



# LUND UNIVERSITY

## Low kilovoltage computed tomography to reduce contrast medium dose in patients at risk of acute kidney injury

Holmquist, Fredrik

2021

*Document Version:*

Publisher's PDF, also known as Version of record

[Link to publication](#)

*Citation for published version (APA):*

Holmquist, F. (2021). *Low kilovoltage computed tomography to reduce contrast medium dose in patients at risk of acute kidney injury*. Lund University, Faculty of Medicine.

*Total number of authors:*

1

### General rights

Unless other specific re-use rights are stated the following general rights apply:

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal

Read more about Creative commons licenses: <https://creativecommons.org/licenses/>

### Take down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

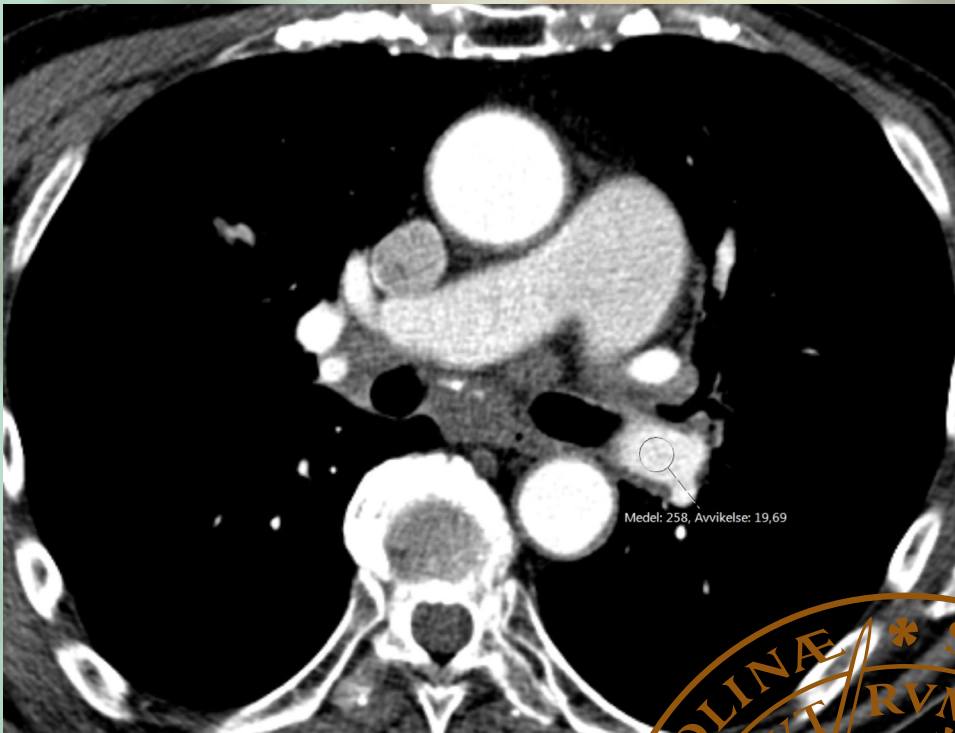
LUND UNIVERSITY

PO Box 117  
221 00 Lund  
+46 46-222 00 00

# Low kilovoltage computed tomography to reduce contrast medium dose in patients at risk of acute kidney injury

FREDRIK HOLMQUIST

CLINICAL SCIENCES LUND | FACULTY OF MEDICINE | LUND UNIVERSITY





# Low kilovoltage computed tomography to reduce contrast medium dose in patients at risk of acute kidney injury

Fredrik Holmquist



**LUND**  
UNIVERSITY

## AKADEMISK AVHANDLING

Som för avläggande av doktorexamen i medicinsk vetenskap vid  
Medicinska fakulteten, Lunds universitet, kommer att offentlig försvaras i  
Biblioteket, Plan 4, Bild och Funktion, Skånes universitetssjukhus Lund,  
fredagen den 12 februari 2021, kl 09.00

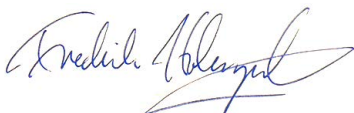
*Fakultetsopponent*

Docent Tomas Bjerner, Institutionen för kirurgiska vetenskaper, Radiologi  
Uppsala Universitet

Organization LUND UNIVERSITY Clinical Sciences Lund, Faculty of Medicine Author Fredrik Holmquist	Document name Doctoral Dissertation	
	Date of issue	
	Sponsoring organization	
Low kilovoltage computed tomography to reduce contrast medium dose in patients at risk of acute kidney injury		
<p>Abstract</p> <p><b>Background:</b> Patients with reduced renal function may be at risk of contrast medium-induced acute kidney injury (CI-AKI) following intravenous iodine contrast medium (CM) enhanced computed tomography (CT). Reducing the CM dose may reduce this risk. Decreasing the X-ray tube potential (kilovoltage, kV) from commonly used 120 to 80 kV results in higher CM attenuation due to the photoelectric properties of iodine, which may permit reduction of the iodine dose while keeping the attenuation unchanged. Lower tube potential, however, increases image noise which may be controlled by increasing the X-ray tube loading (milliampere seconds, mAs) to keep image quality, e.g. contrast-to-noise ratio (CNR) unchanged. Complete compensation of tube loading increases the radiation dose to the patient, but the introduction of noise reducing iterative reconstruction algorithms may prevent this.</p> <p><b>Aim:</b> To investigate if low-kV CT with reduced CM doses is a feasible alternative in examinations of the thorax and abdomen in patients considered at risk of CI-AKI.</p> <p><b>Material and methods:</b> In three cross-sectional studies 80-kV CT protocols with 40-50% reduction of CM dose and increased tube loading to control image noise was compared with standard 120-kV protocols, in two studies to diagnose pulmonary embolism and in one hepatic study. Based on a phantom study and a clinical hepatic CT study, iterative reconstruction algorithms were used to control image noise with no increase in tube loading. Image quality was evaluated objectively and subjectively.</p> <p><b>Results:</b> Using 80-kV CT protocols with reduced CM doses (40-50%) and mAs compensation seems to provide satisfactory diagnostic quality in pulmonary CT angiography and hepatic CT for patients with GFR &lt;45-50 mL/min and a body mass index &lt;30 kg/m<sup>2</sup>. However, the use of iterative reconstruction algorithms to control image noise without increased mAs resulted in inferior subjective image quality.</p> <p><b>Conclusion:</b> Using low-kV CT protocols with reduced CM dose could benefit patients at risk of CI-AKI. The usefulness of iterative reconstruction algorithms to control image noise and not increase radiation dose remains unclear.</p>		
Key words Computed tomography; image quality; radiation dose; contrast medium induced nephropathy; iterative reconstruction		
Classification system and/or index terms (if any)		
Supplementary bibliographical information		Language English
ISSN and key title 1652-8220		ISBN 978-91-8021-019-5
Recipient's notes	Number of pages	Price
	Security classification	

I, the undersigned, being the copyright owner of the abstract of the above-mentioned dissertation, hereby grant to all reference sources permission to publish and disseminate the abstract of the above-mentioned dissertation.

Signature



Date 2020-12-15

Low kilovoltage computed tomography  
to reduce contrast medium dose in patients  
at risk of acute kidney injury

Fredrik Holmquist



**LUND**  
UNIVERSITY

Department of Medical Imaging and Physiology,  
Skåne University Hospital,  
Clinical Sciences Lund,  
Faculty of Medicine,  
Lund University,  
2021

Cover photo To our knowledge the first CT of the pulmonary arteries at 80-kV in the world, April 15, 2003 Trelleborg

Cover image by Fredrik Holmquist

Copyright © Fredrik Holmquist, pp 1-77

Paper I © Acta Radiologica

Paper II © European Radiology

Paper III © Acta Radiologica

Paper IV © Acta Radiologica

Paper V © by the Authors (published in Acta Radiologica Open)


Faculty of Medicine  
Clinical Sciences Lund  
Department of Medical Imaging and Physiology  
Skåne University Hospital  
Lund University

ISBN 978-91-8021-019-5

ISSN 1652-8220

Printed in Sweden by Media-Tryck, Lund University  
Lund 2021



MADE IN SWEDEN 

Media-Tryck is an environmental-ly certified and ISO 14001 certified provider of printed material. Read more about our environmental work at [www.mediatryck.lu.se](http://www.mediatryck.lu.se)

*Dedicated to Ulf Nyman who with fatherly patience has endured  
this extended process when I have been otherwise engaged*



# Contents

Summary .....	8
Sammanfattning på svenska.....	11
List of abbreviations .....	14
Original papers.....	15
Introduction.....	17
Background.....	21
Computed tomography .....	21
Technique .....	22
Radiation dosimetry .....	22
Image reconstruction.....	23
120 kV versus 80 kV .....	24
Contrast media.....	25
Contrast media induced acute kidney injury.....	26
Image quality .....	26
Parameters of image quality .....	26
Objective evaluation .....	27
Subjective evaluation.....	27
Aims.....	29
Material and methods.....	31
Study subjects .....	31
CT parameters .....	33
Phantom study .....	34
Contrast medium dose .....	36
Contrast medium-induced acute kidney injury.....	37
Radiation dose .....	37
Image reconstruction .....	38
Image quality .....	39

Objective evaluation .....	39
Subjective evaluation.....	40
Statistical evaluation.....	41
Ethical considerations.....	42
Results.....	43
Paper I.....	43
Paper II .....	44
Paper III.....	45
Paper IV.....	48
Paper V .....	50
Discussion.....	53
Contrast medium.....	54
Contrast medium dose and CI-AKI .....	55
Image quality .....	56
Image reconstructions.....	59
Radiation dose .....	60
Clinical impact.....	61
Conclusion .....	63
Future perspectives.....	64
Acknowledgement .....	67
References.....	69

# Summary

Computed tomography (CT) is an increasingly important diagnostic tool in radiology. The main benefit of CT compared with conventional radiography is the low-contrast resolution i.e., the ability to differentiate between two structures with small differences in attenuation. Despite this, in many cases, there is a need to enhance certain structures such as vessels and parenchymal organs using an iodine contrast medium (CM) to make a proper diagnosis. A major drawback of CM is that it has a potentially toxic effect on the kidneys, especially in patients with reduced renal function, so-called CM-induced acute kidney injury (CI-AKI). This has been reported to occur in 5-20% of patients that undergo a CM-enhanced CT examination and may be a condition associated with both short and long-term increased morbidity and mortality. Other risk factors associated with CI-AKI include diabetes, congestive heart failure and obstructive lung disease with hypoxia.

Renal function deteriorates with age. In a growing elderly population other risk factors such as heart and/or lung disease and diabetes are also more prevalent. Thus, there is a growing number of patients who have an increased potential risk of developing CI-AKI when undergoing a CM-enhanced CT examination. These patients are therefore at risk of being denied a CM-enhanced CT examination or subjected to a suboptimal non-CM CT examination which in the end could risk delaying or preventing making the correct diagnosis and making them ineligible for the right type of medical care and treatment.

Reducing the CM dose may reduce the risk of developing CI-AKI. One potential way to reduce CM doses in CT is to reduce the X-ray tube potential (kilovoltage, kV), from the commonly used 120 kV to 80 kV. This results in higher CM attenuation due to the photoelectric properties of iodine which may permit reduction of the iodine dose of approximately 40% while keeping the attenuation unchanged.

The downside of lower tube potential is increased image noise, which affects image quality. In order to control image noise, the radiation output from the X-ray tube (tube loading, milliamperere seconds (mAs)) has to be increased. For unchanged image noise, complete compensatory increase of the tube loading would result in an increased radiation dose to the patient. In recent years advances in image reconstruction techniques with the introduction of iterative noise-reducing reconstruction (IR) algorithms have emerged. They were originally intended for image optimization as a way to reduce radiation dose but could potentially also be

used as a way to mitigate the need increased radiation dose when using lower tube potentials.

The aim of this thesis was to investigate the possibilities and limitations of reducing CM dose in patients at risk of CI-AKI undergoing CT by reducing X-ray tube potential.

### *Paper I*

A cross-sectional clinical study on CT pulmonary angiography (CTPA) in patients with clinical suspicion of pulmonary embolism. Eighty-nine consecutive patients considered at risk of CI-AKI were examined with an 80-kV protocol with 40% CM dose reduction and tube loading compensation. The result was compared with patients without risk of CI-AKI using the 120-kV standard protocol. Signs of CI-AKI or any diagnosed venous thromboembolism (VTE) in patients with a negative CTPA were evaluated in a three-month follow-up.

### *Paper II*

A cross-sectional clinical study on CTPA in patients with clinical suspicion of pulmonary embolism. Fifty consecutive patients considered at risk of CI-AKI were examined with an optimized 80-kV protocol with 50% CM dose reduction and tube loading compensation. The results were compared with the 80-kV cohort from Paper I. Signs of CI-AKI or any diagnosed venous thromboembolism (VTE) in patients with a negative CTPA were evaluated in a three-month follow-up.

### *Paper III*

Objective and subjective evaluation of the impact of different strengths of iterative reconstruction (IR) algorithms (Siemens SAFIRE 1-5) on image noise, iodine attenuation and low-contrast object detection at different X-ray tube potentials and radiation doses using an image quality phantom.

### *Paper IV*

A cross-sectional clinical study on hepatic CT. Forty consecutive patients considered at risk of CI-AKI where examined with an 80-kV protocol with 40% reduced CM dose and compensated tube loading to control image noise. Objective and subjective image quality was compared with the standard 120-kV protocol.

### *Paper V*

The use of IR algorithms to control image noise instead of tube loading compensation in 80-kV hepatic CT was evaluated in the same 80-kV cohort as in Paper IV. Objective and subjective image quality was assessed in 40 patients who served as their own controls.

The results from our studies indicated that the 80-kV protocols with reduced CM doses (40-50%) and tube loading compensation provide satisfactory diagnostic quality, comparable with our standard protocols, in CTPA and hepatic CT for patients with body mass index (BMI) <30 kg/m<sup>2</sup>. However, the use of IR algorithms to control image noise without tube loading compensation resulted in inferior subjective image quality. We found no increased incidences of CI-AKI in our studies.

In conclusion, using 80-kV CT protocols with reduced CM dose and maintained image quality seems feasible and could benefit patients considered at risk of CI-AKI. To what degree iterative reconstruction algorithms may be used to control image noise with maintained image quality without increased radiation dose in low-kV protocols remains unclear.

# Sammanfattning på svenska

Datortomografi (DT) är ett viktigt diagnostiskt verktyg inom radiologin. Datortomografins främsta styrka jämfört med konventionell röntgen av t.ex. lungor och buk är den goda lågkontrastupplösningen, dvs. förmågan att särskilja mellan två strukturer med snarlik täthet (attenuering). Trots detta finns det ofta ett behov av att förstärka kontrasten i vissa strukturer som t.ex. kärl och parenkymatösa organ med hjälp av jodbaserade kontrastmedel (KM) för att kunna ställa rätt diagnos. En begränsning med användandet av KM är att det kan ha en potentiell toxisk effekt på njurarna, i synnerhet hos patienter med reducerad njurfunktion. Så kallad kontrastmedelsinducerad akut njurskada (CI-AKI, engelsk förkortning). I litteraturen har det rapporterats kunna drabba 5–20 % av alla patienter som genomgår en DT-undersökning med kontrastmedel och kan vara associerad med ökad dödlighet och sjuklighet på både kort som lång sikt. Riskfaktorer som associerats med CI-AKI inkluderar diabetes, hjärtsvikt och obstruktiv lungsjukdom med andnöd.

Njurfunktionen försämras med åldern. Riskfaktorer som hjärt-lungsjukdomar och diabetes ökar också i en åldrande befolkning. Således ökar antalet patienter som riskerar att utveckla CI-AKI efter en DT-undersökning med kontrastmedel. Eftersom detta är välkänt riskerar dessa patienter att inte få sin diagnostiska undersökning utförd, och om alternativa undersökningsmetoder saknas riskerar de försenad eller missad diagnos och felaktig behandling.

Reducering av KM-dosen kan potentiellt minska risken för att utveckla CI-AKI. Ett möjligt tillvägagångsätt kan vara att reducera röntgenrörets rörspänning (kilovolt, kV) från vanligen använda 120 kV till 80 kV. Vid lägre rörspänning ökar tätheten för KM på grund av jodatomens fotoelektriska egenskaper. Detta gör att KM-dosen kan reduceras med ca 40 % vid 80 kV jmf med 120 kV utan att förändra kontrasttätheten.

Nackdelen med att sänka rörspänningen är att röntgenstrålningen får lägre medelenergi, vilket innebär att färre fotoner når detektorn. Då ökar bruset i bilden, och bildkvaliteten försämras. För att kontrollera bruset måste därför mängden strålning ökas. För att hålla bildbruset oförändrat skulle en fullständig kompensatorisk ökning av strålningen till detektorn innebära ökad stråldos till patienten. Under de senaste åren har det utvecklats bildrekonstruktionstekniker för att bättre kunna hantera bildbruset. Dessa har i första hand skapats för

bildoptimering och stråldosreducering, men skulle möjligen även kunna användas för att minska behovet av fullständig kompensatorisk ökning av stråldosen vid användning av lägre rörspänning

Syftet med den här avhandlingen var att undersöka möjligheter och begränsningar med att reducera KM-dosen till patienter med förmodad ökad risk för att utveckla CI-AKI vid DT-undersökningar genom att reducera rörspänningen.

