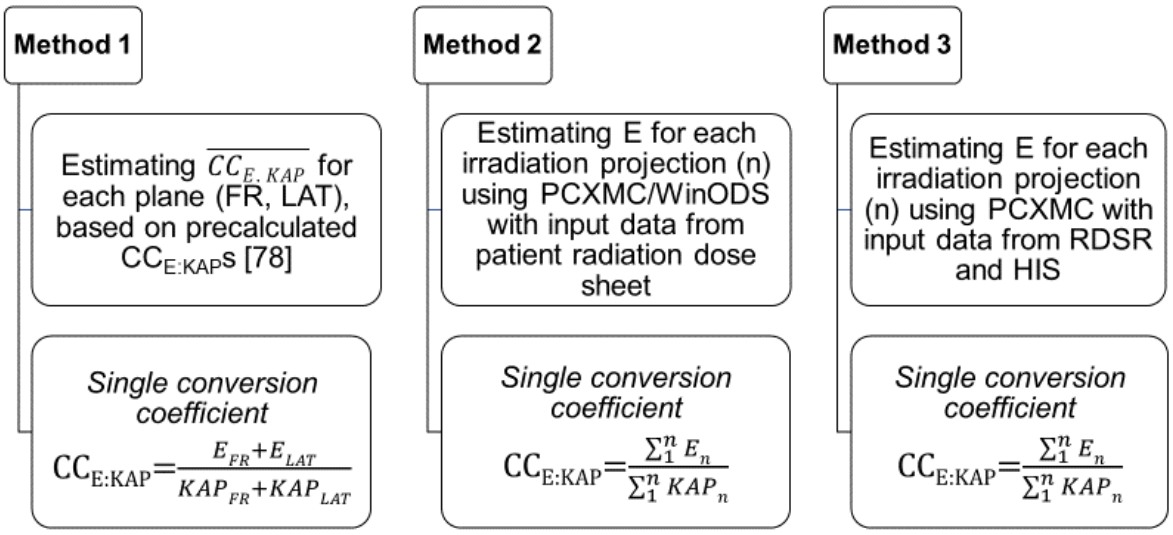
#### Study design

The first report on the dependence of E with KAP and with patient age in cardiac interventional procedures was published by Schmidt *et al* in 2000 [78]. The publication provides $CC_{E:KAP}$ for a range of projection angles, x-ray spectra and patient age groups.

In our studies II, III and V, three different methods to take into account the irradiation geometry during the procedure are evaluated. In all studies, a single $CC_{E:KAP}$ is calculated for each procedure. The different study designs are summarized in figure 8. All three methods are based on MC simulations of radiation transport to calculate dose. Method 1 is the less accurate method and is based on precalculated $CC_{E:KAP}$s [78] and method 3 is the most accurate as it uses all relevant exposure and geometric data from the RDSR file as input data to PCXMC v.2.0 [73]. More detailed information on the assumptions applied for the different methods, is described in paragraph 3.2. (method 1, no 1; method 2, no 2, and method 3, no 3).

All three studies are retrospective cohort studies. Study II and III include 249 and 202 paediatric patients, respectively, while study V is based on data from 22 adult patients. The studies were performed at the Karolinska University Hospital over a period of 17 years, in total. This means that x-ray systems based on different technologies were included (study II, image intensifier; studies III and V, flat panel detectors). During this period, the current ICRP data for tissue weighting factors ($w_T$) were published.

In summary, study II was based on methods 1 and 2 for the irradiation geometry and uses $w_T$ from ICRP 60, study III was based on methods 2 and 3 with $w_T$ from ICRP 103, and study V was based on method 2 with $w_T$ from ICRP 103.




$CC_{E:KAP}$, conversion coefficient for effective dose; $\overline{CC_{E,KAP}}$, mean value of conversion coefficients stated by Schmidt *et al.* [78] (includes the most frequent projection angles used in our hospital); E, effective dose; RDSR, DICOM Radiation Dose Structured Reports; HIS, hospital information system; KAP, Kerma-area product; FR, frontal plane; LAT, lateral plane; n, irradiation projection.

Figure 8 The three methods used to account for the irradiation geometry in patient cardiac interventions in estimations of conversion coefficients for effective dose ($CC_{E:KAP}$) for each procedure. Method 1 is the less accurate technique while method 3 is the most accurate.

As given by the definition of E, it is calculated as a weighted sum of $H_T$ (equation 3). This implies that if E depends on KAP [78] then $H_T$ should also depend on KAP. In study III the dependence of $CC_{HT:KAP}$ with age in cardiac catheterization procedures is estimated and reported for the first time in the literature.

The dose to the lung (critical organ) is of special concern in cardiac interventions. The calculational efforts required for a reasonably robust prediction of lung dose is therefore of interest. The methodologies studied in this work (table 3) allow for some conclusions to be drawn in this respect.

Table 3 Methods to estimate conversion coefficients for organ dose ($CC_{HT:KAP}$).

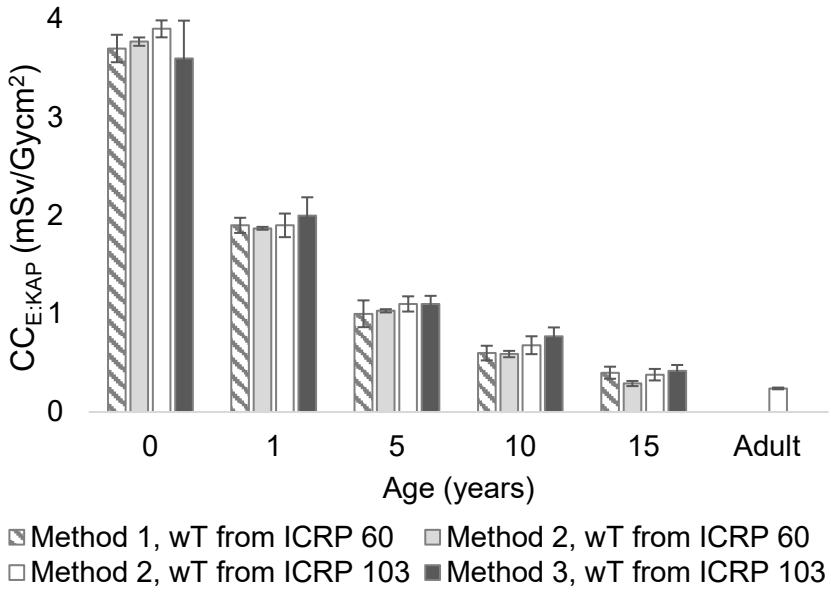
| | | |
|---|---|---|
| Paper I | WinODS [74] with input data from patient radiation dose sheets (method 2) | |
| Paper III | PCXMC [73] with input data from patient radiation dose sheets (method 2) | PCXMC [73] with input data from RDSR and HIS (method 3) |

RDSR, DICOM Radiation Dose Structured Report; HIS, Hospital Information System

## Results

### *Variation of E, $H_T$ and KAP with patient age using different methods to account for the irradiation geometry*

The results (fig. 9; mean value of conversion coefficients with 95% confidence interval (CI) using the t-distribution) showed a decrease in the conversion coefficient E/KAP ($CC_{E:KAP}$; upper panel) and $H_T$/KAP ($CC_{HT:KAP}$ for lung; lower panel) with increased patient age and with an indication of reaching a plateau around the age group of 15 years, for patients undergoing cardiac catheterizations. The average $CC_{E:KAP}$- and $CC_{HT:KAP}$ results corresponding to the three ($CC_{E:KAP}$) and two ($CC_{HT:KAP}$) different methods to account for irradiation geometry are included. The impact of the new $w_T$ on the resulting $CC_{E:KAP}$ is demonstrated for method 2.



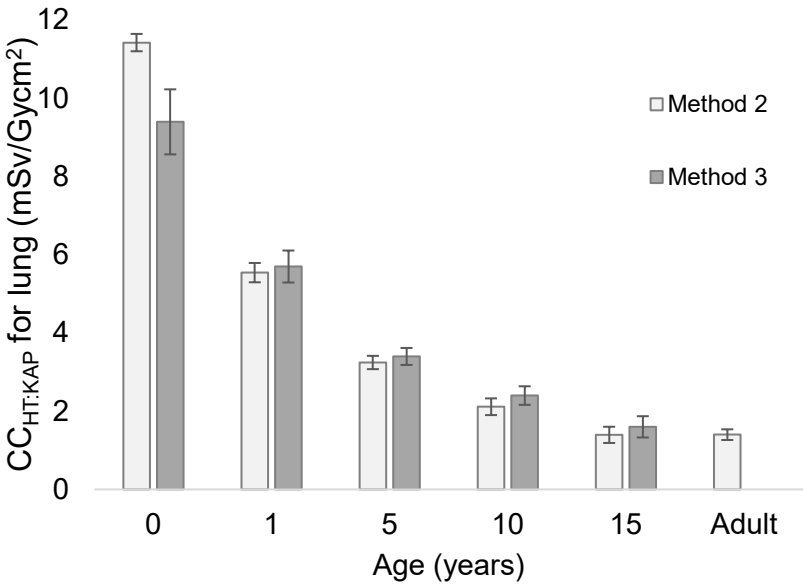




Figure 9 Upper panel: Conversion coefficient for effective dose ($CC_{E:KAP}$ ± 95% CI) as a function of age for patients undergoing cardiac procedures. The data include results from study II (tissue weighting factors ($w_T$) from ICRP 60, method 1 and 2), study III ($w_T$ from ICRP 103, method 2 and method 3) and study V ($w_T$ from ICRP 103, method 2). Lower panel: Conversion coefficient for lung equivalent dose ($CC_{HT:KAP}$ ± 95% CI) as a function of age. The data include results from study III (children; $w_T$ from ICRP 103, method 2 and method 3) and study I (adults; $w_T$ from ICRP 60, method 2).

### *Outcome and clinical implementation of the results*

The results were conclusive in that there is indeed a clear dependence on age, in the paediatric age range, on the $CC_{E:KAP}$ and $CC_{HT:KAP}$ in patients undergoing cardiac

interventions. This is not unexpected as the organs in the youngest patients are situated very close to each other in this body region which makes it difficult to restrict the collimation of the beam only to the area of interest. This results in irradiation of larger proportion of individual organs and also of other, nearby organs, compared to in elderly patients.

The average $CC_{E:KAP}$ results using different methods to account for irradiation geometry were very close to each other. Notably, for the two methods using the $w_T$ from ICRP 103, the CIs overlapped for each age group where they were calculated (figure 9).

The results of paper III indicated no difference in mean convergence coefficient between method 2 and method 3 for both $CC_{E:KAP}$ and $CC_{HT:KAP}$ (lung). In the paper, however, the test was applied to all patients, without dividing into age groups. The results displayed in figure 9 are generally consistent with the conclusion on paper III. However, the stratification into age groups indicates a difference in $CC_{HT:KAP}$ (lung) for new-borns (clearly separated CIs).

One important use of these results is to increase the awareness among clinical staff on the dose levels that are frequently encountered in cardiac procedures and that paediatric patients can receive doses, especially from the II-technology, that exceeds other x-ray imaging techniques. Table 4 below summarizes the results for E from cardiac procedures that have been estimated in this thesis work. For comparison, levels of typical E from abdominal adult CT examinations are indicated. As heart procedures in general are performed by staff trained in other specialties than radiology, special attention is needed to inform the staff of the patient doses involved so that relevant actions can be taken to monitor patient dose and to optimize irradiation techniques.

Table 4 Effective dose (mean, range) for different radiological examinations.

| Procedure | Type of image receptor | Age (years) | E (mean; range) (mSv) |
|---|---|---|---|
| CA[1, 2] | II | >18 | 12; 4.1-24 |
| PTCA/PCI[1, 2] | II | >18 | 12; 4.0-30 |
| TAVI[3] | FP | >18 | 8.2; 2.6-21 |
| Paediatric cardiac catheterization[2] | II | 0-18 | 9.3; 0.23-77 |
| Paediatric cardiac catheterization[3] | FP | 0-18 | 2.1; 0.025-18 |
| Abdominal CT[4] | | >16 | 7.6; 1.5-14 |

[1]Effective dose (E) estimated using conversion coefficients from the paper by Hansson *et al*. [58]; [2]$w_T$ from ICRP 60 [21]; [3]$w_T$ from ICRP 103 [13]; II, image intensifier; FP, flat panel detector; [4]National dose levels in Sweden, 2019; CA, coronary angiography (diagnostic procedure); PTCA, percutaneous transluminal coronary angiography; PCI, percutaneous coronary interventions; TAVI, transcatheter aortic valve implantation.

### 4.2.2 **Outcome from question IV [Studies IV and V]**

#### Scientific question IV

Does the relation between risk of exposure-induced cancer death (REID) and air kerma-area product (KAP), and between organ-specific risk of exposure-induced cancer death ($REID_{HT}$) and KAP, vary with age and gender?

#### Study design

In studies IV and V the variation of the risk for stochastic effects from cardiac catheterization procedures with age, gender and KAP, are evaluated.

The risk estimations are based on retrospective cohort studies and include 238 (study IV; newborn-18 years) and 22 (study V; 69-93 years) patients that had undergone different types of cardiac interventional and diagnostic procedures at the Karolinska University Hospital during the years 2013 to 2016. The REID and $REID_{HT}$ were estimated using PCXMC v.2.0 [73].

Study IV is a continuation of study III and contains the first published data on conversion coefficients for risk of exposure-induced cancer death in patients undergoing cardiac interventions. Both organ specific coefficients, $CC_{REIDHT:KAP}$,

and whole body coefficients, $CC_{REID:KAP}$ are reported.
A novel risk surveillance tool – *risk reference value* (RRV) – related to the population cancer risk, is further introduced. The RRV for a given age and gender is given by the KAP-value corresponding to a REID of 0.1%.

Study V focuses on the TAVI (transcatheter aortic valve implantation) procedure and reports conversion coefficients for REID and $REID_{HT}$ in an elderly patient subgroup (>70 years). In addition, estimated lifetime risks for younger patients (40-50 years) are reported.

## Results

### *Dependence of the conversion coefficients for risk with age and gender*

Patients undergoing cardiac catheterization procedures at younger age are expected to suffer an increased risk for cancer at a given KAP compared to elderly patients due to their higher radiation sensitivity. In the same way, gender differences are expected. Figure 10 illustrates how the conversion coefficients for risk ($CC_{REID:KAP}$, $CC_{REIDHT:KAP}$, 95% CI, t-distribution; $H_T$ for lung) decrease with increasing age (newborn-90 years old) in the patient cohorts included in studies IV and V (cardiac procedures). The differences in risk between genders are also shown here.

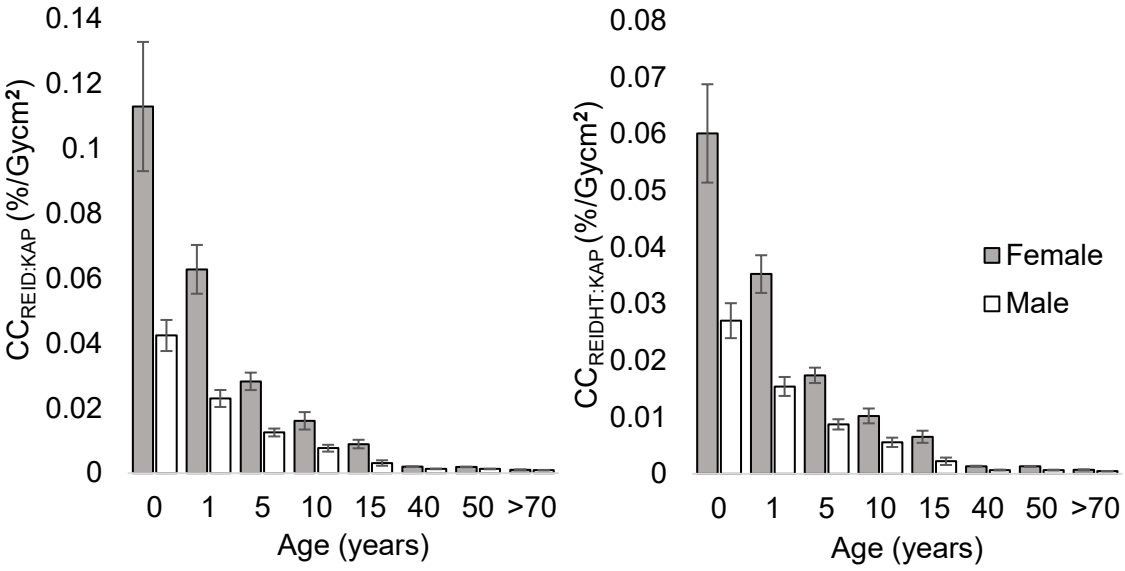



Figure 10 Conversion coefficients for total risk ($CC_{REID:KAP} \pm$ 95% CI) (left panel) and conversion coefficients for lung specific risk ($CC_{REIDHT:KAP} \pm$ 95% CI) (right panel) from cardiac procedures for the different age- and gender groups.