### *Studie I*

En klinisk tvärsnittsstudie för DT-angiografi av lungartärerna på patienter med klinisk misstanke om lungemboli. Åttionio patienter med förmodad ökad risk för att utveckla CI-AKI undersöktes med ett 80-kV DT-protokoll med 40 % reducerad KM dos och kompenserad stråldos. Bildkvalitet, brus och KM-täthet jämfördes med patienter som undersökts med 120-kV standardprotokollet. Patienterna följdes upp under tre månader för att leta efter tecken på CI-AKI och episoder av tromboembolisk sjukdom.

### *Studie II*

En klinisk tvärsnittsstudie för DT-angiografi av lungartärerna på patienter med klinisk misstanke om lungemboli. Femtio patienter med förmodad ökad risk för att utveckla CI-AKI undersöktes med ett optimerat 80-kV DT protokoll med 50 % reducerad KM-dos och kompenserad stråldos. Bildkvalitet, brus och KM-täthet jämfördes med 80 kV kohorten från Studie I. Patienterna följdes upp under tre månader för att leta efter tecken på CI-AKI och episoder av tromboembolisk sjukdom.

### *Studie III*

Fantomstudie för objektiv och subjektiv utvärdering av hur iterativa rekonstruktionsalgoritmer (Siemens SAFIRE 1–5) påverkar brus, jodattenuering och låg-kontrastupplösning vid olika rörspänning.

### *Studie IV*

En klinisk tvärsnittsstudie för DT av levern. Fyrtio patienter med förmodad ökad risk för CI-AKI undersöktes med ett 80-kV DT-protokoll med 40 % reducerad KM dos och kompenserad stråldos. Objektiv och subjektiv bildkvalitet jämfördes med 40 patienter som undersökts med 120-kV standardprotokoll.

### *Studie V*

Användandet av iterativa rekonstruktionsalgoritmer för att kontrollera bruset istället för kompensatorisk ökning av stråldosen vid 80-kV DT av levern utvärderades i samma 80-kV kohort som i Studie IV. Objektiv och subjektiv bildkvalitet utvärderades.

Resultaten från våra studier indikerar att 80-kV protokoll med reducerad KM-dos (40–50%) och kompensatoriskt ökad stråldos ger acceptabel bildkvalitet som är jämförbar med våra standardprotokoll för DT-angiografi av lungkärnen samt DT av levern hos patienter med BMI (body mass index)  $<30 \text{ kg/m}^2$ . Användandet av iterativa rekonstruktionsalgoritmer som substitut för kompensatoriskt ökad stråldos för att kontrollera bruset resulterade i försämrad bildkvalitet. Vi hittade inga tecken på ökad incidens av CI-AKI i våra studier.

Sammanfattningsvis förefaller användandet av 80-kV DT-protokoll med reducerad KM dos och bibehållen bildkvalitet vara möjlig och skulle kunna vara till gagn för patienter med ökad risk för att utveckla CI-AKI. I vilken utsträckning iterativa rekonstruktions-algoritmer kan användas för att kontrollera bruset med bibehållen bildkvalitet utan att öka stråldosen vid sänkt rörspänning är fortfarande oklart.



# List of abbreviations

ALARA	As low as reasonably achievable
AUC	Area under the curve
CI-AKI	Contrast medium-induced acute kidney injury
CM	Contrast medium
CNR	Contrast-to-noise ratio
COPD	Chronic pulmonary obstructive disease
CT	Computed tomography
CTA	Computed tomography angiography
CTDI <sub>vol</sub>	Volume pitch-corrected computed tomography dose index
CTPA	Computed tomography pulmonary angiography
DLP	Dose length product
ED	Effective radiation dose
FBP	Filtered back-projection
eGFR	Estimated glomerular filtration rate
HU	Hounsfield unit (attenuation)
I	Iodine
IR	Iterative reconstruction
i.v.	Intravenous
keV	Kiloelectron volt
kV	Kilovoltage (tube potential)
mA	Milliamperes (tube current)
mAs	Milliamperes second (tube loading)
MDCT	Multi-detector row computed tomography
mGy	Milligray (absorbed radiation dose)
mSv	Millisievert (equivalent radiation dose or effective dose)
NPS	Noise power spectrum
PA	Pulmonary artery
PE	Pulmonary embolism
ROC	Receiver operating characteristic
ROI	Region of interest
SD	Standard deviation
SNR	Signal-to-noise ratio
SSUR	Swedish Society of Urogenital Radiology
TLC	Tube loading compensation
VGA	Visual grading analysis
VGC	Visual grading characteristic
VTE	Venous thromboembolism

# Original papers

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals. The papers are appended at the end of the thesis.

- I. **Holmquist F**, Hansson K, Pasquariello F, Björk J, Nyman U.  
*Minimizing contrast medium doses to diagnose pulmonary embolism with 80-kVp multidetector computed tomography in azotemic patients.*  
Acta Radiol 2009;50:181–193.
- II. Kristiansson M, **Holmquist F**, Nyman U.  
*Ultralow contrast medium doses at CT to diagnose pulmonary embolism in patients with moderate to severe renal impairment: a feasibility study.*  
Eur Radiol 2010;20:1321–1330.
- III. **Holmquist F**, Nyman U, Siemund R, Geijer M, Söderberg M.  
*Impact of iterative reconstructions on image noise and low-contrast object detection in low kVp simulated abdominal CT: a phantom study.*  
Acta Radiol 2016;57(9):1079–1088.
- IV. **Holmquist F**, Söderberg M, Nyman U, Fält T, Siemund R, Geijer M.  
*80-kVp hepatic CT to reduce contrast medium dose in azotemic patients: a feasibility study.*  
Acta Radiol 2020; 61(4):441–449.
- V. **Holmquist F**, Söderberg M, Nyman U, Fält T, Siemund R, Geijer M.  
*Can iterative reconstruction algorithms replace tube loading compensation in low kVp hepatic CT? Subjective versus objective image quality.*  
Acta Radiologica Open 2020;9(3):1-9.

Other related publications by the author not included in the thesis:

**Holmquist F**, Nyman U.

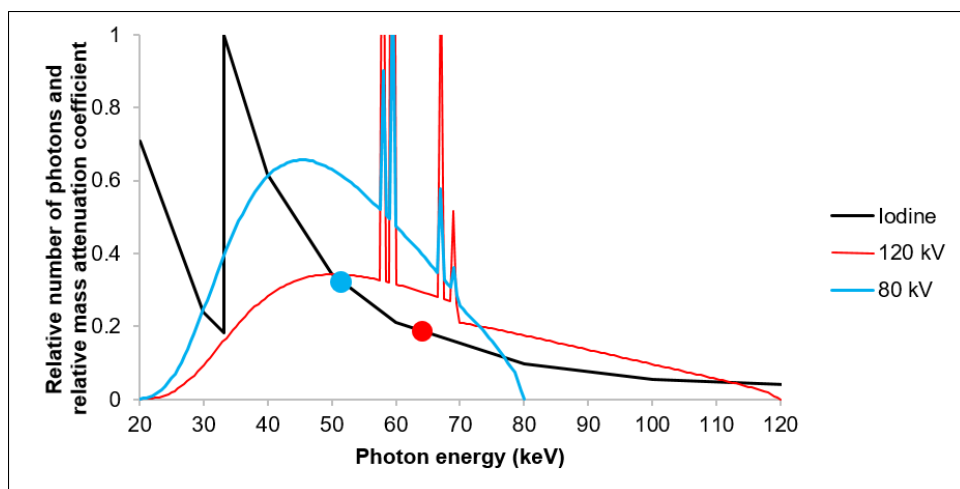
*Eighty-peak kilovoltage 16-channel multidetector computed tomography and reduced contrast-medium doses tailored to body weight to diagnose pulmonary embolism in azotaemic patients.*

Eur Radiol. 2006;16(5):1165–76.

# Introduction

Intravascular organic contrast media (CM) based on iodine, introduced by Moses Swick in 1929<sup>33,87</sup> are still today the primary contrast medium for X-ray examinations including computed tomography (CT). One of the major obstacles with iodine CM (I-CM) since the 1940-50s has been the fear of CM-induced acute kidney injury (CI-AKI)<sup>4,11,70</sup>, a condition with few effective prophylactic measures<sup>64,65</sup> apart from reducing the CM dose<sup>60</sup>. The required diagnostic CM dose is dependent on the X-ray attenuation of iodine which in turn is tightly linked to the photon energy.

With decreasing photon energy, the attenuation of iodine increases until it reaches the binding energy of the innermost electron shell (the k-shell) at 33.2 kiloelectron volt (keV), the so-called *k-edge* of iodine (Figure 1).



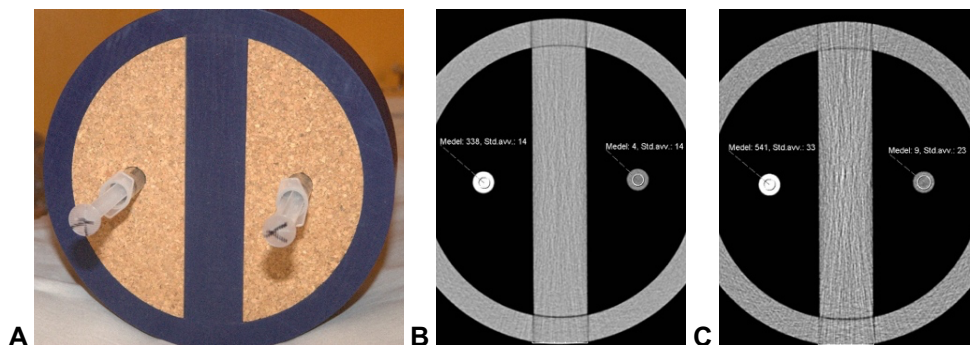
**Figure 1 Photonenergy spectrum of 120 kV and 80 kV**  
Photonenergy spectrum at 120 kV and at 80 kV for the same radiation dose (generated in SpekCalc) compared to the attenuation curve of iodine (gathered from NIST Standard Reference Database). Red and blue dots indicate mean photon energy of the 120 and 80 kV spectra, showing the increase in iodine attenuation at 80 kV compared to 120 kV.

The long tradition of performing urography and angiography with I-CM has taught us to aim for an X-ray tube potential as low as possible, in practice at about 70 to 80 kilovoltage (kV), to optimize the diagnostic ability. However, when CT was

introduced during the 1970s it was performed at 120-140 kV, even when I-CM was used, and has continued in that way until the 21<sup>st</sup> century. Decreasing the tube potential to 70-80 kV requires compensated increased tube loading (milliamperere seconds, mAs) to preserve image noise and maintain image quality. However, the ability to increase tube loading was limited by insufficient capacity of previous generations of X-ray tubes to handle several tens of scans with the initial stepwise/sequential (“step and shoot”) CT technique or the long exposure times during the first generations of helical (“spiral”) CT equipment using single-row detectors.

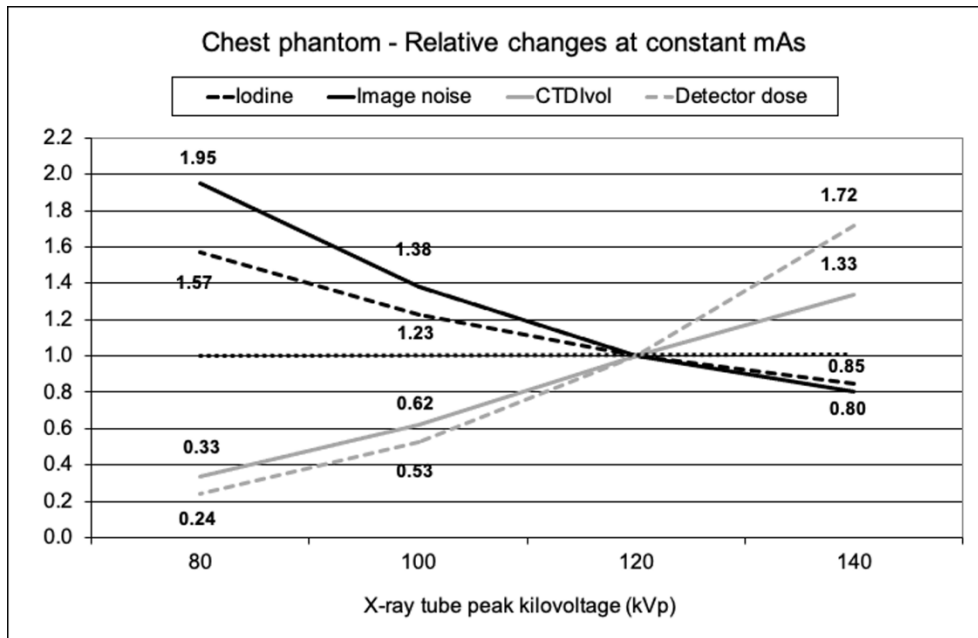
In the beginning of the 21<sup>st</sup> century the development of multi-detector row CT systems (MDCT), which decreased acquisition time, and combined with increased capacity of the X-ray tubes created the technical conditions to permit high enough tube loadings when decreasing the tube potential. In 2002 a 16-row MDCT was installed at the X-ray department of Lasarettet Trelleborg, Sweden, and the first tests were performed of using 80-kV CT in the chest. It was simply chosen since it for obvious reasons requires less tube loading than the abdomen due to less density.

An initial unpublished phantom experiment (Figure 2, 3) indicated that when decreasing tube potential from 120 to 80 kV the CM-dose can be reduced with a factor 1.6 which was in accordance with a few published studies<sup>15,38</sup>. However, image noise increased by a factor two. Since noise is inversely proportional to the square root of the radiation dose<sup>66</sup>, tube loading has to be increased by a factor four. This is in accordance with the theory that the intensity of the radiation beam at the detector array may vary with the quote between the final and initial X-ray tube potential to the power of 3.5<sup>66</sup>, i.e.  $80/120^{3.5} = 0.24$ .



**Figure 2 Chest phantom**

**A.** 30-cm diameter chest phantom composed of cork simulating lung tissue (-790 HU) and 2.5-cm-wide nylon material (70 HU at 120 kV) simulating thoracic wall and mediastinum. One 20-ml syringe was filled with distilled water and one with I-CM, 12 mg I/ml **B.** A 120-kV CT of the chest phantom, CM attenuation 338 HU and mean image noise 14 HU (1SD). **C.** 80-kV CT, CM attenuation 541 HU and mean image noise 28 HU (1SD); thus, a factor 1.6 increase in attenuation and roughly a factor 2 increase in image noise.



**Figure 3 Relative changes at a constant mAs**

Diagram with relative changes of CM attenuation, image noise and radiation dose in terms of CTDI<sub>vol</sub> when scanning the 30-cm chest phantom (Figure 2) with a Siemens Somatom Sensation with 16 detector rows and an X-ray tube filtration equivalent to 11 mm aluminium<sup>72</sup>. Detector radiation dose changes according to Nagel, (kV<sub>1</sub>/kV<sub>2</sub>)<sup>3.5</sup><sup>66</sup>. Published with permission from Acta Radiologica.

Based on our initial phantom study we targeted patients with suspected pulmonary embolism (PE), often elderly with reduced renal function. The first examination was performed on April 15, 2003, on a 93-year old woman with an estimated glomerular filtration rate (eGFR) of 32 ml/min. The result was encouraging (see cover page) and eventually resulted in a publication of the first 29 cases<sup>36</sup>. Subsequently the technique has also been applied in abdominal CT.

Decreasing the tube potential from 120 to 80 kV, the radiation dose to the detector, which directly correlates with image noise, is reduced with about three quarters (0.24). The averaged radiation dose to the object, computed tomography dose index by volume (CTDI<sub>vol</sub>), is also reduced but only by two thirds (0.33) as illustrated in Figure 3. The required about four-time increase in tube loading ( $1/0.24 = 4.2$ ) following tube loading compensation (TLC) to leave image noise unchanged has several drawbacks. Radiation dose to the object will increase by about 40% from 0.33 to 1.39 ( $4.2 \times 0.33$ ) at 80 kV relative 120 kV. It will possibly also result in shorter life expectancy of the X-ray tubes due to increased wear. In large patients even modern high output X-ray tubes may not have the capacity to deliver the required increase in tube current. If sufficient effective tube loading (pitch-corrected, mAs/pitch) is possible by increasing rotation time or decreasing pitch,

scan time increases which may jeopardize image quality by e.g., breathing artefacts and CM escape during CT angiography.

The introduction of iterative reconstruction (IR) algorithms during the last decade has opened for a new approach to control image noise instead of TLC when decreasing X-ray tube potential<sup>92,94</sup>. However, there have been concerns as to how these algorithms may change image noise texture, which may negatively affect lesion detection<sup>41</sup>.

This thesis explores the feasibility to utilize the increased iodine attenuation when reducing X-ray tube potential to reduce CM doses in chest and abdominal CT in patients considered at risk of CI-AKI while using TLC or IR algorithms to control image noise.