*The contribution to the total REID from the different organs*

The organ specific risks $REID_{HT}$ normalized to total REID for different age and gender groups are shown in figure 11. The top panel shows results for paediatric patients (newborns-18 years) while the lower panel includes data for adult patients (40-93 years).

Although the data is consistent in that only cardiac procedures are included, it is clear that the relative contribution from different organs to the total risk differs between adults and children; the common denominator being that lung is the organ that contributes most to the risk for all ages (between 55% and 75%). In paediatric patients, the second highest contribution to the total REID is the breast (breast ca, females; (15-30) %), while the risk for leukaemia is the second highest contributor ((15-30) %) in adults. Noteworthy is that the contribution from breast to the total cancer risk in adult female patients is considerably lower than in paediatric patients, or < 5 %.

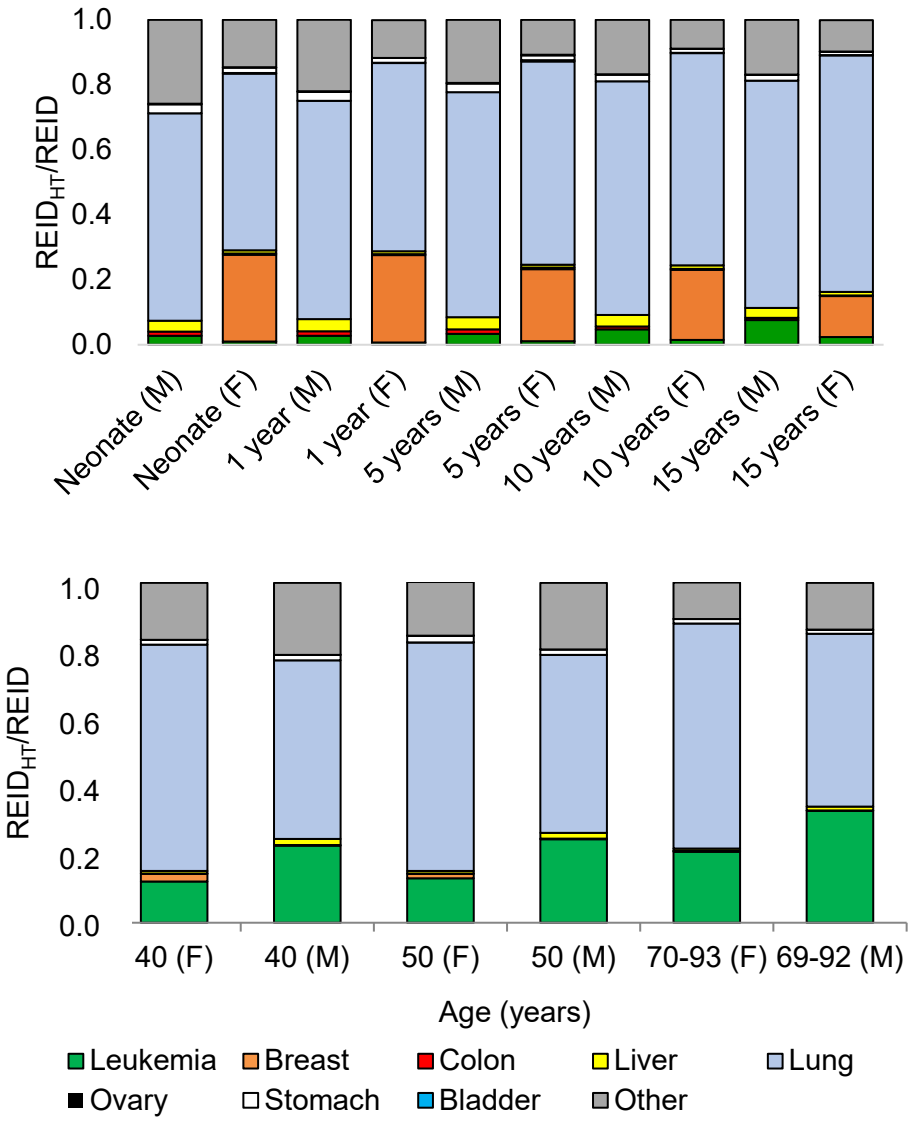



Figure 11 The contribution to the total risk of exposure-induced cancer death (REID) from the risk of exposure induced cancer death for different organs (REID$_{HT}$). Top panel reports data for paediatric patients while the lower panel reports data for adults. Female (F); Male (M).

### *Risk Reference Values (RRVs)*

The RRVs in table 5 correspond to a REID of 0.1%. About 90% of the patients included in study IV had a REID-value below 0.1%. The RRV increases with age and is, as expected, higher for males than females.

Table 5 Risk reference values (RRVs) corresponding to a REID of 1 in 1000 (0.1%) for paediatric patients undergoing cardiac interventions.

| Age (years) | RRV (female) ($Gycm^2$) | RRV (male) ($Gycm^2$) |
|---|---|---|
| 0 | 0.77 | 2.1 |
| 1 | 1.5 | 4.3 |
| 5 | 3.7 | 8.7 |
| 10 | 6.5 | 15 |
| 15 | 11 | 25 |

REID, Risk for exposure-induced cancer death

### *Outcome and clinical implementation of the results*

The results showed significant differences in risk conversion coefficients ($CC_{REID:KAP}$, $CC_{REIDHT:KAP}$) with age and gender for the paediatric patient group as the CIs didn't overlap. Differences between the age groups 40 and 50 years, both female and male, were not clear for $CC_{REID:KAP}$ and $CC_{REIDHT:KAP}$. Neither were differences between genders for the elderly patients (>70 years). In these cases, the CIs overlapped.

Estimates of population cancer risk from the use of radiation in different kinds of medical procedures (here: cardiac interventional procedures) will help in the justification of a diagnostic and/or treatment procedure that involves the use of radiation. It can also be used to guide the responsible physician in communicating the risk involved to different groups of patients undergoing such procedures. The data on risks obtained from the studies IV and V are helpful for both these purposes.

The cancer risk surveillance tool, RRV, provides the operator with an alert level that, if frequently reached, could call for a discussion of the need for improvements of irradiation techniques and optimization of machine settings. In our hospital a RRV-level that corresponds to a REID of 1 in 1000 has been implemented and is used to call the attention of the operator in this way.

# 5 UNCERTAINTIES IN ESTIMATING PATIENT DOSE AND RISK IN CARDIAC X-RAY ANGIOGRAPHY AND INTERVENTION

The uncertainty budget for film calibration (Gafchromic and EDR2 Kodak) comprises of uncertainties in dose, scanner or film processor and densitometer, and film. The uncertainty budgets for the two types of films are presented in table 6 and 7. Although the number of measurements used to define the calibration curve also affects the uncertainty [82], this was not accounted for. The overall uncertainty for the Gafchromic film is at the same order as the level indicated by Farah *et al.* [82], commenting that an overall uncertainty of about 20% (k=1) is realistic within interventional radiology.

The uncertainties in organ dose estimation with the MC code PCXMC v.2.0 are listed in table 8. The accuracy in the MC code used in PCXMC v.2.0 was evaluated in the paper by Borrego et al. [83] by comparing with the more elaborate MCNPX code [84]. The phantom model implemented in MCNPX code was an ORNL adult male phantom, which is almost the same mathematical phantom used in PCXMC v.2.0. Note that the total organ dose uncertainty estimated in table 8 assumes that the patient phantom is a perfect representation of patient anatomy. The effects due to mismatches between phantom and true organ geometry can certainly be expected to be large but is difficult to quantify and have not been included.

The relative crudity of PCXMC's stylized phantom compared to modern hybrid or voxelized phantoms is one source of anatomical mismatch, however it may not be the largest. In adult cardiac examinations, even when scaling for weight and height, the average mean absolute error in organ doses for a modern hybrid phantom compared to segmented CT scans has been estimated at still around 50% [85]. The average mean absolute error for a reference stylized phantom (ORNL phantom, not scaled for weight or height), however, was only 12% larger. This suggests, for cardiac examinations at least, the variation in organ size and location between patients of a similar size may be more significant for organ dose errors than the primitive geometrical definitions of stylized phantoms.

The uncertainties presented in tables 6 to 8 are expressed for k=1 and the final expanded uncertainty for k=2.

Table 6 Uncertainty budget for k=1, using XR-RV3 Gafchromic films and expressed in percent.

| Source of uncertainty | Value (%) | Probability distribution | Divisor | Standard uncertainty (%) | Values taken from |
|---|---|---|---|---|---|
| Air kerma measurement | ±2.2 | Normal | 2 | 1.1 | Calibration certificate |
| Backscatter radiation | ±8 | Rectangular | √3 | 4.6 | McCabe *et al.* [86] |
| Scanner nonuniformity | - | - | - | - | Corrected in this study |
| Short term stability | ±0.7 | Normal | 1 | 0.7 | Table IV, Farah *et al.* [82] |
| Long term stability | ±3 | Normal | 1 | 3 | Table IV, Farah *et al.* [82] |
| Film-to-film uniformity within the same batch | ±5 | Normal | 2 | 2.5 | McCabe *et al.* [86] |
| Dose rate film dependence for 60kVp | ±3 | Normal | 2 | 1.5 | McCabe *et al.* [86] |
| Film response with radiation beam quality | ±5 | Rectangular | √3 | 2.9 | Fig. 5, McCabe *et al.* [86] |
| Fitting equation | ±5 | Rectangular | √3 | 2.9 | This study |
| Air kerma per film response uncertainty, k=1 | | Assumed normal | | 7.6 | |
| **Air kerma per film response expanded uncertainty, k=2** | | Assumed normal | | **15** | |

Table 7 Uncertainty budget for k=1, using EDR2 Kodak films and expressed in percent.

| Source of uncertainty | Value (%) | Probability distribution | Divisor | Standard uncertainty (%) | Values taken from |
|---|---|---|---|---|---|
| Air kerma measurements (unfors) | ±6 | Normal | 2 | 3 | Calibration certificate |
| Backscatter radiation | | - | | - | Calibrated with backscatter |
| Densitometer | ±2.2 | Normal | 2 | 1.1 | Accuracy and repeatability from manual (X-rite) added in quadrature |
| Film-to-film uniformity between batches and processor performance | ±4.4 | Rectangular | √3 | 2.5 | Morell *et al.* [87] |
| Dose rate film dependence | | | | Negligible | Fig. 3, Ying et al [88] |
| Film response with radiation beam quality | | | | Negligible | Fig. 1, Ying et al [88] |
| Fitting equation* | | Normal | | 16 | This study |
| Air kerma per film response uncertainty, k=1 | | Assumed normal | | 17 | |
| **Air kerma per film response expanded uncertainty, k=2** | | Assumed normal | | **34** | |

*Fitting equation: root-mean-square deviation is estimated as follow:

$$\sqrt{\frac{\sum_{k=1}^{n}\left(\frac{measured\ dose_k - calculated\ from\ the\ fitted\ curve_k}{measured\ dose_k}\right)^2}{n}}$$

Table 8 Uncertainty in organ dose estimation using PCXMC v.2.0 code combined with an in house developed framework [77] and expressed in percent for k=1.

| Source of uncertainty | Value (%) | Probability distribution | Divisor | Standard uncertainty (%) | Values taken from |
|---|---|---|---|---|---|
| PCXMC, MC code accuracy | ±8 | Rectangular | √3 | 4.6 | Table V, Borrego *et al.* [83] |
| PCXMC, statistical of MC simulations | ±1 | Normal | 1 | ±1 | This thesis |
| X-ray field positioning | ±14 | Rectangular | √3 | 8.1 | Table III, Omar *et al.* [79] |
| KAP | ±10 | Rectangular | √3 | 5.8 | Yearly check against a reference KAP-meter |
| Organ dose uncertainty, k=1 | | Assumed normal | | 11 | |
| **Organ dose expanded uncertainty, k=2** | | Assumed normal | | **22** | |

# 6 DISCUSSION

This thesis presents methods to monitor and evaluate the radiation dose and related risk to patients undergoing cardiac catheterization procedures.

## 6.1 MONITORING AND ESTIMATION OF DETERMINISTIC EFFECTS OF RADIATION

### *Skin injuries*

Built-in monitoring (KAP) of radiation dose in angiographic equipment was introduced in 1997 following requirements stated in the EURATOM directive 97/43 [8]. Already three years later (2000) the International Commission on Radiological Protection, ICRP, published recommendations for counseling and follow-up of patients with risk for skin injuries from interventional procedures [10]. A skin dose level of 1 Gy per procedure in case of repeated interventions, and 3 Gy for a single intervention, were recommended as trigger levels for patient follow-up [10]. This illustrates how a technological development (built-in monitoring of a radiation dose-related quantity) and recommendations for follow-up of adverse effects in patients need to be synchronized in order to facilitate compliance by the health care providers.

In study I and V, the skin dose conversion coefficient ($CC_{MESD:KAP}$) for CA, PCI and TAVI procedures were estimated (see table 9) and as expected, the $CC_{MESD:KAP}$ varied with the type of procedure (diagnostic- or interventional). Comparing our results with other publications, a variation in the $CC_{MESD:KAP}$ for a given type of procedure between hospitals is noted [table 9]. Differences in beam projection techniques between operators are believed to be important contributors to such variation, although the results of this thesis were unable to confirm this. Jarvinen H et al. [89] made similar conclusions by recommending hospital-specific values for such conversion coefficients.

Table 9 Mean $CC_{MESD:KAP}$ (mSv/Gycm$^2$) for CA, PCI and TAVI

| Procedure type | CA | PCI | TAVI |
|---|---|---|---|
| This thesis[1] | 4 | 10 | 10 |
| Järvinen J *et al.* [90][1] | | | 10 |
| Jarvinen H *el al.* [89][1] | | 14 | |
| Pasquino M *et al.* [91][1] | 3 | 7 | |
| Kulkarni A R *et al.* [92][1] | 3 | 6 | |
| Krajinovi´c M *et al*. [93][2] | | 12 | |
| Greffier J *et al.* [51][1] | 7 | | |

$CC_{MESD:KAP}$, conversion coefficient for maximum entrance skin dose; CA, coronary angiography; PCI, percutaneous coronary interventions; TAVI, transcatheter aortic valve implant; [1]Film measurement; [2]Calculated from $K_{a,i.}$

Based on local estimates of $CC_{MESD:KAP}$ for various procedures, patients with increased risk for developing a skin injury can be identified. The choice of the limiting KAP-value used to find such patients should preferably take into account the variation of $CC_{MESD:KAP}$ between patients and between operators for the same type of procedure. In practice, there will always be a trade-off in cost-benefit when it comes to define a KAP alarm level. Selecting “too many” patients for follow-up (low alarm level) will be very costly without a clear benefit to many of the patients (false positive), while a high alarm level risk missing patients that have been affected (false negative).

Film dosimetry continues to be the golden standard for accurate skin dose measurement from this kind of x-ray based procedures. At the same time, several software programs for monitoring skin dose distributions in real-time have been developed by manufacturers of angiography equipment. Given the complexity and time required to perform film dosimetry at large scale, software-based skin dose estimation has a clear role in a clinical setting. However, the validation of these softwares have not been performed in a structured way, which makes the comparison difficult [94].