# Background

## Computed tomography

Computed tomography was developed by Sir Godfrey Hounsfield in 1971 based on the theoretical calculations of Allan McLeod Cormack<sup>17,18</sup> on a practical application of the mathematical basis for tomographic imaging by Johann Radon<sup>79</sup> using X-rays.

Since its introduction CT has revolutionized modern medicine and is today one of the most useful and prevalent radiological diagnostic tools in health care, and the number of examinations continues to increase every year. In Sweden (population 10 million) almost 1.5 million CT examinations were performed in 2018, which is an 130% increase compared to 2005<sup>2</sup>. This is most probably due to the rapid technological development of CT with dramatically improved spatial and temporal resolution that has led to a shift from planar radiography and fluoroscopy examinations to CT. It does however raise concerns over the risks associated with an increased radiation exposure to the population (30% 2018 compared with 2005). New CT technology and increasing number of examinations puts further emphasis on the need for optimization of protocols and managing radiation and CM doses to ensure diagnostic efficacy.

The goal of clinical CT is to produce images of the body with diagnostic quality at the lowest possible radiation dose. The reduction of radiation dose is limited by the degradation of image quality due to increase in image noise<sup>14,32</sup> which may affect diagnostic quality. The image quality needed may however vary depending on the clinical question that needs to be answered.

This thesis stretches over more than a decade of advances in CT technology with a starting point a few years after the introduction of 16-MDCT systems in the beginning of the 21<sup>st</sup> century. Since the start of this work we have seen the introduction of many technical advances from automatic exposure control to the gradual increase in number of detector rows with increased collimation, from 16 to the present 64-320 rows, enabling us to cover a larger volume per rotation resulting in shorter scan times. The introduction of stronger and more powerful X-ray tubes and, maybe most importantly, a seemingly never diminishing increase in



computational capacity has allowed for faster and ever more advanced reconstruction algorithms and iterations of the image data.

## Technique

A CT system consists of a gantry with a rotating X-ray tube that emits photons that are detected by detectors that is placed on the diametrically opposite side. The detectors measure the beam intensity at different angles (projections). In the image reconstruction process the collected projection data, called raw data or sinogram data are processed through complex mathematical algorithms to compute the attenuation coefficient for each voxel to obtain an image. Thus, a CT image reflects the attenuation of different tissues in the body. The attenuation is presented as CT numbers relative to the attenuation of water, expressed in Hounsfield units (HU).

Multi-detector row CT (MDCT) allows for simultaneous acquisition of parallel slices in one rotation. Increasing the number of slices per rotation results in larger volume coverage and faster scan times. MDCT systems used in this thesis range from 16 to 64×2 rows (using z-flying focal spot technique the number of simultaneously acquired slices can be doubled).

## Radiation dosimetry

CT utilizes ionizing radiation which is associated with a potential risk of inducing cancer. The radiation dose is principally dependent on the selected tube current (mA), peak tube potential (kV) and exposure time. In CT as in conventional radiology there is a linear relationship between the tube current-time product (tube loading, mAs) and radiation dose. The radiation dose affects image noise in such a way that image noise is inversely proportional to the square root of the dose<sup>66</sup>, valid for a linear reconstruction process.

The tube potential has a more complex exponential relationship to radiation dose. When changing the tube potential, the radiation dose to the detector varies according to the fraction of the final versus the initial tube potential to the power of 3.5.

$$\text{Radiation dose to detector} = \left( \frac{kV^2}{kV^1} \right)^{3.5}$$

The radiation dose to the patient also change but only to the power of 2.5<sup>66</sup>.

$$\text{Radiation dose to patient} = \left( \frac{kV^2}{kV^1} \right)^{2.5}$$

Computed tomography dose index by volume (CTDI<sub>vol</sub>, mGy) is the fundamental descriptor of radiation dose in CT. It represents a weighted average of radiation output standardized to a 32 cm (body), or 16 cm (head) phantom. The patient dose is dependent on the CTDI<sub>vol</sub> but since the effective dose per energy imparted is inversely proportional to body size<sup>89</sup>, patient dose would be higher than indicated by the CTDI<sub>vol</sub> for a patient smaller than the phantom and vice versa.

By multiplying the CTDI<sub>vol</sub> with the scan length the total radiation exposure of the CT examination is obtained and defined by the dose-length-product (DLP, mGy×cm)<sup>32</sup>. The estimated effective dose (ED, mSv) which represent the estimated stochastic risk of cancer induction may be obtained by multiplying DLP with an appropriate conversion ED/DLP factor depending on anatomical region<sup>14,37</sup>.

## **Image reconstruction**

A prerequisite for the development of the first CT in 1970 was the calculative capacity of the newly developed computer. The computational power is needed to make all the mathematical calculations to reconstruct all the projection (raw) data into an image. In the beginning an algebraic reconstructive technique, which is a form of iterative reconstruction technique, was used but was quickly superseded by faster analytic reconstruction techniques, notably filtered back-projection (FBP). With increasing computational capacity iterative reconstructive techniques has once again been introduced in the last decade in an effort to improve signal-to-noise ratio<sup>26</sup>.

### *Filtered back-projection (FBP)*

FBP is an analytic linear reconstruction algorithm that assumes an ideal relationship between the attenuation measurements in the projection data with the pixel attenuation in the image domain. All projection measurements are treated equally and is processed only once. The acquired projection data is filtered through a convolution filter (kernel) to prevent blurring and is then projected back into image space to reconstruct an image<sup>31</sup>. Different convolution filters may be applied to enhance or diminish certain image characteristics depending on specific anatomical applications such as soft tissue (smoothing) or bone (edge enhancement). FBP is a fast and adequate reconstruction method that has been the golden standard almost since the beginning of the CT era. The major drawback of FBP is the introduction of noise caused by the convolution filters, which becomes apparent with increasing image noise and artifacts when radiation dose is reduced.

### *Iterative reconstruction (IR)*

Basic principle of IR algorithms begins with a model image created through back projection which is then compared with the actual measured values repeatedly and

adjusted until they are in agreement. Despite longstanding knowledge of the theoretical advantages of IR to reduce noise and artifacts it was not until about a decade ago that computational power was sufficient to allow IR into clinical implementation. Commercially available IR algorithms from different vendors have applied different approaches to the use of IR and the iterations may take place in the projection domain or in the image domain or both depending on the algorithm used.<sup>93</sup> The first generation of IR mainly used adaptive statistical IR methods taking into account photon statistics, radiation attenuation and other statistics in the image reconstruction process to reduce image noise. In later generations IR has moved onto model-based IR methods or forward projected model-based IR. For the iterations to take place in the projection domain forward projection is needed to reconstruct projection data from image data. The complex non-linear mathematical algorithms of forward projecting aim to model the acquisition process (CT system, X-ray attenuation and detection process) as accurately as possible. It can take into account photon statistics, allowing the algorithm to take lower noise projections into higher considerations compared to higher noise projections. It can also take into account general assumptions such as objects tend to have smooth changes in CT numbers except at the edges. This enables iterative reconstruction algorithms to reduce image noise while maintaining high-contrast spatial resolution. For low contrast detectability however the IR algorithms may have difficulties in differing between the edge of low contrast objects and noise making low-contrast spatial resolution hard to maintain. IR algorithms can be said to have a contrast dependent spatial resolution<sup>62</sup>.

In this thesis the second-generation IR algorithm by Siemens, Sinogram-Affirmed Iterative Reconstruction (SAFIRE) was used. This algorithm iterates both in the projection and in image domain with five levels of noise reduction (strengths). Noise modelling for each iteration is performed by estimating the noise in each volume element (voxel) by analyzing the contribution of raw data, then noise is removed<sup>95</sup>.

## **120 kV versus 80 kV**

By shifting the X-ray tube potential from 120 to 80 kV the mean photon energy is reduced, from typically 69 to 54 keV (Siemens Definition Flash), but may vary depending on CT system and filtration used. This brings the energy spectrum of the photons closer to the binding energy of the electrons in the K-shell (33.2 keV) of the iodine atom. This adds a photoelectric absorption component with direct interaction with the electrons to the Compton effect that generally makes up for most of the X-ray absorption. The Compton effect consists of photon interaction with free or loosely bound electrons and is mainly dependent on the density of the materia. Because of this added absorption the iodine attenuation increases from about 25 HU per mg I/ml at 120 kV to 41 HU per mg I/ml at 80 kV as calculated

from reference<sup>73</sup>. The amount of iodine can thus be reduced by 40% or a factor 1.6 for the same attenuation.

## Contrast media

Even though one of the biggest advantages with CT compared to projection radiography is the improved low contrast resolution, this may be further improved by the use of CM to enhance the attenuation differences between pathological lesions and various structures in the body such as vessels, bowels or parenchymatous organs.

This thesis is based on the concept that by lowering the tube potential when performing CT, the mean photon energy shifts towards a lower energy spectrum and thereby making better use of the photoelectric properties of iodine, the principle intravascular contrast medium for CT. Increasing the attenuation of iodine by decreasing the X-ray tube potential may have two practical advantages. It could either be used to increase the contrast in the images and thereby allowing for reduction of the radiation dose while keeping the CNR unchanged. Or it could be used to lower the amount of CM needed while maintaining the same attenuation level. The reason for doing the latter is the potential nephrotoxic effects iodine CM may have on the kidneys. This holds especially true for elderly patients, that has a higher prevalence of reduced renal function, diabetes and other risk factors.

According to the guidelines of the Swedish Society of Urogenital Radiology<sup>70</sup> regarding patients at risk of CI-AKI the CM dose should be kept as low as reasonably achievable according to the ALARA principle and preferably the gram-iodine/absolute GFR ratio should not exceed 0.5 at CT.

In CT pulmonary angiography (Paper I and II) the crucial thing is to give enough CM to achieve adequate enhancement of the pulmonary vessels and to time scanning with peak enhancement, usually by bolus tracking technique. The primary factor that influence vascular CM enhancement is the CM dose rate, i.e. the amount of CM administered per kg body weight and time unit, mg I/kg/sec<sup>6,24,54</sup> the injection time should be adapted to the scanning delay set after enhancement has reached the bolus tracking threshold and expected scan-time with some margin to account for individual differences. An important patient related factor affecting both scan timing and CM enhancement is cardiac output. If cardiac output is reduced the CM will take longer time to arrive in the pulmonary circulation but the peak enhancement will increase because of less dispersion of the CM bolus and less dilution from inflowing non-CM containing blood<sup>8</sup>.

In CT of parenchymatous organs such as the liver the CM injection rate is of minor importance as the CM enhancement is principally determined by the total amount of iodine administered into the body<sup>9</sup>.

## **Contrast media induced acute kidney injury**

CI-AKI has been a feared complication with increased morbidity and mortality<sup>61</sup>. More recent studies, based on retrospective propensity-scored controlled studies suggests that the risk has been overestimated, especially regarding i.v. injections following CT<sup>19,59</sup>. Thus, the ESUR guidelines regarding the GFR threshold indicating a risk of CI-AKI following i.v. CM injections has gradually been lowered throughout the years, from 60 mL/min/1.73 m<sup>2</sup> (ESUR guidelines 7.0, 2008) to 45 mL/min/1.73 m<sup>2</sup> in 2011<sup>85</sup> and finally 30 mL/min/1.73 m<sup>2</sup> in 2018<sup>23</sup>. The 2017 Swedish guidelines by SSUR holds a more conservative attitude with a GFR threshold of 45 mL/min, since retrospective controlled studies implies a risk for selection bias and their level of evidence has been graded as low in a systematic review by the Radiological Society of the Netherlands<sup>78</sup>. These guidelines reflect the GFR risk thresholds for CI-AKI selected during the course of time in the papers of the present thesis<sup>70</sup>.

## **Image quality**

The aim of clinical CT imaging is to produce images of clinically important anatomical structures and pathological processes for the diagnostic task at hand using the lowest possible radiation and CM dose.

### **Parameters of image quality**

Image quality in CT reflects how well the acquired images represents the real anatomy and depends on four basic factors:

- Low contrast resolution – the ability to differentiate between objects with small attenuation difference primarily influenced by image noise.
- Spatial resolution (high contrast resolution) – the ability to resolve two objects close together as separate objects. Usually determined using high-contrast objects. This ability is mainly dependent on detector size, focal spot size, reconstruction matrix, field-of-view (FOV) and slice thickness.

- Noise – the random fluctuation of CT numbers in individual image elements within a homogenous structure. The noise is inversely proportional to the number of photons that contribute to each detector measurement.
- Artifacts – structures seen on images that are not representative of the actual anatomy. Artifacts can be related to the technical issues (beam hardening, photon starvation and partial volume) or patient related (metal and motion artifacts)

Depending on the diagnostic task these factors interact to determine the quality of the examination.

## **Objective evaluation**

There are several ways to evaluate image quality. The following objective measurable parameters were used in this thesis to evaluate image quality in patients and/or phantom:

- Mean attenuation (HU) in a homogenous region of interest (ROI) to evaluate density or contrast medium enhancement.
- Image noise (HU) is expressed as one standard deviation (SD) of the mean attenuation in the ROI, assuming normal distribution. Noise power spectrum (NPS) show the distribution of noise over the spatial frequencies.
- Signal-to-noise ratio (SNR) represents the attenuation to image noise
- Contrast-to-noise ratio (CNR) represents the difference in attenuation between two structures divided by image noise. May be used to assess low-contrast resolution.
- Spatial resolution can be measured by scanning an image quality phantom including a wire or bar pattern and calculating the modulation transfer function (MTF). The MTF describes the spatial frequency response, i.e. the relative contrast at a given spatial frequency reproduced by the imaging system<sup>44</sup>. Spatial resolution is often presented as frequency for a given percent of the MTF, usually 10%, often called the limiting spatial resolution i.e. the frequency where the contrast has dropped to 10 % of the maximum value.

## **Subjective evaluation**

The subjective image quality may either be assessed using diagnostic acceptability based on image quality characteristics or diagnostic performance.

Diagnostic acceptability reflects image quality and may be assessed by visual grading analysis (VGA) of different image criteria such as reproduction of anatomical structures, noise and the presence of artifacts. The grading may either be

used in an absolute manner where the observer uses a predefined scale, usually of four to five steps, or in a relative manner where the observer compares images in a side-by-side manner. The assessment of diagnostic acceptability is not a direct measure of diagnostic performance as it does not depend on pathological finding but rather rests on the assumption that reproduction of anatomical structures correlates with the ability to find pathology. The advantage of using diagnostic acceptability is that it makes study design easier. Diagnostic performance studies can be difficult to perform as they require a good balance between known cases with and without pathology determined by a reference standard.

The grading may either be used on the overall image quality (Paper I and II) or dichotomized into several different specific criteria (Paper IV and V). The grading scale chosen should be adapted to the purpose of the study and reflect clinically relevant differences.

#### *Visual grading characteristics (VGC) analysis*

Grading of image quality is done on an ordinal scale as the differences between grading steps may not be proportional. This means that, from a statistical point of view, statistical methods that require interval scales and normal distribution of data cannot be used. Instead a non-parametric rank invariant statistical method such as VGC<sup>12</sup> may be used to compare image quality between two groups. In the VGC analysis image quality ratings between two groups, reference and test, are compared by producing a VGC curve. VGC analysis uses methodology developed in ROC analysis and the VGC curve is obtained by plotting the cumulative distributions of rating data for the two groups compared against each other. Observers are not compared to each other and may therefore use different definitions to the grading scales without affecting the result. The figure of merit in the VGC analysis is the area under the curve ( $AUC_{VGC}$ ) with a confidence interval of 95%. This is a measure of separation between the two rating distributions for the two groups and receives a value between 0 and 1,  $AUC_{VGC} = 0.5$  indicates that the two groups have received similar ratings on average. If  $AUC_{VGC} > 0.5$  indicates that the test group has received higher ratings and  $AUC_{VGC} < 0.5$  indicates that the reference group has received higher ratings. If the value 0.5 is not included in the confidence interval a statistically significant difference is established.

The VGC analysis only provides information about the relative image quality in one group compared to that of another group, not about the image quality *per se*.

# Aims

The main objective of this thesis was to evaluate the feasibility to use low kV technique CT in patients considered at risk of CI-AKI to minimize the amount of potentially nephrotoxic contrast medium needed to produce diagnostic images.

## *Paper I*

- To assess the diagnostic quality and potential risk of CI-AKI when using 80-kV CTA of the pulmonary arteries with reduced CM dose adapted to body weight and scan time in patients with moderately to severely decreased renal function.

## *Paper II*

- To assess the feasibility to further optimize our CTA protocol of the pulmonary arteries from Paper I when using 80 kV with automatic exposure control and further reduced CM dose by decreasing injection time.

## *Paper III*

- To evaluate the potential impact of iterative reconstructions (Siemens SAFIRE) on image quality, image noise and low-contrast object detection at different X-ray tube potentials and radiation doses in an abdominal CT phantom model.

## *Paper IV*

- To evaluate image quality in 80-kV CT of the liver with reduced CM dose and tube loading compensation to control image noise in patients with decreased renal function.

## *Paper V*

- To evaluate the impact of iterative reconstruction algorithms (Siemens SAFIRE) to control image noise in 80-kV hepatic CT without tube loading compensation.





# Material and methods

## Study subjects

This thesis includes three cross-sectional patient studies with a total of 179 patients considered at risk of CI-AKI and 188 patients not considered at risk as controls. In both instances risk assessment was based on eGFR. Patient data are summarized in Table 1.