### *Heart disorders*

Recently, radiation induced effects of the heart have received attention due to possible side effects and a threshold absorbed dose of 0.5 Gy to the heart related to the risk of circulatory disease has been presented [12]. Although heart disorders have not been specifically addressed in this thesis, it can be concluded that the threshold dose for circulatory disease has not been exceeded in the paediatric cohort in this work for single procedures ($H_T$ up to 60 mSv/procedure). The equivalent organ dose to the heart for adult patients is higher ($H_T$ up to 275 mSv/procedure, [95]) but still under the threshold dose for circulatory disease. However, as children are more sensitive than adults to radiation induced circulatory disease [19], awareness of this risk is advised.

## 6.2 ESTIMATION OF STOCHASTIC EFFECTS OF RADIATION – CANCER INDUCTION

Younger patients undergoing cardiac catheterization procedures are primarily exposed to other radiation related effects than adults. Given that younger persons have more radiation resistant skin combined with that the skin doses encountered are generally much lower than in adults, this is not an issue for this clientele. Instead the focus should be on radiation induced cancer. The risk for radiation induced cancer can be estimated using the dose metrics E or $H_T$. In the 2007 ICRP report [13], the commission highlights the importance of using mean equivalent organ dose (or absorbed organ dose) as the basis for risk estimation. In practical terms, the use of E should be restricted to situations when different examination protocols and/or different equipment, are compared.

In this thesis the concept of risk has been addressed by estimating conversion coefficients for $H_T$ and E in cardiac catheter-based procedures. The approach allows to link the KAP-values monitored by the x-ray angiography equipment to $H_T$ and to E. In the case of cardiac procedures, the breast poses special challenges and only presents a weak correlation to KAP in this work. This is most likely related to that the breast tissue is only partially irradiated during such procedures [96], thus causing also relatively small variations in beam angle to potentially have a significant impact on the mean dose to the breast.

In the clinical context it is not possible to estimate organ dose from cardiac procedures in real-time on a patient-by patient basis and other ways to provide the operator with an indication of the radiation dose is needed. This thesis reports for the first time $CC_{HT:KAP}$ for paediatric cardiac catheterization procedures. This allows to

estimate organ doses directly from the registered KAP-value of the procedure. One important finding of the work is the clear dependence of age on the organ dose conversion coefficients, demonstrated by a $CC_{HT:KAP}$ for the lung that decreases with increased age within the paediatric age range.

When it comes to the $CC_{E:KAP,}$ the results presented in this thesis [paper II, paper IV, paper V] are within the same range as the $CC_{E:KAP}$ from the most recent publications in this area [69, 72, 95]. As reported in paper II, the dependence of irradiation geometry on $CC_{E:KAP}$ is of minor importance for patients in the same age group, resulting in similar conversion coefficients for different types of procedures. From this perspective, the $CC_{E:KAP}$ is more robust to technique variations than the organ dose conversion; all provided that the age dependence is properly accounted for.

## 6.3 RISK COMMUNICATION

Until now, communicating the increased risk for cancer from x-ray based cardiac procedures to patients/parents has been challenging as information connecting the exposure to risk has not been available to medical staff. Compliance to the directive 2013/59/Euratom [9] has consequently been very poor. In this thesis, we present gender-specific and age-specific conversion coefficients ($CC_{REID:KAP}$, $CC_{REIDHT:KAP}$) for radiation induced cancer risk from cardiac procedures, starting from newborn and including the whole life span. The importance of gender on such risk is illustrated in the youngest age group where the $CC_{REID:KAP}$ is a factor of three higher in females than males. The higher carcinogenetic risk in female paediatric patients undergoing cardiac catheterizations is supported by results from Johnson et al. [44]. This reflects the gender difference in radiation sensitivity of lung [97] and breast tissue.

Moreover, by combining the information in figures 10 and 11, an overall picture of the risk levels and the organs contributing to the risk for all age groups is given. As shown in this thesis and in other published papers [71, 80, 98], lung (female, male) and breast (female) are the organs contributing most to the risk in paediatric patients. In adult patients, the relative contribution to the risk for cancer induction from different organs looks somewhat different (figure 11). Lung remains an organ at risk [paper V, 95], followed by leukemia. This is the case both in adult females and males. The explanation for the increased risk for leukemia in adults is related to the different distribution of the active bone marrow in the human body at different age. In the youngest children the active bone marrow is concentrated to the skull and lower limbs while in adults it is concentrated to the chest, abdomen and pelvis [99].

An understanding of which are the organs at risk at different patient age is fundamental to be able to perform optimization of the irradiation techniques and related machine settings.

One of the aims of this thesis was to develop a surveillance tool - risk reference values (RRV) – that helps to monitor situations where the radiation dose exceeds a certain threshold risk level for a given patient. In our clinic we have implemented a RRV that corresponds to a REID of 0.1 %. This means that the operator will be alerted (by the integrated KAP-value) when the increased population risk for cancer induction reaches 0.1%. An important use of the RRV includes monitoring risk levels for different operators and how they develop with increased experience. This is expected to increase the operators' awareness of how they can affect the risk for late effects to the patient.

# 7 CONCLUSIONS AND REFLECTIONS ON THE NEED FOR FUTURE RESEARCH

In this thesis, four clinically relevant scientific questions related to radiation dose and risk from x-ray cardiac procedures have been analyzed. The results have been used to develop tools to support clinical staff in complying with EC directives and international recommendations on radiation protection.

The first and second scientific question (paper I and V) addressed conversion coefficients for skin dose from cardiac interventional procedures. A dependence with procedure type was demonstrated. The golden standard for skin dose estimations, film dosimetry, was used to estimate the dose. As film is not feasible to implement on a routine basis in the clinic, an alternative would be to use real-time skin dose monitoring software integrated into the angiography equipment. Some manufacturers provide such solutions for their own equipment. A platform that can be interfaced with any vendor's equipment could be an alternative choice and, maybe, the ultimate choice if skin dose monitoring is to be implemented on a large scale. Such softwares are available [94] but with limitations in the accuracy.

The third scientific question (paper I, II, III and V) was formulated with the aim to estimate the relations between E and KAP, and between $H_T$ and KAP for different patient age. A clear dependence on age was found within the paediatric age range regardless whether using procedure specific data from RDSR (paper III) or data from patient radiation dose sheets (paper I, III) or a simplified method based on predetermined conversion coefficients (paper II). Further, no significant difference between the different calculation methodologies could be demonstrated for the population-averaged conversion coefficients, except in an isolated case (lung $H_T$, newborns). The use of voxelized phantoms instead of mathematical phantoms used in our work could possibly minimize the errors in the $H_T$ and E estimations. The effect on the conversion coefficients is unclear and would need further work to evaluate.

Organ dose conversion coefficients are of special interest when performing epidemiological studies. By collecting KAP-values from patient cohorts that have undergone examinations/interventions, the conversion coefficients allow for a link between organ doses and late effects to be established. Future research includes to estimate the radiation doses for large patient cohorts and to correlate the findings with cancer registers in Sweden. This work is in the planning stage.

Conversion coefficients for cancer risk ($CC_{REID:KAP}$, $CC_{REIDHT:KAP}$) were addressed in paper IV and V (fourth scientific question), demonstrating both an age- and gender-dependence within the paediatric age range of these coefficients. Even though the same body area is exposed to radiation in both paediatric and adult patients undergoing cardiac catheterization, it is important to recognize that the organs contributing most to the risk differs between them (paediatric patients: lung and (female) breast; adults: lung and active bone marrow). The knowledge gained in these studies provides the operator with information that will help in the communication of radiation risks from cardiac procedures to patients/parents.

Until now, there has been a lack of a risk surveillance tool that considers age and gender in x-ray based paediatric cardiac catheterization. A novel concept based on the cancer risk (risk reference value, RRV) has been introduced in this thesis. It is suggested as a tool to monitor typical risk levels from cardiac procedures and as an educational tool during operator training.

In conclusion, this thesis increases the knowledge of radiation induced side effects within cardiac interventional radiology. The work encompasses the entire life span in both female and male patients. The suggested tools facilitate the follow-up of patients with risk for radiation induced skin injuries [10], in risk communication with patients/parents [9] and in monitoring of dose/risk levels (RRV). All of these can be used to better understand and, to some extent, limit radiation-induced effects in cardiac interventional radiology.

# 8 ACKNOWLEDGEMENTS

First and foremost, I would like to express my sincere gratitude to my main supervisor Associate Professor Annette Fransson for her excellent guidance and support during the process that led to a doctoral thesis. I would like to thank you for the academic support you gave me, your understanding and empathy.

I am particularly grateful to my co-supervisor Gavin Poludniowski who generously imparted his knowledge and expertise in this thesis. Gavin, thank you for your support and guidance, it made it way easier to achieve my goal.

I wish to send my appreciation to Birgitta Hansson for introducing me in the area of interventional radiology and my mentor Cathrine Jonsson as well.

Thanks to all my colleagues who helped me throughout this journey. I am particularly grateful to Shahla Mobini and Jan Lindström for motivated me to continue when the road got tough. In addition, the “angiography-group” Artur Omar and Markus Hulthén for the stimulating physics discussions, and Jörgen Scherp Nilsson for sharing his knowledge on how to present images on an aesthetic way. Furthermore, a big thank to all colleagues at the department of cardiology, department of pediatric cardiology and department of pediatric radiology at Karolinska University Hospital.

Last but not least, I would like to express my gratitude towards my family for the encouragement that helped me complete this dissertation. Thank you, Konstantinos and Leandros for understanding that the vacations in Greece with mom not only include sunbathing and swimming but also many hours of hard work.

# 9 REFERENCES


1. https://www.socialstyrelsen.se/en/statistics-and-data/statistics/statistical-databases/
2. Dagenais GR, Leong DP, Rangarajan S, et al. Variations in common diseases, hospital admissions, and deaths in middle-aged adults in 21 countries from five continents (PURE): a prospective cohort study [published correction appears in Lancet. 2020 Mar 7;395(10226):784]. Lancet. 2020;395(10226):785-794. doi:10.1016/S0140-6736(19)32007-0.
3. Wijns W, Kolh P, Danchin N, et al., Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2010;31:2501–55.
4. Fokkema, M. L. et al. Population trends in percutaneous coronary intervention: 20-year results from the SCAAR (Swedish coronary angiography and angioplasty registry). J. Am. Coll. Cardiol. 61, 1222–1230 (2013).
5. Samara, E. T, Aroua, A, Bochud, F. O, Ott, B, Theiler, T, Treier, R, Trueb, P. R., Vader, J. P., Verdun, F. R. Exposure of the Swiss population by medical x-rays: 2008 review. Health Phys. 102, 263–70 (2012).
6. Picano, E., Santoro, G. and Vano, E. Sustainability in the cardiac cath lab. Int. J. Cardiovasc. Imaging. 23, 143–147 (2007).
7. https://www.ucr.uu.se/swedeheart/dokument-sh/arsrapporter-sh/1-swedeheart-annual-report-2019/viewdocument/2948.
8. European Community Council Directive 97/43/Euratom of 30 June 1997 on health protection of individuals against the dangers of ionizing radiation in relation to medical exposure. Official J. European Commun. L180, 0022–0027 (1997).
9. European Council Directive 2013/59/Euratom on basic safety standards for protection against the dangers arising from exposure to ionising radiation and repealing Directives 89/618/Euratom, 90/641/Euratom, 96/29/Euratom, 97/43/ Euratom and 2003/122/Euratom. OJ of the EU. L13; 57: 1-73.
10. ICRP, 2000. Avoidance of Radiation Injuries from Medical Interventional Procedures. ICRP Publication 85. Ann. ICRP 30 (2).
11. Wunderle K, Gill S. A. Radiation-Related Injuries and Their Management: An Update. Semin Intervent Radiol 2015;32:156–162.

12. ICRP, 2012 ICRP Statement on Tissue Reactions / Early and Late Effects of Radiation in Normal Tissues and Organs – Threshold Doses for Tissue Reactions in a Radiation Protection Context. ICRP Publication 118. Ann. ICRP 41(1/2).
13. ICRP, 2007. The 2007 Recommendations of the International Commission on Radiological Protection. ICRP Publication 103. Ann. ICRP 37(2–4).
14. Preston DL, Ron E, Tokuoka S, Funamoto S, Nishi N, Soda M, Mabuchi K, Kodama K. Solid cancer incidence in atomic bomb survivors: 1958–1998. Radiat. Res. 2007;168:1–64.
15. Preston DL, et al. Cancer incidence in atomic bomb survivors. Part III: Leukemia, Lymphoma and Multiple Myeloma, 1950–1987. Radiat. Res. 1994;137:S68-S97.
16. Preston DL, Pierce DA, Shimizu Y, Cullings HM, Fujita S, Funamoto S, Kodama K. Effect of recent changes in atomic bomb survivor dosimetry on cancer mortality risk estimates. Radiat. Res. 2004;162:377-389.
17. National Research Council of the National Academies. Health risks from exposure to low levels of ionizing radiation: BEIR VII Phase 2. Washington, DC: National Academies Press; 2006.
18. United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) 2006 UNSCEAR 2006 Report—Effects of Ionizing Radiation Annex A: United Nations (New York: United Nations).
19. UNSCEAR (2013) Sources, effects and risks of ionizing radiation, United Nations Scientific Committee on the Effects of Atomic Radiation UNSCEAR 2013 Report to the General Assembly, with Scientific Annexes, http://www.unscear.org/unscear/en/pub lications/2013_1.html
20. UNSCEAR (2012) United Nations Scientific Committee on the Effects of Atomic Radiation UNSCEAR 2012 Report to the General Assembly, with Scientific Annexes, http://www.unscear. org/unscear/en/publications/2012.html
21. ICRP, 1991. 1990 Recommendations of the International Commission on Radiological Protection. ICRP Publication 60. Ann. ICRP 21 (1-3).
22. Kellerer AM, Nekolla EA, Walsh L. On the conversion of solid cancer excess relative risk into lifetime attributable risk. Radiat Environ Biophys. 2001;40(4):249-257.
23. U.S. Environmental Protection Agency. EPA radiogenic cancer risk models and projections for the U.S. population. EPA Report 402-R-11-001. 2011;16-48.

24. ICRU, 2005. International Commission on Radiation Units and Measurements. Patient dosimetry for X rays used in medical imaging. Journal of the ICRU Report 74.
25. INTERNATIONAL ATOMIC ENERGY AGENCY, Dosimetry in Diagnostic Radiology: An International Code of Practice, Technical Reports Series No. 457, IAEA, Vienna (2007).
26. Benmakhlouf H, Bouchard H, Fransson A, Andreo P. Backscatter factors and mass energy-absorption coefficient ratios for diagnostic radiology dosimetry. Phys Med Biol. 2011;56(22):7179-7204. doi:10.1088/0031-9155/56/22/012
27. Thomas D, Darby S, Fagnani F, Hubert P, Vaeth M and Weiss K. Definition and estimation of lifetime detriment from radiation exposures: Principles and methods. Health Physics 1992;63(3): 259-272.
28. IEC, 2010 Medical Electrical Equipment—part 2-43: Particular Requirements for the Safety of X-Ray Equipment for Interventional Procedures vol 60601, 2nd edn (Geneva: International Electrotechnical Commission).
29. Song S, Liu C, Zhang M. Radiation dose and mortality risk to children undergoing therapeutic interventional cardiology. Acta Radiol 2015;56(7):867e72.
30. Yakoumakis EN, Gialousis GI, Papadopoulou D, et al. Estimation of children's radiation dose from cardiac catheterisations, performed for the diagnosis or the treatment of a congenital heart disease using TLD dosimetry and Monte Carlo simulation. J Radiol Prot. 2009;29(2):251-261. doi:10.1088/0952-4746/29/2/011.
31. Kawasaki T, Fujii K, Akahane K. Estimation of Organ and Effective Doses for Neonate and Infant Diagnostic Cardiac Catheterizations. AJR Am J Roentgenol. 2015 Sep;205(3):599-603.
32. FDA, 1994. Avoidance of serious x-ray-induced skin injuries to patients during fluoroscopically-guided procedures. Statement 9 Sept. 1994, Food and Drug Administration, Rockville, MD, USA.
33. Lichtenstein D. A, Klapholz L, Vardy D. A, Leichter I, Mosseri M, Klaus S. N and Gilead L. T. Chronic radiodermatitis following cardiac catheterization. Arch. Dermatol. 132, 663–667 (1996).
34. Sovik, E., Klow, N. E., Hellesnes, J. and Lykke, J. Radiation-induced skin injuries after percutaneous transluminal coronary angioplasty. Acta Radiol. 37, 305–306 (1996).
35. Barnea Y, Amir A, Shafir R, Weiss J, Gur E. Chronic radiodermatitis injury after cardiac catheterization. Ann Plast Surg. 2002; 49(6): 668–672. PMID: 12461452