In Paper I 89 consecutive patients with clinical suspicion of acute PE and reduced renal function defined as eGFR <50 ml/min were included and examined with a 80-kV CT pulmonary angiography (CTPA) protocol with a reduced CM dose and tube loading compensation (TLC) to control image noise. As a reference group 148 consecutive patients with clinical suspicion of acute PE and eGFR  $\geq$ 50 ml/min were included and examined with the standard CTPA protocol at 120-kV.

In Paper II another 50 consecutive patients with the same inclusion criteria as the previous study were examined with an optimized 80-kV CTPA protocol with further reduced CM dose, shorter injection time and automatic exposure control. This group was then compared with the 80-kV cohort from Paper I

Paper III was a phantom study.

In Paper IV and V 40 consecutive patients with reduced renal function, defined as eGFR <45 ml/min referred for CT of the abdomen were examined with a 80-kV protocol with reduced CM dose containing two scans in the portal venous phase, one scan of the liver without TLC immediately followed by one scan of the entire abdomen with TLC. The extra scan led to an increased radiation exposure, therefore approval from the ethical and radiation protection committee and informed consent was needed.

In Paper IV 40 consecutive patients with eGFR  $\geq$ 45 ml/min were included as a control group and examined with our standard abdominal 120-kV CT protocol. In Paper V the patients served as their own control when comparing the two 80-kV scans.

**Table 1.**

Overview of study subjects, median values (2.5 and 97.5 percentiles) presented unless otherwise stated.

Examined organ	Paper I		Paper II	Paper IV and V	
	Thorax		Thorax	Abdomen	
Cases / controls	Cases	Controls	Cases	Cases	Controls
Inclusion time	April 2004 – March 2006	April 2004 – March 2006	November 2007 – October 2008	June 2015 – March 2016	June 2015 – July 2015
Number of patients	89	148	50	40	40
Male : female	26 : 63	80 : 68	11 : 39	22 : 18	17 : 23
Age (years)	84 (58–95)	69 (26–86)	84 (67–96)	79 (69–89)	71 (42–85)
Weight (kg)	68 (43–96)	77 (50–111)	65 (43–84)	62 (46–88)	73 (49–95)
Body mass index (kg/m <sup>2</sup> )	NR <sup>a</sup>	NR	24 (18–31)	23 (19–30)	25 (17–29)
Plasma creatinine (μmol/l)	101 (48–165)	77 (47–124)	97 (66–156)	117 (75–168)	77 (48–117)
eGFR (ml/min)	38 (22–82)	83 (43–161)	36 (21–45)	39 (31–45)	70 (50–102)
Number of scans	1	1	1	2	1
Radiation protection approval	No	No	No	Yes	No
Research ethical approval	No	No	No	Yes	Yes
Informed consent <sup>b</sup>	No	No	No	Yes	Yes

<sup>a</sup>NR =not reported

<sup>b</sup>All patients received written information that examination data including national identification number was collected in a registry as a part of the hospital's quality assurance program. The registry was reported to the Data Protection Officer according to the Personal Data Act.

## CT parameters

In three studies (Paper I, II and IV) the 80-kV CT protocols were designed to provide the same image quality and image noise as the clinical routine 120-kV protocols by increasing effective tube loading (mAs). In the first two studies this was done in the thorax on a 16-MDCT system. In Paper IV the abdomen was examined with a modern 128-MDCT system with a more powerful X-ray tube that had the capacity to produce effective tube loadings required for abdominal examinations at 80 kV.

In Paper III the potential of mitigating the need for extensive increase of tube loading when using low-kV protocols by using IR algorithms was investigated on an abdominal phantom and in the last study (Paper V) this was put to the test in a clinical setting.

An overview of the scanning parameters used in the clinical studies are summarized in Table 2.

In the first study (Paper I) the effective tube loading was manually adapted to patient circumference<sup>69,74</sup>. To keep image noise at 80 kV unchanged compared with 120 kV effective tube loading had to be increased by roughly a factor of four<sup>66</sup>. To reach a high enough effective tube a pitch of 0.5 had to be used. The downside to this meant doubling the scan-time from 3-5 seconds to 6-10 seconds. To mitigate the risk of breathing artefacts due to prolonged scan time the scanned area was reduced to include only the pulmonary arteries from above the aortic arch to below the base of the heart. On newer faster CT systems this limitation has been overcome.

At the time of the second study (Paper II) the introduction of automatic exposure control meant that the manual adaptation of radiation dose to patient circumference could be omitted. In the last two studies the technique for automatic exposure control had evolved even further to include modulation in the longitudinal direction of the scan as well.

In the last study (Paper V) the results from the phantom study (Paper III), that showed a potential for managing image noise when using iterative reconstructions, was used in a clinical setting. Image quality based on our standard 80-kV protocol with TLC in patients with risk of CI-AKI was compared with an 80-kV protocol using IR algorithms to control image noise without TLC with the patients acting as their own controls. The extra scan was covering approximately 10 cm of the liver in a caudo-cranial fashion just before the standard 80-kV abdominal scan and done in the same breath hold. This added approximately 4-5 seconds on the total scan-time.

**Table 2.**

Overview of CT scanning parameters in the clinical studies

	Paper I		Paper II	Paper IV and V		
Examined organ	Thorax			Abdomen		
CT system	Siemens Somatom Sensation 16			Siemens Somatom Definition Flash		
Tube voltage (kV)	80	120	80	80	80	120
Mean photon energy (keV)	53.3	66.7	53.3	54		69
Maximum tube current (mA)	380	500	380	650		800
Reference effective tube loading (mAs)	380	100	350	170	680	170
Detector configuration	16 x 1.5	16 x 1.5	16 x 1.5	128 x 0.6 <sup>b</sup>		128 x 0.6 <sup>b</sup>
Pitch	0.5	1	0.5	1	0.5	1
Rotation time (sec)	0.5	0.5	0.5	0.5		0.5
Exposure control	Manual <sup>a</sup>		CareDose	CareDose 4D		
Scan direction	Cranio - caudal	Cranio - caudal	Cranio - caudal	Caudio - cranial	Cranio - caudal	Cranio - caudal
Scanned area	Aortic arch – base of the heart	Aortic arch – base of the heart	Aortic arch – base of the heart	Approx. 10 cm of the liver	Diaphragm – iscial tuberosity	Diaphragm – iscial tuberosity
Approximate scan time (sec)	6-10	3-5	6-10	4-5	9-13	5-7
Matrix	512 x 512		512 x 512	512 x 512		
Convolution kernel	B40f	B40f	B40f	I30f	B30f	B30f
Reconstruction algorithms	FBP	FBP	FBP	SAFIRE 3,5	FBP	FBP
Slice thickness/increment (mm)	3/2	3/2	3/2	5/3	5/3	5/3

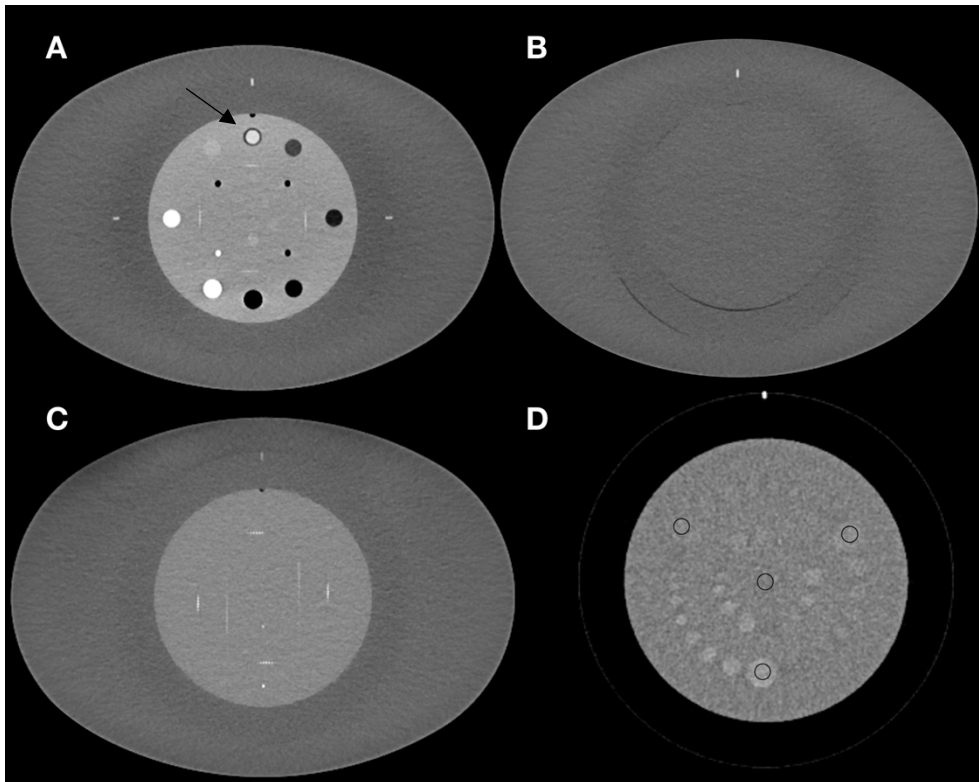
<sup>a</sup> Individual tube loading was based on a standard reference patient with 88 cm circumference and then adapted to each patient by measuring the thoracic circumference and using a “half-value thickness” of 9 cm i.e. the change in diameter that doubled or halved the tube loading.

<sup>b</sup> z-axis “flying focal spot” technique is used to obtain twice as many projections per rotation as detector rows

## Phantom study

In Paper III the impact of IR algorithms (Siemens SAFIRE) on iodine attenuation, quantum noise, noise characteristics, spatial resolution and low-contrast object detection at different tube potentials was performed on an image quality phantom Catphan 600 (The Phantom Laboratory Greenwich, NY, USA). This phantom consists of different modules for assessment of image quality shown in Figure 3. To

simulate a “normal-sized” patient of about 80 kg an oval annulus (25 x 35 cm; 95 cm circumference) was applied around the phantom.



**Figure 4. Image quality phantom Catphan 600®**

Various assessed modules. Module A: Rounded objects of different materials with various CT numbers including a chamber with iodine contrast medium (7 mg I/ml) (arrow). Module B: Homogenous section without objects for measuring and characterizing image noise. Module C: High density wires to evaluate spatial resolution. Module D: Three sets of low-contrast objects with descending size at different attenuation. Black circles for measuring attenuation. Published with permission from Acta Radiologica.

The scanning parameters were based on our clinical standard abdominal CT protocol at 120 kV with a reference effective tube loading of 170 mAs. Acquisitions were then made at different tube potentials (70 – 120 kV) at a fixed effective tube loading (170 mAs) and at a fixed absorbed radiation dose ( $CTDI_{vol} = 10$  mGy). The radiation dose was measured for each tube potential in a 32 cm CTDI-phantom using a CT Dose Profiler (RTI, Mölndal, Sweden). Acquisition parameters are summarized in Table 3.

**Table 3.**

Acquisition parameters from the Catphan 600® phantom study (Paper III).

CT system	Siemens Somatom Definition Flash						
Detector configuration	128 x 0.6						
Reconstruction algorithms	FBP and SAFIRE 1 – 5						
Kernel (FBP/SAFIRE)	B30f/I30f						
Slice thickness/increment (mm)	5/5						
<b>Tube potential (kV)</b>	<b>70</b>		<b>80</b>		<b>100</b>		<b>120</b>
Mean photon energy	49		54		62		69
Maximum tube current (mA)	500		650		650		800
<b>Effective tube loading (mAs)</b>	<b>170</b>	<b>932</b>	<b>170</b>	<b>568</b>	<b>170</b>	<b>279</b>	<b>170</b>
Pitch	0.6	0.5	0.6	0.5	0.6	0.6	0.6
Rotation time (s)	0.5	1.0	0.5	0.5	0.5	0.5	0.5
<b>CTDI<sub>vol</sub> (mGy)</b>	<b>1.9</b>	<b>10</b>	<b>3.1</b>	<b>10</b>	<b>6.1</b>	<b>10</b>	<b>10</b>

## Contrast medium dose

In all the clinical studies the CM dose was adapted to body weight up to 80 kg with the rationale that weight exceeding 80 kg to an increasing extent is made up of adipose tissue that contributes only minimal to the extracellular volume, the principal distribution volume of iodine CM. A summary of the injection parameters used are summarized in Table 4.

**Table 4.**

Overview of contrast medium injection protocols used in the clinical studies.

	Paper I		Paper II	Paper IV and V	
Examined organ	Thorax			Abdomen	
CT system	Siemens Somatom Sensation 16			Siemens Somatom Definition Flash	
Contrast medium dose (mg I/kg)	200	320	150	300	500
Injection duration (s)	15		12	30	
CM dose rate (mg I/kg/s)	13.3	21.3	12.5	12	20
Salin chaser (50 ml)	Yes	Yes	Yes	Yes	Yes
Automatic bolus tracking (ROI)	Central pulmonary artery	Central pulmonary artery	Central pulmonary artery	Upper abdominal aorta	Upper abdominal aorta
Scan delay <sup>a</sup> (s)	5	5	4	50	50

<sup>a</sup> Delay from the time when CM enhancement reach the set threshold value during automatic bolus tracking.

Automatic bolus tracking with a region of interest (ROI) in the central pulmonary artery (Paper I and II), or in the upper abdominal aorta (Paper IV and V) was used. A saline “chaser” injection immediately followed the CM injection with the same injection rate to push the remaining CM from the arm veins into the central circulation. By dosing per kg body weight, adapting injection duration to scan time, using bolus tracking and a saline chaser we could reduce the CM dose at CTPA from the, at the time (Paper I), commonly used 28-55 grams of iodine<sup>42</sup> to approximately 25 grams in our standard 120-kV protocol which was set to 320 mg I/kg. In our 80-kV protocol the amount of CM was reduced by 40% to 200 mg I/kg since iodine attenuation increases by approximately a factor 1.6 when decreasing tube voltage from 120 to 80 kV<sup>15,38</sup>. Both protocols used a fixed injection time of 15 seconds and a variable injection rate.

In the following study (Paper II) based on the results from the first study the CM dose was further reduced to 150 mg I/kg by shortening the injection time but keeping the CM dose rate virtually unchanged.

In paper IV and V, the CM injection parameters used were based on the routine clinical protocol for the abdomen at 120 kV (500mg I/kg) and then adapted to the 80-kV protocol with reduction of CM dose by 40% (300mg I/kg), while keeping the injection duration, automatic bolus tracking and scan delay unaltered.

## Contrast medium-induced acute kidney injury

In the first two studies (Paper I and II) a retrospective follow-up over three months was conducted reviewing the patient medical charts, laboratory systems, death certificates and the regional radiological request system for signs of kidney injury and venous thromboembolic events. Comorbid conditions associated with the development of CI-AKI were also collected in Paper I. CI-AKI was defined as rise in plasma creatinine  $>44.2 \mu\text{mol/l}$  from baseline within one week after CTPA.

## Radiation dose

The mean effective tube loading (mAs), CTDIvol and DLP as presented by the CT system was registered. The effective radiation dose (ED) was calculated from DLP by multiplication with the region-specific ED/DLP conversion factor (Table 5)<sup>20,37,91</sup>. In Paper V the DLP was not applicable since the extra scan was not a complete abdominal scan. As the patients in this study served as their own controls



instead the  $CTDI_{vol}$  for each scan level used for attenuation measurements in the liver was registered and presented for comparison.

**Table 5.**  
ED/DLP conversion factors that were used.

	80 kV	120 kV
Thorax	0.015	0.017
Abdomen	0.0151	0.0153
Pelvis	0.0128	0.0129

## Image reconstruction

Filtered back-projection (FBP) reconstruction was used as a baseline for all studies included in this thesis. In the phantom study (Paper III) the effect of using IR algorithms from Siemens Healthineers (Forchheim, Germany), Sinogram affirmed iterative reconstruction (SAFIRE) at different strengths (1-5), and at different tube potentials to control image noise was investigated and compared to FBP. In Paper V the results from the phantom testing were investigated in a clinical setting with the utilization of IR algorithms SAFIRE strength 3 and 5.

In all other aspects of image preparation, choosing slice thickness, increment and kernels the clinical routine used at the time for CTPA (Paper I and II) or abdominal CT (Paper III, IV and V) was applied.

**Table 6.**  
Overview of image reconstruction data

	Paper I	Paper II	Paper III	Paper IV	Paper V
Examination type	CTPA	CTPA	CT Abdomen	CT Abdomen	CT Abdomen
CT system	Siemens Somatom Sensation 16		Siemens Somatom Definition Flash		
FBP	Yes	Yes	Yes	Yes	Yes
IR algorithm	No	No	SAFIRE	No	SAFIRE
IR levels	–	–	1, 2, 3, 4, 5	–	3, 5
Convolution kernel	B40f	B40f	B30f, I30f	B30f	I30f
Slice thickness (mm)	3	3	5	5	5
Increment (mm)	2	2	5	3	3

# Image quality

Objective image quality was measured in a similar way in all the clinical studies by measuring attenuation, CM enhancement, image noise and calculating SNR and CNR. Subjective image quality was graded using a variety of methods (Table 7).

All objective and subjective evaluations were done on axial images using a radiological PACS (Picture Archiving and Communication System) workstation (Sectra AB, Linköping, Sweden) with a medical grade high luminance display monitor.

**Table 7.**  
Overview of methods and measures used for image quality assessment.

	Paper I	Paper II	Paper III	Paper IV	Paper V
<b>Objective methods</b>					
CT numbers (HU)	•	•	•	•	•
Noise (SD)	•	•	•	•	•
Signal-to-noise ratio (SNR)	•			•	•
Contrast-to-noise ratio (CNR)	•	•	•	•	•
Noise-power spectrum (NPS)			•		
Spatial resolution (MTF)			•		
<b>Subjective methods</b>					
Number of observers	2	2	4	4	4
Overall image quality	•	•		•	•
Low-contrast resolution			•		
Inter-observer agreement		•			
Intra-observer agreement				•	•

## Objective evaluation

In the clinical CTPA studies (Paper I and II) vascular density and image noise (1 standard deviation, SD) was measured in Hounsfield units (HU) using a ROI in the left pulmonary artery and in a lower lobe segmental artery. SNR was calculated as the vascular density divided by image noise. Because this was a clinical study where the aim of the examination was to depict the presence or absence of pulmonary embolism, CNR was calculated as the vascular density minus the density of a fresh emboli, set to 70 HU, divided by image noise.

In the clinical hepatic CT studies (Paper IV and V) CM enhancement of the liver and image noise was measured in a standardized fashion placing a ROI in nine different locations for an averaged mean hepatic attenuation and image noise. SNR was calculated as the hepatic attenuation divided by image noise. CNR was

calculated as the hepatic attenuation minus the attenuation of the rectus abdominis muscle divided by hepatic image noise.

In the phantom study (Paper III) the image quality statistical data and the spatial resolution (MTF) was obtained using an automated program (AutoQA Lite v.3.1.01; Iris QA, LLC, Frederick, MD, USA) to assess the relevant modules in the phantom. The iodine attenuation and image noise were obtained by using a region of interest (ROI) in module A and B respectively, (Figure 4). The distribution of the noise over the frequency spectra (NPS) was calculated from a ROI of 84.7 cm<sup>2</sup> in the center of the phantom in module B (Figure 4) using an imaging process program ImageJ (v1.48; National Institute of Health Bethesda, MD, USA) with the plug-in Radial Profile Plot (by Paul Baggethun, v14, May 2009; Pittsburgh, PA, USA). The low-contrast resolution was assessed in module D (Figure 4) which contained three sets of cylinders of diminishing size from 15 to 2 mm with nominal contrast of 1.0 %, 0.5% and 0.3%, which corresponds to approximately 10, 5 and 3 HU respective difference in attenuation compared to the background. The attenuation was measured with a ROI placed in the largest of the cylinders for each set. CNR was calculated as the cylinder attenuation minus the background attenuation divided by the image noise.

## **Subjective evaluation**

In Paper I subjective overall image quality was evaluated by two of the authors and reached by consensus. In Paper II image quality was evaluated by two independent readers. In both studies image quality was assessed at a fixed window level of 100 HU and a width of 400 HU. A grading scale of four steps was used.

- Excellent – Good opacification of PA without visible noise or artifacts
- Adequate – Good opacification of PA with visible noise and/or artifacts but with clear depiction of all pulmonary arteries including the subsegmental
- Suboptimal – When subsegmental PA could not be adequately evaluated
- Non-diagnostic –When segmental PA could not be evaluated.

In the phantom study (Paper III) the subjective evaluation of low-contrast resolution was done in consensus between four observers deciding on the smallest discernible cylinder in each of the three cylinder sets on randomly presented images using the viewing and scoring software Viewer for Digital Evaluation of X-Ray images (ViewDEX v 2.0, The Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden).

In the last two studies (Paper IV and V) a subjective visual grading characteristics (VGC) assessment was made by four radiologists blinded to acquisition parameters. All image stacks were graded individually in a randomized order using eight quality

criteria statements based on the European guidelines on quality criteria<sup>14</sup> and graded on a 5-point ordinal scale to what degree they agreed with the statement (Table 8).

**Table 8.**

Subjective evaluation criteria selected based on European guidelines and a 5-point grading scale

Evaluation criteria (A-H)	Grading scale (1–5)
<b>Visual sharp reproduction of:</b>	1. Confident that the criterion is not fulfilled
A. Interface between liver parenchyma and intrahepatic veins	2. Somewhat confident that the criterion is not fulfilled
B. Adrenal glands from adjacent structures	3. Indecisive whether the criterion is fulfilled or not
C. Non-calcified part of the aortic wall	4. Somewhat confident that the criterion is fulfilled
D. Extrahepatic bile ducts	5. Confident that the criterion is fulfilled.
E. Pancreatic contours	
<b>To what degree do you concur with following statements:</b>	
F. There is overall low or minimal noise	
G. There are no significant artifacts	
H. There is overall high image quality	

Scoring was done using the ViewDEX software and analyzed using the VGC Analyser, version 1.0.2 software (The Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden). Intra observer agreement data was obtained by six randomized stacks that were analyzed twice.

## Statistical evaluation

In Paper I parametric statistical methods were used to compare the mean pulmonary artery attenuation, quantum noise and CNR between the two patient groups. Our null hypothesis was tested using a t-test and, because the cohorts were not paired a regression model with adjustments for differences in gender, age, body weight, cardiac disease and chronic obstructive pulmonary disease were applied. A p-value of <0.05 was considered statistically significant.

In Paper II a non-parametric Mann-Whitney U test was used to analyze differences in subjective grading of the image quality between the two patient groups. The degree of inter-observer agreement was assessed using Cohen's kappa statistics.

In Paper IV and V normal distribution of data and homogeneity in variances was tested with Shapiro-Wilk test and the F-test. Comparison between the groups regarding objective measurements was done using an independent samples t-test in Paper IV and with a paired sample t-test in Paper V. The degree of intra-observer agreement was assessed using Cohen's kappa statistics. After Bonferroni correction for multiple comparisons the level of statistical significance was set to 0.004 in Paper IV and 0.002 in Paper V. Subjective image quality was compared between

the included cohorts using Visual grading characteristics (VGC) analysis software, a non-parametric rank-invariant statistical method for comparing visual grading.

## Ethical considerations

Paper I and II were cross-sectional retrospective register studies and a part of the hospital's (Lasarettet Trelleborg) quality assurance program and by that time no informed consent or approval from the local ethical committee was needed. However, all patients were informed according to the local Personal Data Act, that examination data regarding name, national identification number, diagnostic quality, CM and radiation doses, laboratory data and diagnoses were to be saved for 5 years and then be anonymized, and each patient has the right to apply for information regarding these data.

Paper III was a phantom study.

Paper IV and V were approved by the ethical and radiation protection committee of Lund (Dnr 2015/63) and as the examination involved an additional CT scan with subsequent increased radiation informed consent was required.

# Results

## Paper I

This study evaluated the feasibility to reduce the amount of contrast medium by 40% when performing CTPA with reduced tube potential from 120 kV to 80 kV and TLC to control image noise.

Because the patients were recruited consecutively based on their estimated renal function the patients in the 80-kV cohort were generally older, to a larger extent female and weighed less than in the 120-kV cohort. The prevalence of diabetes in the 80-kV cohort was also twice that of the 120-kV cohort.

Results are summarized in Table 9. The pulmonary artery (PA) attenuation was not significantly different between the two protocols. Though the 80-kV protocol resulted in slightly higher image noise, CNR was not significantly different between the two groups in the unadjusted analyses. However, when adjusted for age, gender, body weight, cardiac disease and chronic obstructive pulmonary disease (COPD), CNR was significantly lower in the 80-kV cohort. Both protocols showed a significant association between decreasing CNR and increasing body weight because of increasing image noise with increasing body weight.

In the subjective evaluation both protocols performed equally with about 5% of the examinations being regarded as suboptimal in each group.

The prevalence of pulmonary embolism in the 80-kV cohort was twice that of the 120-kV cohort (22% vs 11%). During the 3-month follow-up there was one patient in the 80-kV cohort and two patients in the 120-kV cohort with initially negative studies that were diagnosed with thromboembolic disease. Re-evaluation of the CTPA studies for these patients did not show any evidence of pulmonary embolism. No evidence of CI-AKI was found in either cohort.

## Paper II

The aim of this study was to see if an optimized 80-kV CTPA protocol with further reduction of CM dose by shortened injection time better adapted to the scan time would perform at the same level as the 80-kV cohort from Paper I.

There was no significant difference in basic patient characteristics in the new patient cohort regarding age, gender, body weight and kidney function compared to the 80-kV cohort from Paper I. Despite a lower CM dose there was no significant difference in PA attenuation, image noise or CNR between the two 80-kV protocols (Table 9).

**Table 9.**

Summary of results from Paper I and II, median values (2.5 and 97.5 percentiles) presented unless otherwise stated

	Paper I 120kV	Paper I 80 kV	Paper II 80 kV	
<b>Contrast medium dose</b>				
Gram iodine	25 (16–26)	13 (8.2–16)	9.6 (6.4–12)	
mg iodine/kg	320 (231–320)	200 (160–207)	150 (129–160)	
Dose rate (mg l/kg/sec)	21 (15–21)	13 (11–14)	13 (11–13)	
<b>Radiation dose</b>				
CTDI <sub>vol</sub> (mGy)	7.7 (5.1–14)	5.6 (2.6–8.3)	5.6 (4.5–8.2)	
DLP (mGy×cm)	251 (144–433)	166 (74–247)	159 (125–215)	
Effective dose (mSv)	4.3 (2.4–7.4)	2.8 (1.3–4.2)	2.4 (1.9–3.2)	
<b>Objective evaluation of image quality</b>				
PA attenuation (HU)	344 (184–531)	351 (199–563)	353 (164–495)	
Image noise, 1 SD (HU)	22 (13–31)	23 (13–39)	26 (16–51)	
Contrast-to-noise ratio	13 (5.9–24)	12 (6.4–26)	11 (4.4–22)	
<b>Subjective evaluation of image quality</b>				
			Observer	
			1	2
Excellent (%)	62	43	44	34
Adequate (%)	33	52	48	54
Suboptimal (%)	5	5	8	12
Non-diagnostic (%)	0	0	0	0
Interobserver agreement (kappa)			0.76	
<b>Pulmonary embolism</b>	17 patients (11%)	20 patients (22%)	7 patients (14%)	
<b>Follow-up 3-months after negative CTPA</b>				
Number of patients (excluded <sup>a</sup> )	119 (12)	65 (4)	40 (2)	
VTE after negative CTPA	1 patient (1.4%)	2 patients (1.7%)	0 <sup>b</sup>	
CI-AKI	0	0	0	
Deaths <sup>c</sup>	15 patients (13%)	16 patients (26%)	8 patients (20%)	

<sup>a</sup> Patients excluded were on long-term anticoagulation for reasons other than VTE

<sup>b</sup> One patient was retrospectively found to have a small PE in a sub-segmental branch. 3-month follow-up without anticoagulation was however uneventful

<sup>c</sup> None of the deaths were attributed to VTE

There was no significant difference in basic patient characteristics in the new patient cohort regarding age, gender, body weight and kidney function compared to the 80-kV cohort from Paper I. Despite a lower CM dose there was no significant difference in PA attenuation, image noise or CNR between the two 80-kV protocols (Table 9). As in the previous study image noise tended to increase with increasing body weight. As PA attenuation also tended to increase, CNR showed only a weak tendency to decrease.

There was no significant difference in subjective image quality between the two groups and there was good inter-observer agreement.

The prevalence of PE was 14%. During subjective image quality analysis one false negative diagnosis was found in a subsegmental pulmonary artery, three-month follow-up without anticoagulation was however uneventful. None of the remaining patients with negative CTPA was diagnosed with venous thromboembolism (VTE) during the three-month follow-up. There was no evidence of CI-AKI found during follow-up.

PA attenuation, image noise and CNR in the 80-kV cohort in Paper II using 150 mg I/kg were also comparable to that of a 120-kV cohort using 300 mg I/kg examined on the same CT equipment in 2007, with the same injection time (12 sec) and delay following bolus tracking (4 sec) as in Paper II; median values for PA attenuation 332 HU, image noise 22 HU and CNR 12<sup>13</sup>. This implies that the CM dose at 80 kV may be halved compared with that of a standard 120-kV protocol.

## Paper III

This phantom study evaluated the impact of iterative reconstructions (Siemens SAFIRE) on iodine attenuation, quantum noise, noise characteristics, spatial resolution and low-contrast object detection at different tube potentials, both with a fixed radiation dose of 10 mGy (CTDI<sub>vol</sub>) and with a fixed tube loading of 170 mAs.

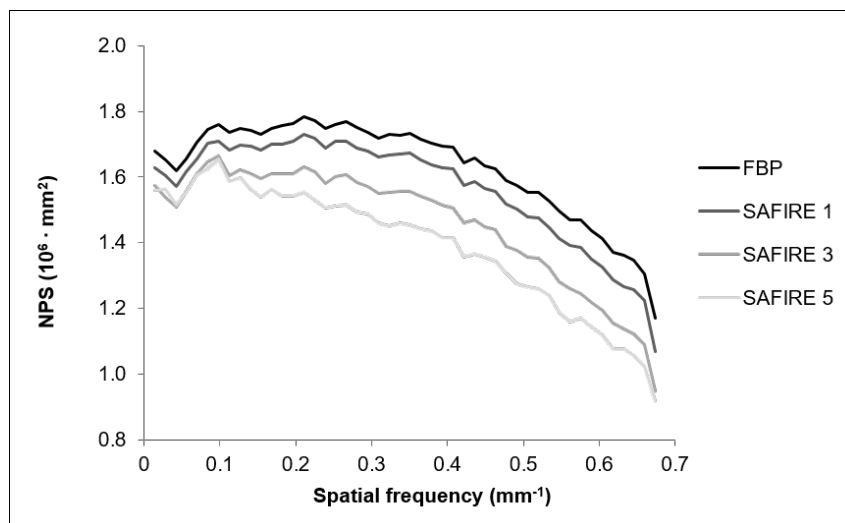
The iodine attenuation increased with a factor 1.6 and image noise by a factor 1.9 when decreasing the tube potential from 120 to 80 kV. Iterative reconstructions did not influence the attenuation of iodine

Image noise decreased in a linear fashion with increasing iterative strength. At SAFIRE 5 the image noise decreased with about 50% compared with FBP at all tube potentials.

There was a tendency for increased high-contrast spatial resolution with increasing SAFIRE strength. The noise power spectra (NPS) had a similar profile for all tube potentials. The curve form (Figure 5) represents the distribution of noise over the



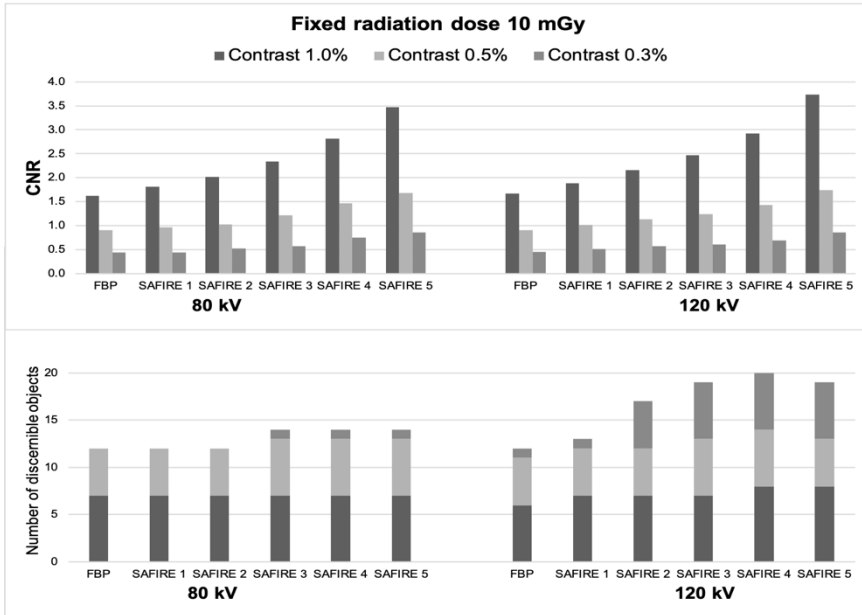
spatial frequencies and the area under the curve corresponds to the amount of noise. With increasing SAFIRE strength the noise was lower, but the impact was more profound in the higher spatial frequencies leading to a relative shift in noise distribution towards the lower spatial frequencies (Figure 5).