36. Aerts A, Decraene T, van den Oord JJ, Dens J, Janssens S, Guelinckx P, et al. Chronic radiodermatitis following percutaneous coronary interventions: a report of two cases. J Eur Acad Dermatol Venereol. 2003; 17(3):340–343. PMID: 12702082
37. Banaag LdeO, Carter MJ. Radionecrosis induced by cardiac imaging procedures: a case study of a 66-year-old diabetic male with several comorbidities. J Invasive Cardiol. 2008; 20(8): E233–236. PMID: 18688069
38. Garcia Reitbock J, Feldmann R, Ruhringer K, Breier F, Steiner A. Chronic radiodermatitis following percutaneous transluminal coronary angioplasty. J Dtsch Dermatol Ges. 2013; 11(3): 265–266. doi: 10.1111/ddg.12004 PMID: 23279977.
39. Tsapaki V, Rehani MM. I perform more than 100 interventional procedures every year but have never seen radiation-induced skin injury: am I missing something?. AJR Am J Roentgenol. 2014;203(5):W462-W463. doi:10.2214/AJR.13.11765.
40. El Sayed MH, Roushdy AM, El Farghaly H, El Sherbini A. Radiation exposure in children during the current era of pediatric cardiac intervention. Pediatr Cardiol 2012;33(1):27-35.
41. Marelli AJ, Mackie AS, Ionescu-Ittu R, et al. Congenital heart disease in the general population: changing prevalence and age distribution. Circulation 2007;115:163–172.
42. Beausejour Ladouceur V, Lawler PR, Gurvitz M, Pilote L, Eisenberg MJ, Ionescu-Ittu R, et al. Exposure to low-dose ionizing radiation from cardiac procedures in patients with congenital heart disease: 15-year data from a population-based longitudinal cohort. Circulation. 2016;133:12–20.
43. Ait-Ali L, Andreassi M, Foffa I, Spadoni I, Vano E, Picano E. Cumulative patient effective dose and acute radiation-induce chromosomal DNA damage in children with congenital heart disease. Heart (British Cardiac Society). 2010;96:269–74.
44. Johnson JN, Hornik CP, Li JS, Benjamin DK Jr, Yoshizumi TT, Reiman RE, et al. Cumulative radiation exposure and cancer risk estimation in children with heart disease. Circulation. 2014;130:161–7.
45. Justino H 2006 The ALARA concept in pediatric cardiac catheterization: techniques and tactics for managing radiation dose Pediatr. Radiol. 36 146–53.
46. IEC, 2009 Medical electrical equipment - Part 2-54: Particular requirements for the basic safety and essential performance of X-ray equipment for radiography and radioscopy (Geneva: International Electrotechnical Commission).

47. NCRP, Report 168: Radiation dose management for fluoroscopically-guided interventional procedures, NCRP Report No.168 (2010).
48. Bogaert E, Bacher K, Lemmens K, Carlier M, Desmet W, De Wagter X, et al. A large-scale multicentre study of patient skin doses in interventional cardiology: dose-area product action levels and dose reference levels. Br J Radiol 2009;82:303–12.
49. Bor D, Olgar T, Toklu T, Caglan A, Onal E, Padovani R. Patient doses and dosimetric evaluations in interventional cardiology. Phys Med 2009;25:31–42.
50. Bordier C, Klausz R, Desponds L. Patient dose map indications on interventional X-ray systems and validation with Gafchromic XR-RV3 film. Radiat Prot Dosim 2015;163:306–18.
51. Greffier J, Moliner G, Pereira F, Cornillet L, Ledermann B, Schmutz L, Lomma M, Cayla G, Beregi JP. Assessment of Patient's Peak Skin Dose Using Gafchromic Films During Interventional Cardiology Procedures: Routine Experience Feedback. Radiat Prot Dosimetry. 2017 Apr 28;174(3):395-405.
52. Jones AK, Pasciak AS. Calculating the peak skin dose resulting from fluoroscopically guided interventions. Part I: Methods. J Appl Clin Med Phys 2011;12:3670.
53. Ying CK, Kandaiya S. Patient skin dose measurements during coronary interventional procedures using Gafchromic film. J Radiol Prot 2010;30:585–96.
54. Journy N, Sinno-Tellier S, Maccia C, Le Tertre A, Pirard P, Pages P, et al. Main clinical, therapeutic and technical factors related to patient's maximum skin dose in interventional cardiology procedures. Br J Radiol 2012;85:433–42.
55. Giordano C, D'Ercole L, Gobbi R, Bocchiola M, Passerini F. Coronary angiography and percutaneous transluminal coronary angioplasty procedures: Evaluation of patients' maximum skin dose using Gafchromic films and a comparison of local levels with reference levels proposed in the literature. Phys Med 2010;26:224–32.
56. Satish C. Uniyal, Vineet Chaturvedi, Sunil D. Sharma and Anurag Rawat. PROCEDURES IN A DEDICATED CATHETERIZATION LABORATORY Radiation Protection Dosimetry (2017), Vol. 175, No. 2, pp. 201–208.
57. Koichi Chida, Mamoru Kato, Yohei Inaba, Ryota Kobayashi, Masaaki Nakamura, Yoshihisa Abe, Masayuki Zuguchi. Real-time patient radiation

dosimeter for use in interventional radiology.Physica Medica 32 (2016) 1475–1478.
58. Hansson B, Karambatsakidou A. Relationships between entrance skin dose, effective dose and dose area product for patients in diagnostic and interventional cardiac procedures.Radiat Prot Dosim 2000;90:141–4.
59. Rana VK, Rudin S, Bednarek DR. Updates in the real-time Dose Tracking System (DTS) to improve the accuracy in calculating the radiation dose to the patients skin during fluoroscopic procedures. Proceedings of SPIE–the International Society for Optical Engineering; 2013; 8668:86683Z.
60. Bordier C, Klausz R, Desponds L. Patient dose map indications on interventional X-ray systems and validation with Gafchromic XR-RV3 film. Radiat Prot Dosim 2015;163:306–18.
61. Van Ngoc Ty C, Bonniaud G, Coulot J. Development of an analytical peak skin dose calculation tool in interventional radiology. Phys Med 2014;30:e123–45.
62. Attix FH. Introduction to Radiological Physics and Radiation Dosimetry [Internet]. Wiley; 1986. Available from: https://onlinelibrary.wiley.com/doi/book/10.1002/9783527617135
63. Sandby-Møller J, Poulsen T, Wulf HC. Epidermal thickness at different body sites: relationship to age, gender, pigmentation, blood content, skin type and smoking habits. Acta Derm Venereol. 2003;83(6):410-3.
64. Bacher K, Bogaert E, Lapere R, De Wolf D, Thierens H. Patient-specific dose and radiation risk estimation in pediatric cardiac catheterization. Circulation 2005;111:83–9.
65. Aly A. E, Duhaini I. M, Manaa S. M, Tarique S. M, Kuniyil S. E and Naemi H. M. A. Patient peak skin dose and dose area product from interventional cardiology procedures. Int. J. Med. Phys. Clin. Eng. Radiat. Oncol. 4, 7–12 (2015).
66. Saeed, M. K. Dose measurement using Gafchromic film for patients undergoing interventional cardiology procedures. Radiat. Prot. Dosim. 2016. (In press. doi: 10.1093/rpd/ncw082).
67. Morrish, O. W. E. and Goldstone, K. E. An investigation into patient and staff doses from x-ray angiography during coronary interventional procedures. Br. J. Radiol. 81, 35–45 (2008).
68. Balter S, Miller D. L, Vano E, Ortiz L. P, Bernardi G, Cotelo E, Faulkner K, Nowotny R, Padovani R and Ramirez A. A pilot study exploring the possibility of establishing guidance levels in x-ray directed interventional procedures. Med. Phys. 35, 673–680 (2008).