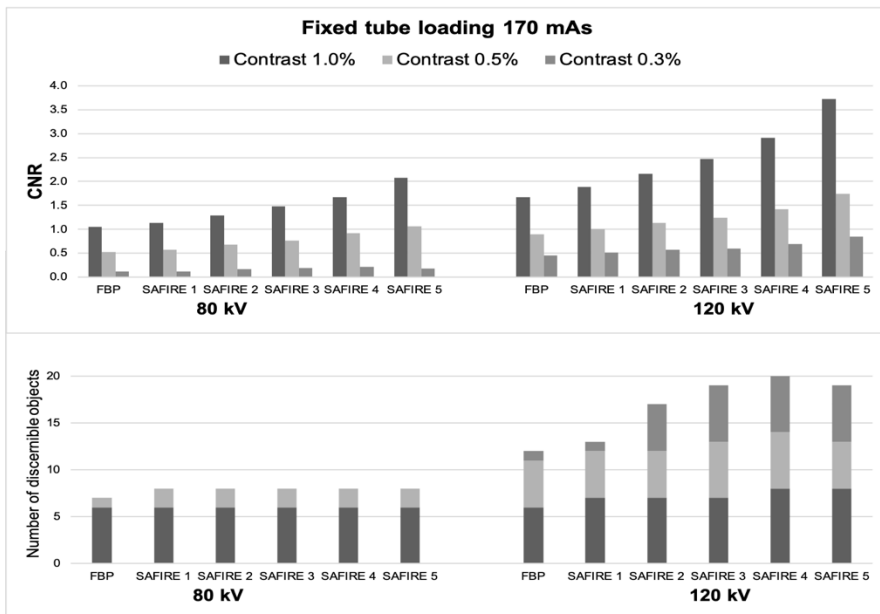
**Figure 5. Noise power spectra at 120 kV**  
**D.** Noise power spectra at 120 kV for FBP, SAFIRE 1, 3 and 5, the profile was the same for all other tube potentials. Published with permission from Acta Radiologica.

The evaluation of low-contrast resolution at 80 and 120 kV is presented in Figure 6 and 7. At a fixed radiation dose CNR and the number of discernible objects with a nominal contrast 1.0% (about 10 HU) was similar at 80 and 120 kV (Figure 6a).

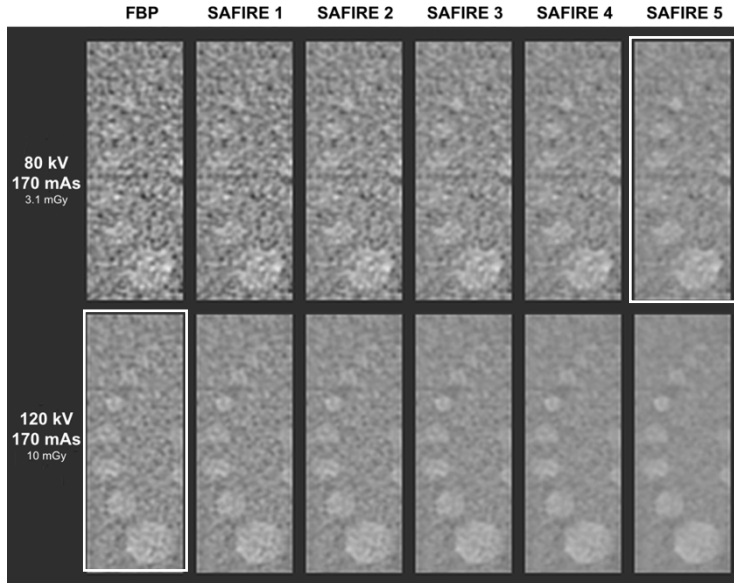
At a fixed tube loading (170 mAs) the noise increased when the tube potential was decreased from 120 to 80 kV resulting decreased CNR (Figure 6b). CNR increased with increasing SAFIRE strength at both potentials. In the initial subjective evaluation where each image was viewed separately the number of discernible objects did not seem to improve with increasing SAFIRE strength at 80 kV as opposed to 120 kV. A side-by-side comparison (Figure 7) did however indicate an increasing discernability of low-contrast objects with increasing SAFIRE strength at 80 kV. Moreover, the discernibility of objects with a nominal contrast 1.0% at 80-kV with SAFIRE 5 was similar to 120-kV with FBP even though more objects with less contrast was seen at 120-kV. This was the motive for the study in Paper V.



**Figure 6a. Evaluation of low-contrast resolution at a fixed radiation dose (10 mGy) at 80 and 120 kV**  
 Low-contrast resolution evaluated both objectively by measuring CNR compared to the background attenuation and subjectively by the number of discernable objects at a fixed radiation dose (CTDI<sub>vol</sub> = 10 mGy). Extract from published data, published with permission from Acta Radiologica.



**Figure 6b. Evaluation of low-contrast resolution at a fixed tube loading (170 mAs) at 80 and 120 kV**  
 Low-contrast resolution evaluated both objectively by measuring CNR compared to the background attenuation and subjectively by the number of discernable objects at a fixed tube loading (170 mAs). Extract from published data, published with permission from Acta Radiologica.



**Figure 7. Side-by-side comparison of low-contrast objects**

Side-by-side comparison of discernability of low-contrast objects (1.0%) for FBP and IR SAFIRE strength 1-5 at 80 and 120 kV tube potential with a fixed tube loading (170 mAs). The discernability of objects at 120 kV/FBP is similar to that of 80 kV/SAFIRE 5 at a fixed tube loading (white rectangles). Extract from published data, published with permission from Acta Radiologica..

## Paper IV

This study assessed the image quality of hepatic CT at 80-kV with TLC and 40% reduction of CM dose compared with a standard hepatic CT 120-kV protocol in a clinical patient cohort. Results are presented in Table 10.

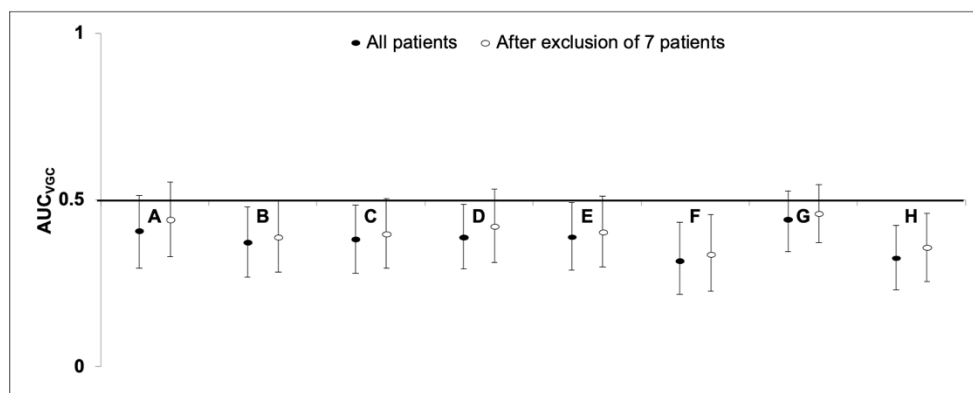
There was no significant difference between the two groups regarding the objective image quality parameters. In the evaluation of the subjective image quality the 80-kV cohort scored significantly lower than the 120-kV cohort with substantial intra-observer agreement though there was some diversity in the subjective grading between the four observers. Retrospective image quality analysis did however reveal that six patients in the 80-cohort had inferior image quality not related to the 80-kV technique such as poor cardiac function or low body weight with a lack of fat planes. In the 120-kV cohort only one such patient could be identified. After excluding these seven patients only three of the eight evaluation criteria were statistically scored inferior for the 80-kV cohort (Figure 8).

**Table 10.**

Summary of outcome parameters from patients included in Study IV, median values (2.5 and 97.5 percentiles) presented unless otherwise stated.

	80 kV	120 kV
Number of patients	40	40
<b>Contrast medium dose</b>		
Gram iodine	18 (13–24)	37 (24–40)
mg iodine/kg	298 (229–302)	500 (420–502)
<b>Radiation dose</b>		
CTDI <sub>vol</sub> (mGy)	9.1 (6.1–11)	8.8 (5.8–12)
DLP (mGy×cm)	377 (231–545)	417 (274–627)
Effective dose (mSv)	5.3 (3.2–7.6)	5.9 (3.9–8.8)
<b>Objective evaluation of image quality</b>		
Liver attenuation pre-contrast (HU)	60 (48–66)	58 (26–67)
Liver attenuation post-contrast (HU)	114 (90–142)	110 (76–131)
Muscle attenuation (HU)	56 (45–66)	58 (39–67)
Image noise, 1 SD (HU)	14 (12–21)	14 (11–18)
Contrast-to-noise ratio	3.8 (2.3–5.8)	3.5 (1.5–5.7)
<b>Subjective evaluation of image quality</b>		
Suboptimal examination <sup>a</sup> (n)	6	1
Overall image quality rated < 3 (%)	5	0
Intra-observer agreement (kappa)	0.64	

<sup>a</sup> Three patients in the 80-kV cohort had suboptimal contrast enhancement due to poor cardiac function. Two patients in the 80-kV group and one in the 120-kV group were considered suboptimal due to lack of fat planes. One examination was regarded as suboptimal due to beam hardening artifacts from the spine



**Figure 8 Subjective comparison of image quality at 80-kV with TLC to 120-kV reference standard**

The staples represent how the images were scored for each criterion (Table 8) and for all observers with confidence intervals of 95% outlined. The area under the curve of the visual grading characteristics (AUC<sub>VGC</sub>) indicates how the images compare to each other. A number below 0.5 indicates that the 80-kV images tested were of inferior quality to the 120-kV images, a value above 0.5 indicates that the 80-kV images were of superior quality.

## Paper V

In this study the image quality of hepatic CT at 80 kV with TLC was compared with 80 kV and the use of IR algorithms (SAFIRE 3 and 5) but without TLC to control image noise in the same patient.

There was no significant difference in objective image quality between the images with TLC and the images without TLC reconstructed with SAFIRE 5. The images reconstructed with SAFIRE 3 did however show significantly higher image noise and consequently lower CNR and SNR (Table 11).

In the subjective grading both groups without TLC scored significantly lower compared to the images with TLC. A considerable difference between the observers as to whether SAFIRE 5 was superior to SAFIRE 3 was also noted.

Increasing SAFIRE strength was associated with increased pixelated blotchy appearance which may affect detection of small liver lesions (Figure 10).

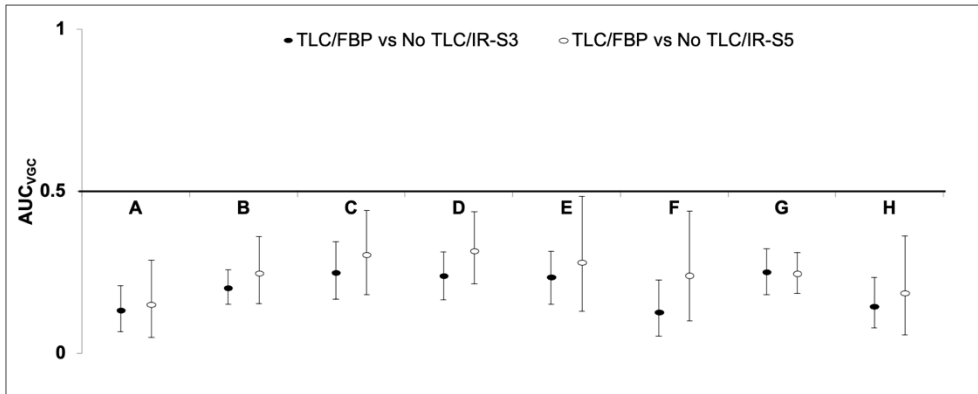
**Table 11.**

Outcome parameters from paper V, median values (2.5 and 97.5 percentiles) presented unless otherwise stated.

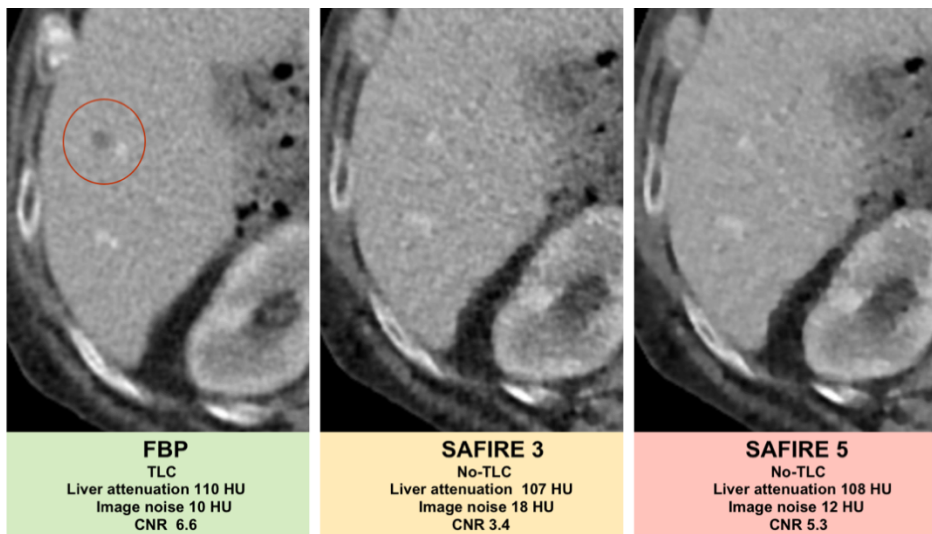
	80 kV FBP	80 kV SAFIRE 3	80 kV SAFIRE 5
Tube loading compensation	Yes	No	
Effective tube loading (mAs)	463 (312–570)	97 (56–190)	
<b>Objective evaluation of image quality</b>			
Liver attenuation pre-contrast <sup>a</sup> (HU)	60 (48–66)		
Muscle attenuation <sup>b</sup> (HU)	56 (45–66)		
Liver attenuation post-contrast (HU)	114 (90–142)	115 (87–143)	115 (87–143)
Image noise (SD)	14 (12–21)	20 (17–26)	14 (12–18)
Signal-to-noise ratio (SNR)	8.0 (5.1–11)	6.0 (3.7–8.1)	8.4 (5.3–10)
Contrast-to-noise ratio (CNR)	3.8 (4.7–11)	2.9 (1.6–4.5)	4.0 (2.2–6.4)
<b>Subjective evaluation of image quality</b>			
Image quality criteria rated <3 (%)	8	39	34
Intra observer agreement (kappa)	0.71		

<sup>a</sup> Pre-contrast scan performed at 120 kV was available for 32 patients.

<sup>b</sup> Mean post contrast attenuation measured in the rectus abdominis muscle



**Figure 9 Subjective comparison of image quality at 80 kV IR SAFIRE 3 and 5 without TLC to 80 kV with TLC**  
 The staples represent how the images were scored for each criterion (Table 8) and for all observers with confidence intervals of 95% outlined. The area under the curve of the visual grading characteristics (AUC<sub>v<sub>gc</sub></sub>) indicates how the images compare to each other. A value below 0.5 indicates that the 80-kV images with IR algorithms are of inferior quality to 80-kV images with TLC, a value above 0.5 indicates that the 80-kV images with IR algorithms are of superior quality.



**Figure 10. Liver lesion disappearing on images without TLC**  
 6 mm lesion with an attenuation of 45 HU not clearly visible on the images without TLC.



# Discussion

Results from the first two studies (Paper I and II) indicate that it is possible to maintain diagnostic clinical performance in CTPA when using 80 kV with TLC and reduced CM dose compared to the reference standard at 120 kV. The X-ray tube of the CT equipment available at that time did not have the capacity to fully compensate for the increased image noise at 80 kV especially in larger patients, resulting in significantly higher image noise compared with that at 120 kV. The follow-up data did however not indicate that the increased image noise was of clinical importance. The relatively high prevalence of PE in the 80-kV groups may be explained by the fact that patients with reduced renal function tended to be elderly patients with more co-morbid factors. It also highlights the importance of having adequate diagnostic capabilities at a minimum risk of CI-AKI for this patient group.

The results from the abdominal phantom study (Paper III) showed that iodine attenuation increased with a factor 1.6 when decreasing tube potential from 80 to 120 kV while at the same time image noise increased by almost a factor two at constant tube loading, i.e. similar effects as in the thorax. Results also indicate that at a fixed tube loading there are improvements in objective image quality parameters such as image noise and CNR when using iterative reconstructions compared to conventional FBP reconstructions and without loss of spatial resolution. The subjective evaluation of low-contrast objects did reveal that in settings of low radiation dose there did not seem to be any increase of discernible objects regardless of improved image noise and CNR. The increasing artificial, blotchy appearance with increasing iteration was noted, which is in accordance with the shift towards relatively lower frequency noise in the NPS curve compared to FBP.

The clinical study performed based on the results from the phantom study was presented in Paper IV and V. Paper IV indicated that modern CT systems have made it possible to perform hepatic CT at 80-kV with reduced CM dose and preserved image quality if the tube loading is adequately compensated. Results from paper V showed that image noise and CNR could be controlled using iterative reconstructions without TLC, but the subjective evaluation indicated inferior image quality compared with FBP and TLC.



## Contrast medium

CM enhancement in CT is dependent on several factors. The most important patient related factor is body size, as it correlates with the extracellular volume, the principle volume of distribution for CM<sup>48,49,75</sup>. In all our study protocols (Paper I, II, IV and V) we adapted the CM dose to patient weight with an upper threshold of 80 kg assuming that increasing weight would mainly consist of fatty tissue in most patients which contributes only minimally to the CM distribution volume. Other parameters for CM dosing have been proposed in the literature, such as lean-body weight<sup>97</sup> and body-surface area<sup>10</sup> which may be beneficial for correct dosing in obese patients. By adapting the CM dose to body weight and scan time our standard CM dose when performing CTPA at 120-kV (Paper I) could be reduced to 320 mg I/kg compared with the doses presented in the literature at the time of non-individualized doses of 28-55 gram iodine<sup>42</sup>, corresponding to approximately 350-700 mg I/kg in a patient with 80 kg bodyweight. When using 80 kV the CM dose could be further reduced to 200 mg I/kg, resulting in a mean iodine dose of 13 gram iodine with maintained arterial enhancement (Paper I).

Another important patient related factor is the hemodynamic situation and cardiac output as it influences the circulation time and the dilution of the CM bolus. Decreasing cardiac output is associated with increased vascular enhancement due to less dispersion of the CM bolus and less dilution from inflowing non-CM containing blood<sup>7</sup>. Cardiac output is however seldom known prior to a CT examination. Though there are non-invasive ways to assess cardiac output<sup>29,55</sup> this has yet to be incorporated into clinical practice when performing CT examinations or designing CT protocols. The variation in enhancement of the pulmonary arteries seen in all the patient groups examined in the first two studies (Paper I and II) may at least in part be explained by differences in cardiac output. Reduced cardiac output should also be expected to be more prevalent among elderly patients with reduced renal function due to the so called cardiorenal syndrome<sup>80</sup>. Since reduced cardiac function is an independent risk factor for developing CI-AKI, reducing CM doses in this patient group becomes even more relevant. In fact, comparison of the 80-kV results in Paper II with those of the 120-kV cohort from the study by Björkdahl et al.<sup>13</sup>, indicate that CM dose may be reduced by a factor 2 instead of the present 1.6 when reducing the tube potential from 120 to 80 kV at CTA, possibly an effect of decreased cardiac output in the 80-kV cohort. This has also been shown in CT of the aorta<sup>50</sup>.

The most important injection related factors in CTA are injection duration and timing of the CM bolus to achieve optimal CM enhancement. In all our clinical studies included in this thesis a fixed injection duration was used adapted to the scan time. By adapting CM dose to body weight and injection time to scan time, a fixed injection dose rate in mg I/kg/sec is achieved resulting in a vascular enhancement

unrelated to body weight <sup>5,56</sup>. Based on our CTPA studies we found that vascular enhancement could be maintained at 80-kV CTPA when shortening injection time from 15 to 12 seconds and reducing the CM dose from 200 mg I/kg to 150 mg I/kg while keeping the CM dose rate virtually unaltered. This corresponds to a mean injection dose rate of 12 mg I/kg/sec. More recent studies, with modern CT equipment and high-pitch low-kV settings, have maintained the same injection dose rate. But with drastically reduced scan times of around one second for a thoracic examination the injection time may be further reduced resulting in a CM dose of only 80mg I/kg <sup>3</sup>.

In Paper IV and V, where we looked at the parenchymal enhancement of the liver injection rate is of less importance compared with vascular CT as the enhancement is principally determined by the total amount of iodine delivered <sup>6,9</sup>. The injection duration is therefore not as critical as in CTA examinations and may be prolonged to avoid unnecessary high injection rates. The use of a fixed injection dose rate was however maintained as it makes scan timing more standardized <sup>6</sup> and may also have an impact on arterial phase scanning of the liver. The selected CM dose in our standard 120-kV protocol was 500mg I/kg which resulted in a 50 HU enhancement of the liver parenchyma in the majority of cases regarded as satisfactory for hepatic scanning<sup>35</sup>. At 80 kV a CM dose of 300 mg I/kg resulted in the same enhancement (Paper IV), and when using 70 kV a further reduction to 250 mgI/kg was reported by Svensson et al. <sup>86</sup>

As stated above the transit time for the CM from the injection site is dependent on the patient's cardiovascular circulation. There are two principal ways of timing the CM bolus in order to get optimal enhancement. Either by using a CM test bolus, and thereby obtaining a time-enhancement curve that can be used to estimate the optimal scan delay. The other way is to use built-in automatic bolus-tracking system with a ROI placed in conjunction with your scan area in the pulmonary trunk (Paper I and II) or the aorta (Paper IV and V). The system registers the temporal variance of the vascular attenuation and a certain threshold level is set to indicate when the CM bolus arrives. A predefined delay is set before scanning is started depending on the vessel or organ to be examined and the indication. In all our studies bolus-tracking was used. As one of the main objectives in all these studies was to reduce the CM dose to patients with reduced renal function a test bolus would counteract that effort. Accordingly, a "saline chaser" was also used to make use of any CM otherwise trapped in the arm veins <sup>21</sup>.

## **Contrast medium dose and CI-AKI**

The main objective of the present studies was to reduce the amount of CM to minimize the risk of CI-AKI in patients regarded to be at risk. Though CM dose,

sometimes reported as ratio between administered CM dose and eGFR, has been regarded as a risk factor at coronary angiography and interventions<sup>34,60,78</sup>, no such correlation has been found in CT studies<sup>64</sup>. Explanations for this may be that a common routine has been to administer the same CM dose to all patients, CM doses are simply not registered<sup>19</sup>, and the lack of studies on CM dose/eGFR ratio. A general opinion also prevails that intraarterial CM injections carry a higher risk of CI-AKI than intravenous injections. However, CM administration during coronary artery angiography and interventions, like CT, implies an indirect, so called, second-pass renal exposure since the CM has to pass the pulmonary circulation before reaching the aorta and renal arteries. At the same time the injected dose rate at CT may be a factor 100 times than that at coronary angiography/interventions<sup>71</sup>. Also multiple recent studies indicate the same rate of PC-AKI for coronary angiography/interventions and CT<sup>16,45,47,58,67,90</sup>. Thus, it does not seem unreasonable to assume that CM dose may also play a role at CT until proven otherwise.

It should also be noted that keeping the gram-iodine/eGFR ratio  $<0.7$  at coronary interventions (assuming a CM concentration of 350 mg I/mL) decreases the risk of PC-AKI to about 4% at eGFR 30-60 and 6% at eGFR  $<30$  mL/min/1.73 m<sup>2</sup>, and a minimal risk of AKI requiring renal replacement therapy<sup>34</sup>. In the CTPA studies (Paper I and II) the resulting median gram-iodine/eGFR ratio was 0.3 and in the hepatic studies (Paper IV and V) 0.5.

Even though some controversy remains on the risk of CI-AKI, the ALARA principle should be adapted on CM administration as well, not giving patients more CM than necessary for the specific diagnostic task, especially since the underlying physiological effects on the kidneys remains unclear.

## **Image quality**

### *Paper I and II*

Objective image quality has traditionally been assessed based on spatial resolution, low-contrast resolution, noise and artifacts. Subjective image quality may either be assessed using diagnostic acceptability based on image quality characteristics or diagnostic performance.

Objective image quality in Paper I and II was similar in all groups regarding pulmonary artery attenuation and CNR. Image noise was slightly higher in the 80-kV cohorts which may be due to limitations in the X-ray tube output of the CT scanner used.

Subjective image quality was evaluated using an absolute visual grading analysis on a four-point scale designed to reflect clinically relevant differences. There was no non-diagnostic examinations and image quality was classified as adequate or

excellent in more than 90% of the examinations in all cohorts which is in line with results in the literature<sup>43</sup>. It can be argued that there is a risk for confirmation bias in both Paper I and II as the evaluation was performed in a non-blinded fashion. In Paper II blinding was not possible since all examinations were made at 80 kV. The diagnostic performance with low frequency of VTE after a negative CT examination during the three-month follow-up was also encouraging.

### *Paper III*

Diagnostic radiology is continuously evolving through optimizations and introduction of new technologies, which necessitates validation before implementation. In Paper III the focus was primarily on evaluation of, at the time, a new IR algorithm (SAFIRE, Siemens Healthineers, Forchheim, Germany) compared to FBP at different tube potentials regarding noise characteristics and objective and subjective image quality parameters. At the time of this study the non-linear behavior using IR was not evident. The objective results clearly stated that the noise level was reduced in a linear fashion with increasing iteration levels regardless of tube potential or radiation dose. The subjective evaluation did not show the same linearity. The number of discernible objects did not increase, regardless of increasing CNR at increasing IR strength, when the radiation dose was significantly reduced, i.e., at lower kV-settings at a constant tube loading. This discrepancy between low-contrast resolution and CNR has later been shown in several studies<sup>30,57,63,82</sup>. However, when the images were evaluated side-by-side the impression was that there was an improved conspicuity of low-contrast objects with higher iteration levels. At a constant radiation absorbed dose ( $CTDI_{vol} = 10$  mGy) discernibility improved with increasing iteration levels regardless of the tube potential used.

There are several limitations in the layout of the phantom used in Paper III. Firstly, the phantom does not model a human liver. Secondly the low-contrast objects were presented in an orderly fashion and not randomly distributed leading to potential recall bias when evaluating subjective discernability. Thirdly the subjective evaluation was done in consensus by four of the authors leading to both potential confirmation bias and lack of data on interobserver variation.

### *Technical consideration in phantom studies*

One effect that we encountered in the phantom studies was that depending on the tube potential used the CT numbers in the different materials in the phantom may change in unexpected ways. In our study this was not significant as the relative difference between object and background was maintained but this is something to wary of in phantom studies when different tube potentials are used.

### *Paper IV and V*

The subjective image quality in Paper IV and V was assessed using a visual grading characteristics (VGC) analysis<sup>12</sup>. An advantage of using VGC analysis to evaluate subjective image criteria is that ratings are not compared between observers, but rather the degree of change in rating for the same observer between the two cohorts. This means that observers may interpret the scale used differently without affecting the result as they are only compared to themselves. VGC analysis only provides information about how the groups compare to each other but does not provide information about absolute level of image quality.

The results in Paper IV showed that despite similar objective image quality with regard to image noise, CM enhancement and CNR, the subjective image quality for the 80-kV scans was scored inferior compared to the 120-kV reference scans. The retrospective analysis revealed that the unpaired design of the study might be responsible for differences between the two groups with regard to intraabdominal fat, cardiac output and other factors that may influence image quality for the chosen criteria. After exclusion of a total of seven patients, six from the 80-kV and one from the 120-kV group, with suboptimal image quality that was regarded as unrelated to the choice of tube potential, only three of the eight quality criteria scored significantly lower for the 80-kV cohort.

Paper V had the advantage of a paired design comparing two 80-kV scans from the same patient, one with TLC and one without TLC but with IR algorithms (SAFIRE 3 and 5) to control image noise. The results were in line with those of the phantom study (Paper III) in that image noise could be controlled with SAFIRE 5 without TLC at 80 kV as compared with FBP and TLC. However, the subjective VGC analysis indicated inferior image quality for scans reconstructed with IR algorithms.

A major limitation in both paper IV and V was that only subjective image quality was evaluated which may be more influenced by the observers' personal preferences, experience and personality and may be difficult to translate into diagnostic performance. This holds especially true when using IR algorithms (Paper V) with the emerging knowledge about contrast dependent spatial resolution. Evaluation of low-contrast detectability might be crucial when comparing IR images with reduced dose to FBP images to ascertain that diagnostic performance does not suffer.

## Image reconstructions

Image reconstruction using FBP follows linear mathematical operations which means that image noise is inversely proportional to the amount of radiation to the detector. Iterative reconstructions may have a nonlinear noise reduction and resolution properties. Therefore traditional objective measures such as noise level and CNR may be misleading and underestimate the radiation level needed to maintain the same level of diagnostic performance. Because the relationship between spatial resolution and image noise does not apply to IR methods, these algorithms can reduce image noise to almost any level without sacrificing high-contrast spatial resolution. Thus, noise and CNR may be less meaningful measures of image quality for IR reconstructed images and does not capture the loss of low-contrast detectability<sup>40,57</sup>.

The non-linearity of IR reconstructions also influences noise texture that has been described as “blotchy”, “pixelated” or “cartoony”. This artificial appearance seems to correspond to a relative increase of lower-frequency noise compared to FBP. This can be illustrated as shift of the peak frequency in NPS to the left and can retrospectively be seen in our data from Paper III though we did not pick up on it at the time (Figure 5).

In order to adequately and reliably evaluate IR images an objective and quantitative method for image quality assessment is called for to ensure that diagnostic performance does not suffer when radiation dose is reduced<sup>25</sup>. A conceivable way to evaluate image quality perception and, most importantly, diagnostic performance for IR algorithms is through observer performance with multi-reader study designs. Performing these studies in a clinical setting are however complicated and time consuming. There are ethical problems with doing multiple scans resulting in increased radiation dose to the patients. There is also a relative shortage of observers (radiologists) available for this time-consuming task. In general the more observers the better and the use of task-based mathematical model-observers have also been tested with promising results<sup>25</sup>. In accordance with the results from Paper IV and V, many multi-reader studies on image quality assessment also show a great variability among the observers that sometimes even exceeds the performance differences among the different reconstructive techniques<sup>28,63</sup>.

There is mounting evidence that there are considerable limitations in using the commercially available IR algorithms of today for radiation dose reduction purposes for low-contrast object detection<sup>27,76,77,84</sup>. Based on present knowledge a conservative approach to using IR for radiation dose reduction efforts is warranted when low-contrast resolution is needed.

## Radiation dose

Throughout this thesis the concept of using 80 kV instead of 120 kV to reduce CM dose in patients at risk of CI-AKI has been investigated. As described previously radiation dose to the patient may vary according to the fraction of final versus initial tube potential to the power of 2.5 and the intensity of the radiation beam to the detector to the power of 3.5<sup>66</sup>. Thus, changing the tube potential from 120 kV to 80 kV at a constant tube loading reduces the radiation dose to the detector by a factor 4.1 and dose to the patient by a factor 2.8. This is illustrated in Paper III where the comparison between different tube potentials at a fixed tube loading (170 mAs) resulted in higher noise at lower tube potentials due to the decreasing radiation dose to the detectors, but even at a fixed radiation absorbed dose of 10 mGy there was a tendency for slightly higher noise at 80 and 70 kV. Thus, for complete TLC when reducing the tube potential from 120 to 80 kV, the tube loading must be increased fourfold to preserve image noise implying that the radiation dose to the patient may increase with about 50% ( $4.1/2.8 = 1.5$ ).

In Paper I, II, IV the radiation dose to the patients in the 80-kV cohorts was surprisingly lower than for the control group. This may in part be explained by the fact that the groups were not matched regarding weight and the patients in the 80 kV cohorts tended to weigh less. Another explanation may be that the tube loading adaption undercompensated in larger patients, at least in the CTPA studies using less powerful X-ray tubes. In Paper I and II the effective reference tube loading was also limited to 350-380 mAs at a rotation time of 0.5 seconds and a pitch of 0.5, i.e. only 3.5-3.8 times that at 120 kV. However using today's CT technology Svensson et al. found that, for the same image noise, the size-specific dose estimate was 50% higher at 80 kV single X-ray source hepatic scanning compared with 120 kV<sup>86</sup>.

## Clinical impact

The results from the first two studies on CTA of the pulmonary arteries led to clinical implementation of 80-kV protocols for patients considered at risk of CI-AKI and have provided a very useful tool when diagnostic alternatives to CM-enhanced CT examination such as scintigraphy is inconclusive or lacking. Further technological development has since then mitigated many of the limitations in the CT systems, allowing for faster scan time, more powerful tube technology and even further reduction of CM doses<sup>3</sup>. In Paper IV the advances in technology meant that the use of low-kV protocols in the abdomen could be tested and have also been implemented into clinical practice.

Although the results from Paper III were somewhat hard to translate due to the uncertainty in phantom studies it nevertheless showed results in line with previous research regarding iodine attenuation. It also showed that the IR algorithm had a similar effect at all tube potentials regarding noise characteristics and spatial resolution. When putting these results through the clinical test in Paper V the results showed that the IR algorithm (SAFIRE) did not manage to compensate for the reduced radiation dose when using 80 kV instead of 120 kV. This gave us an insight into the problems of assessing image quality when using IR algorithms instead of FBP. Further studies are needed to investigate to what extent IR may be used to ensure that diagnostic performance is not compromised when radiation dose is reduced.





# Conclusion

This thesis evaluated the feasibility of using low kV technique CT in patients considered at risk of CI-AKI to minimize the amount of contrast medium needed to produce diagnostic images. The main conclusions are:

- The CM dose can be reduced by 40-50% in CT-angiography when the X-ray tube potential is reduced from 120 to 80 kV for the same iodine attenuation, which should be to the benefit of patients considered at risk of CI-AKI.
- The CM dose can be reduced by 40% in hepatic CT when the X-ray tube potential is reduced from 120 to 80 kV for the same iodine attenuation, which should be to the benefit of patients considered at risk of CI-AKI.
- Image noise can be controlled to preserve image quality at a reduced tube potential if the tube loading can be adequately increased to maintain the radiation dose to the detector.
- Using the iterative reconstruction algorithm (SAFIRE) reduces image noise and improves contrast-to-noise ratios compared to FBP.
- Using the iterative reconstruction algorithm (SAFIRE) to control image noise instead of tube loading compensation when reducing tube potential from 120 to 80 kV in hepatic CT does not provide sufficient subjective diagnostic quality.
- There is no support in our studies for the use of 80 kV protocols in larger patients (BMI >30 kg/m<sup>2</sup>).