69. Barnaoui S, Rehel J L, Baysson H, et al. Local reference levels and organ doses from pediatric cardiac interventional procedures. Pediatr Cardiol 2014;35:1037-45.
70. Harbron R W et al 2015 Radiation doses from fluoroscopically guided cardiac catheterization procedures in children and young adults in the United Kingdom: a multicentre study Br. J. Radiol. 88 20140852.
71. Yakoumakis E, Kostopoulou H, Makri T, Dimitriadis A, Georgiou E, Tsalafoutas I. Estimation of radiation dose and risk to children undergoing cardiac catheterization for the treatment of a congenital heart disease using Monte Carlo simulations. Pediatr Radiol 2013; 43: 339–46. doi: https:// doi. org/ 10. 1007/ s00247- 012- 2510-3.
72. Ubeda C, Miranda P, Vano E, Nocetti D, Manterola C. Organ and effective doses from paediatric interventional cardiology procedures in Chile. Phys Med. 2017 Aug;40:95-103.
73. Tapiovaara M, Lakkisto M, Servomaa A. PCXMC: A Monte Carlo program for calculating patient doses in medical x-ray examinations (2nd Ed.). Report STUK-A231. Helsinki: Finnish Centre for Radiation Nuclear Safety; 2008.
74. Servomaa A, Rannikko S, Nikitin V, et al. A topographically and anatomically unified phantom model for organ dose determination in radiation hygiene, STUK-A87. Helsinki: Finnish Center for Radiation and Nuclear Safety, 1989.
75. Tapiovaara M, Lakkisto M, Servomaa A. PCXMC: A PC-based Monte Carlo program for calculating patient doses in medical x-ray examinations. Helsinki: Finnish Centre for Radiation and Nuclear Safety. Report STUK-A139. 1997.
76. Lee C, Lee C, Shah AP and Bolch WE. An assessment of bone marrow and bone endosteum dosimetry methods for photon sources. Phys. Med. Biol. 2006b;51:5391–5407
77. Cristy M, Eckerman KF. Specific absorbed fractions of energy at various ages from internal photon sources. I. Methods. Report ORNL/TM-8381/V1. Oak Ridge: Oak Ridge National Laboratory; 1987.
78. Schmidt PWE, Dance DR, Skinner CL, Castellano Smith IA, McNeill JG. Conversion factors for the estimation of effective dose in paediatric cardiac angiography. Phys Med Biol 2000;45:3095–107.
79. Omar A, Bujila R, Fransson A, Andreo P, Poludniowski G. A framework for organ dose estimation in X-ray angiography and interventional radiology based on dose-related data in DICOM structured reports. Phys Med Biol 2016; 61: 3063–83. doi: https:// doi. org/ 10. 1088/ 0031- 9155/ 61/ 8/ 3063.

80. Beels L, Bacher K, De Wolf D, Werbrouck J, Thierens H. Gamma-H2Ax foci as a biomarker for patient X-ray exposure in pediatric cardiac catheterization: are we underestimating radiation risks? Circulation 2009; 120: 1903–9. doi: https:// doi. org/ 10. 1161/ CIRCULATIONAHA. 109. 880385
81. Glatz AC, Patel A, Zhu X, Dori Y, Hanna BD, Gillespie MJ, et al. Patient radiation exposure in a modern, large-volume, pediatric cardiac catheterisation laboratory. Pediatr Cardiol 2014:1-9.
82. Farah J, Trianni A, Ciraj-Bjelac O, et al. Characterization of XR-RV3 GafChromic(®) films in standard laboratory and in clinical conditions and means to evaluate uncertainties and reduce errors. Med Phys. 2015;42(7):4211-4226. doi:10.1118/1.4922132
83. Borrego D, Lowe EM, Kitahara CM, Lee C. Assessment of PCXMC for patients with different body size in chest and abdominal x ray examinations: a Monte Carlo simulation study. Phys Med Biol. 2018 Mar 21;63(6):065015. doi: 10.1088/1361-6560/aab13e. PMID: 29465419; PMCID: PMC6376487
84. Pelowitz DB. MCNPX Users Manual Version 2.7.0. 2011
85. Johnson PB, Geyer A, Borrego D, Ficarrotta K, Johnson K, Bolch WE. The impact of anthropometric patient-phantom matching on organ dose: A hybrid phantom study for fluoroscopy guided interventions. Medical Physics. 2011;38:1008–1017.
86. McCabe BP, Speidel MA, Pike TL, Van Lysel MS. Calibration of GafChromic XR-RV3 radiochromic film for skin dose measurement using standardized x-ray spectra and a commercial flatbed scanner. Med Phys. 2011;38(4):1919-1930.
87. Morrell RE, Rogers A. Calibration of Kodak EDR2 film for patient skin dose assessment in cardiac catheterization procedures. Phys Med Biol. 2004;49(24):5559-5570.
88. Ying C.K., Kandaiya S. EDR2 Film for Skin Dose Measurement in Coronary Angiography. Sains Malaysiana 41(1)(2012): 133–140.
89. Jarvinen, H. et al. Feasibility of setting up generic alert levels for maximum skin dose in fluoroscopically guided procedures. Phys. Med. 46, 67–74 (2018).
90. Jukka Järvinen, Joanna Sierpowska, Teemu Siiskonen, Minna Husso, Hannu Järvinen, Tuomas Kiviniemi, Tuomas T. Rissanen, Carita Lindholm, Hanna Matikka, Heli R. S. Larjava, Timo J. Mäkelä, Satu Strengell, Markku Eskola, Teuvo Parviainen, Elina Hallinen, Markku Pirinen, Antti Kivelä and Mika Teräs. CONTEMPORARY RADIATION DOSES IN INTERVENTIONAL CARDIOLOGY: A NATIONWIDE STUDY OF PATIENT SKIN DOSES

IN FINLAND. Radiation Protection Dosimetry (2020), Vol. 188, No. 2, pp. 181–190.

91. M Pasquino, C Cutaia, M Poli, C Valero, G Peroni, M De Benedictis, E Petrucci, M Stasi. Patient's Peak Skin Dose evaluation using Gafchromic films in interventional cardiology procedures and its correlation with other dose indicators. Phys Med. 2018 Sep;53:103-107
92. Kulkarni, A. R., Akhilesh, P. and Sharma, S. D. Measurement of patient skin dose and establishment of local diagnostic reference levels for interventional cardiology procedures. Radiat. Prot. Environ. 42(1), 28–33 (2019).
93. Krajinović M, Dobrić M, Ciraj-Bjelac O. SKIN DOSE MAPPING IN INTERVENTIONAL CARDIOLOGY: A PRACTICAL SOLUTION Radiat Prot Dospimetry. 2020 Jul 2;188(4):508-515.
94. Françoise Malchair, Jérémie Dabin, Marine Deleu, Marta Sans Merce, Olivera Ciraj Bjelac, Aoife Gallagher, Carlo Maccia, Review of skin dose calculation software in interventional cardiology. Physica Medica 2020;80:75-83.
95. Brambilla M, Cannillo B, Matheoud R, Compagnone G, Rognoni A, Bongo AS, et al. Conversion factors of effective and equivalent organ doses with the air kerma area product in patients undergoing coronary angiography and percutaneous coronary interventions. Phys Med. 2017;42:189–96.
96. Rassow J, Schmaltz AA, Hentrich F, Streffer C. Effective doses to patients from pediatric cardiac catheterization. Br J Radiol 2000;73:172–83.
97. Thompson DE, Mabuchi K, Ron E, Soda M, Tokunaga M, Ochikubo S, et al. Cancer incidence in atomic bomb survivors. Part II: solid tumors, 1958-1987. Radiat Res 1994; 137(2 Suppl): S17–67. doi: https:// doi. org/ 10. 2307/ 3578892
98. Harbron RW, Chapple C-L, O'Sullivan JJ, Best KE, Berrington de Gonzalez A, Pearce MS. Survival adjusted cancer risks attributable to radiation exposure from cardiac catheterisations in children. Heart 2017; 103: 341–6. doi: https:// doi. org/ 10. 1136/ heartjnl- 2016- 309773
99. Cristy M. Active bone marrow distribution as a function of age in humans. Phys. Med. Biol., 1981, Vol. 26. No. 3, 389-400