## Future perspectives

When this project was initiated in 2006 the concept of reducing the tube potential to reduce the CM dose needed for adequate image contrast resolution was largely unexploited. The protocols used at the time was to a great extent “One-size-fits-all” with the same CM and radiation dose to all patients regardless of patient size. Over the span of the last 15 years technical developments such as tube current modulation, tailoring the CM dose to patient body weight and more recently automated tube voltage selection, that more routinely utilizes the higher iodine attenuation at lower tube potentials, have improved standardization of image quality and individualisation of radiation exposure and CM delivery.

The usefulness of low-kV protocols has already been recognized and implemented for many CM-enhanced CT protocols in children, small adults, angiography and chest examinations. The evolution of more powerful X-ray tubes will offer this possibility for other protocols to take advantage of the benefits of increased contrast at low kV settings. More powerful X-ray tubes will also provide the possibility for application of stronger prefiltering to ensure that more photons that enter the patient contributes to the detector signal<sup>51</sup>.

The steady increase of detector rows and faster rotation speeds that we have grown accustomed to seems to be slowing down due to physical limitations<sup>53</sup>. Development of new detector technology and further evolution of IR algorithms is probably where we will see the biggest advances in the coming years.

Dual energy CT (DECT) is a technology in clinical use that capitalizes on different materials such as uric acid, calcium and iodine to have different specific signatures at different energy levels. It can improve iodine enhancement with virtual monoenergetic imaging at low keV which may be useful to reduce CM dose especially in CTA examinations. There are a number of different approaches for dual energy acquisition, but for CT systems that has two X-ray tubes installed complete TLC in low-kV setting is possible, even in larger patients, by using both tubes at the same low tube voltage, illustrated by Svenson et al.<sup>86</sup>.

The next emerging technology towards further spectral information in CT is photon counting CT (PCCT)<sup>52</sup> with detectors that has the capability to determine the energy of every individual photon and separating them into several energy levels in each detector and thereby providing a spectral analysis of the transmitted X-ray beam. Beside the increased spectral capabilities e.g., material decomposition and iodine boosting, it offers the possibility to filter out low-energy photons obviously representing scattered radiation, which accounts for a large amount of noise in the sinogram data sampled with conventional detectors. With almost noise-free signal

data image reconstruction only has to handle electronic and quantum noise. This has the potential for decreased image noise and increased low contrast resolution.

The improved spectral capabilities following photon counting detection also opens the path for entirely new contrast materials. Initial tests of alternative contrast agents to iodine with higher atomic numbers such as gold or hafnium and holmium with a K-edge in the range of normal spectral energies show promising results<sup>68</sup>.

The predictable linear relationship between radiation dose and image noise in FBP reconstructions have given way to iterative reconstruction algorithms that has proven better at handling image noise, but also considerably harder to assess with regard to image quality as conventional quality parameters such as image noise, SNR and CNR may not be as useful as before. Further development of IR algorithms with integration of more information like data from prior examinations or material composition and shape of an orthopaedic implant and the use of deep learning and artificial intelligence will most probably push this even further<sup>46,96</sup>. Ongoing research on different approaches on the use of these techniques are under way both for improving the IR algorithms but also to accelerate the reconstruction process<sup>39,83</sup>. In this context it is imperative that we also develop tools to evaluate how these new algorithms influence different image quality parameters.

An alternative approach for radiation dose reduction in CT that is being investigated is sparse sampling techniques. A reduced number of projections are used while radiation exposure remains high for each projection resulting in high signal-to-noise ratio. Under-sampling does however require advanced IR solutions for image reconstruction. This technique will also require the development new X-ray tubes to be clinically implemented<sup>1,81</sup>.

The development of monochromatic X-ray sources is also an interesting field of research<sup>22</sup> that may lead to drastic reduction in radiation dose as only energies needed for image reconstruction can be utilised.

Phase-contrast and dark-field CT, based on an electromagnetic wave model as opposed to photoelectric absorption and Compton scattering, is another field of research<sup>88</sup>. In this technique image contrast represents wave-optical interactions such as phase-shift or small-angle scattering. With these techniques additional and complementary information becomes available. Phase contrast offers higher soft-tissue resolution and dark-field CT offers structural information beyond the spatial resolution of the imaging system. The technique has been hindered by the fact that implementation did not seem feasible in a continuously rotating gantry. With newly developed IR reconstructions however, investigations on implementation of the additional information into the IR algorithms shows promise.

With the rapid evolution of CT technology, the implementations also increase. Ultra-low radiation doses that are at level with conventional radiography but with

superior information are already seen today. Increasing examinations with quantitative and spectral information, improved resolution and image quality will require increased automation of handling all the data. Structures for meeting these requirements, such as clinical decision support systems and integrated diagnostics will have to be developed making use of the technology available. This will probably have a huge impact on the way we work as radiologists.

The increasing automation of CT parameters and the increasing complexity of the CT systems needs constant monitoring whether the underlying image quality actually meets the diagnostic needs. It is crucial that the radiology community together with manufacturers preserve the awareness that increased complexity of CT technique's hardware and software in combination with the constant ambition to reduce radiation dose always carries the inherent risk of producing eye pleasing image material which however lacks critical diagnostic information.

# Acknowledgement

The first two studies (Paper I and II) were carried out at the Department of Radiology, Lasarettet Trelleborg. The remaining studies (Paper III, IV and V) was carried out at the Department of Medical Imaging and Physiology, Skåne University Hospital, Lund.

This thesis would not have been possible without the support of my family, mentors, supervisors, colleagues and friends. I am humbled by your patients during this extended process.

First of all, I would like to thank my mentor and tutor *Ulf Nyman*, for giving me the opportunity to make this thesis possible, for not giving up and believing in me and encouraging me when I needed it the most, for your infinite patience, stubbornness and knowledge. I stand on the shoulder of a giant

My favorite senior supervisor *Mats Geijer* for his elaborate scientific knowledge, good humor, support and guidance in the halls of scientific academia.

My co-supervisor *Marcus Söderberg* for his relentless enthusiasm, the enviable ability of getting things done, technical support and enduringly constructive feedback

My co-supervisor *Roger Siemund* for his knowledge, encouragement, rewarding discussions and mind elevating bicycle rides

My co-author *Mattias Kristiansson*, a man with more strings in his bow than anyone I have ever known

My co-author and dear colleague *Tobias Aho Fält* for his valuable input and pragmatic approach both in science and in the clinical hubbub of trying to make everything work.

My co-authors from the Department of Medicine in Trelleborg *Katarina Hansson* and *Franco Pasquariello* for their valuable input and support

My grateful thanks are due to the Head of the radiology department *Peter Hochbergs* for making this thesis possible by generously allowing for time and resources of the Department to be at my disposal.

To professor *Pia Maly-Sundgren* for her interest in supporting my academic efforts  
*Jonas Björk* for his invaluable statistical guidance and advice

With pride and deep appreciation to all and everyone at the radiology department in Lund. I could not have wished for a better place to work. Particular gratitude to *Ann-Charlotte Ragnar*, *Erica Malberg* and *Cecilia van Toor* for all your extra efforts and keeping track of everything, and with special mention of my colleagues *Eva-Cecilia Salomonson* and *Kerstin Malmgren* for being such an excellent litmus test of image quality.

An undirected but genuine thanks to the many colleuges at Skåne University Hospital, Lund that I have had the fortune to collaborate with, so many bright, kind and dedicated people that this would indeed be a thick book if I was to mention you all.

My sincerest gratitude to the department of radiology in Trelleborg who welcomed me with open arms when I didn't have much to offer. My first colleagues *Staffan Sjöberg*, *Birgitta Nilsson*, *Andre Michalak*, *Pavel Kesek* and *Peter Björkdahl* for sharing your knowledge and for your unwavering support. To all the radiographers who stoically accepted all the experimental tinkering with special mention of *Staffan Wettermark* for his relentless quest for perfection.

To my Friends for sticking by and holding out.

Finally, but closest to heart I would like to thank my family, my parents, my brothers and my sister with respective families, without you I would not have been me.

My everlasting love to my children *David*, *Jacob*, *Julia* and little *Sixten*, for keeping me young at heart and on my toes in the here and now.

My beloved *Maria* for making sure I never forget what is truly important, thank you for everything.

The research presented in this thesis was supported by the Torsten and Karin Almen's foundation. and by grants from Södra Sjukvårdsregionen.

# References

1. Abbas S, Lee T, Shin S, Lee R, Cho S. Effects of sparse sampling schemes on image quality in low-dose CT. *Med Phys*. 2013;40(11):111915. doi:10.1118/1.4825096
2. Almén A, Jangland L. 2020-14 Radiologiska undersökningar i Sverige under 2018. Published online September 2020:52.
3. Alobeidi H, Alshamari M, Widell J, Eriksson T, Lidén M. Minimizing contrast media dose in CT pulmonary angiography with high-pitch technique. *Br J Radiol*. 2020;(93):20190995. doi:10.1259/bjr.20190995
4. Alwall N, Johnsson S, Tornberg A, Werko L. Acute renal failure following angiography especially the risk of repeated examination, revealed by eight cases (two deaths). *Acta Chir Scand*. 1955;109(1):11-19.
5. Awai K, Hiraishi K, Hori S. Effect of contrast material injection duration and rate on aortic peak time and peak enhancement at dynamic CT involving injection protocol with dose tailored to patient weight. *Radiology*. 2004;230(1):142-150. doi:10.1148/radiol.2301021008
6. Awai K, Hori S. Effect of contrast injection protocol with dose tailored to patient weight and fixed injection duration on aortic and hepatic enhancement at multidetector-row helical CT. *Eur Radiol*. 2003;13(9):2155-2160. doi:10.1007/s00330-003-1904-x
7. Bae KT, Heiken JP. Scan and contrast administration principles of MDCT. *Eur Radiol Suppl*. 2005;15(S5):e46-e59. doi:10.1007/s10406-005-0165-y
8. Bae KT, Heiken JP, Brink JA. Aortic and hepatic contrast medium enhancement at CT. Part II. Effect of reduced cardiac output in a porcine model. *Radiology*. 1998;207(3):657-662. doi:10.1148/radiology.207.3.9609887
9. Bae KT, Heiken JP, Brink JA. Aortic and hepatic peak enhancement at CT: effect of contrast medium injection rate--pharmacokinetic analysis and experimental porcine model. *Radiology*. 1998;206(2):455-464. doi:10.1148/radiology.206.2.9457200



10. Bae KT, Seeck BA, Hildebolt CF, et al. Contrast Enhancement in Cardiovascular MDCT: Effect of Body Weight, Height, Body Surface Area, Body Mass Index, and Obesity. *Am J Roentgenol*. 2008;190(3):777-784. doi:10.2214/AJR.07.2765
11. Bartels ED, Brun GC, Gammeltoft A, Gjørup PA. Acute Anuria Following Intravenous Pyelography in a Patient with Myelomatosis. *Acta Med Scand*. 1954;150(4):297-302. doi:10.1111/j.0954-6820.1954.tb18632.x
12. Båth M, Månsson LG. Visual grading characteristics (VGC) analysis: a non-parametric rank-invariant statistical method for image quality evaluation. *Br J Radiol*. 2007;80(951):169-176. doi:10.1259/bjr/35012658
13. Björkdahl P, Nyman U. Using 100- instead of 120-kVp computed tomography to diagnose pulmonary embolism almost halves the radiation dose with preserved diagnostic quality. *Acta Radiol*. 2010;51(3):260-270. doi:10.3109/02841850903505222
14. Bongartz G, Golding SJ, Jurik AG, et al. European guidelines on quality criteria for computed tomography. Published online March 2004. <http://www.dr.dk/guidelines/ct/quality/htmlindex.htm>
15. Boone JM, Geraghty EM, Seibert JA, Wootton-Gorges SL. Dose Reduction in Pediatric CT: A Rational Approach. *Radiology*. 2003;228(2):352-360. doi:10.1148/radiol.2282020471
16. Chaudhury P, Armanyous S, Harb SC, et al. Intra-Arterial versus Intravenous Contrast and Renal Injury in Chronic Kidney Disease: A Propensity-Matched Analysis. *Nephron*. 2019;141(1):31-40. doi:10.1159/000494047
17. Cormack AM. Representation of a Function by Its Line Integrals, with Some Radiological Applications. *J Appl Phys*. 1963;34(9):2722-2727. doi:10.1063/1.1729798
18. Cormack AM. Representation of a Function by Its Line Integrals, with Some Radiological Applications. II. *J Appl Phys*. 1964;35(10):2908-2913. doi:10.1063/1.1713127
19. Davenport MS, Khalatbari S, Cohan RH, Dillman JR, Myles JD, Ellis JH. Contrast Material-induced Nephrotoxicity and Intravenous Low-Osmolality Iodinated Contrast Material: Risk Stratification by Using Estimated Glomerular Filtration Rate. *Radiology*. 2013;268(3):719-728. doi:10.1148/radiol.13122276

20. Deak PD, Smal Y, Kalender WA. Multisection CT Protocols: Sex- and Age-specific Conversion Factors Used to Determine Effective Dose from Dose-Length Product. *Radiology*. 2010;257(1):158-166. doi:10.1148/radiol.10100047
21. Dorio PJ, Lee FT, Henseler KP, et al. Using a Saline Chaser to Decrease Contrast Media in Abdominal CT. *Am J Roentgenol*. 2003;180(4):929-934. doi:10.2214/ajr.180.4.1800929
22. Eggl E, Schleede S, Bech M, et al. X-ray phase-contrast tomography with a compact laser-driven synchrotron source. *Proc Natl Acad Sci U S A*. 2015;112(18):5567-5572. doi:10.1073/pnas.1500938112
23. European Society of Urogenital Radiology. ESUR Guidelines on Contrast Agents 10.0. <http://www.esur.org/esur-guidelines/>. Published 2018. Accessed October 19, 2020. <http://www.esur.org/esur-guidelines/>
24. Faggioni L, Neri E, Sbragia P, et al. 80-kV Pulmonary CT Angiography With 40 mL of Iodinated Contrast Material in Lean Patients: Comparison of Vascular Enhancement With Iodixanol (320 mg I/mL) and Iomeprol (400 mg I/mL). *Am J Roentgenol*. 2012;199(6):1220-1225. doi:10.2214/AJR.11.8122
25. Favazza CP, Ferrero A, Yu L, Leng S, McMillan KL. Use of a channelized Hotelling observer to assess CT image quality and optimize dose reduction for iteratively reconstructed images. *J Med Imaging*. 2017;4(03):1. doi:10.1117/1.JMI.4.3.031213
26. Fleischmann D, Boas FE. Computed tomography—old ideas and new technology. *Eur Radiol*. 2011;21(3):510-517. doi:10.1007/s00330-011-2056-z
27. Fletcher JG, Fidler JL, Venkatesh SK, et al. Observer Performance with Varying Radiation Dose and Reconstruction Methods for Detection of Hepatic Metastases. *Radiology*. 2018;289(2):455-464. doi:10.1148/radiol.2018180125
28. Fletcher JG, Yu L, Li Z, et al. Observer Performance in the Detection and Classification of Malignant Hepatic Nodules and Masses with CT Image-Space Denoising and Iterative Reconstruction. *Radiology*. 2015;276(2):465-478. doi:10.1148/radiol.2015141991
29. Flinck M, Gradén A, Milde H, et al. Cardiac output measured by electrical velocimetry in the CT suite correlates with coronary artery enhancement: a feasibility study. *Acta Radiol Stockh Swed 1987*. 2010;51(8):895-902. doi:10.3109/02841851.2010.503663

30. Goenka AH, Herts BR, Dong F, et al. Image Noise, CNR, and Detectability of Low-Contrast, Low-Attenuation Liver Lesions in a Phantom: Effects of Radiation Exposure, Phantom Size, Integrated Circuit Detector, and Iterative Reconstruction. *Radiology*. 2016;280(2):475-482. doi:10.1148/radiol.2016151621
31. Goldman LW. Principles of CT and CT Technology. *J Nucl Med Technol*. 2007;35(3):115-128. doi:10.2967/jnmt.107.042978
32. Goldman LW. Principles of CT: Radiation Dose and Image Quality. *J Nucl Med Technol*. 2007;35(4):213-225. doi:10.2967/jnmt.106.037846
33. Grainger RG. Intravascular contrast media--the past, the present and the future. Mackenzie Davidson Memorial Lecture, April 1981. *Br J Radiol*. 1982;55(649):1-18. doi:10.1259/0007-1285-55-649-1
34. Gurm HS, Dixon SR, Smith DE, et al. Renal Function-Based Contrast Dosing to Define Safe Limits of Radiographic Contrast Media in Patients Undergoing Percutaneous Coronary Interventions. *J Am Coll Cardiol*. 2011;58(9):907-914. doi:10.1016/j.jacc.2011.05.023
35. Heiken JP, Brink JA, McClelland BL, Sagel SS, Crowe TM, Gaines MV. Dynamic incremental CT: effect of volume and concentration of contrast material and patient weight on hepatic enhancement. *Radiology*. 1995;195(2):353-357. doi:10.1148/radiology.195.2.7724752
36. Holmquist F, Nyman U. Eighty-peak kilovoltage 16-channel multidetector computed tomography and reduced contrast-medium doses tailored to body weight to diagnose pulmonary embolism in azotaemic patients. *Eur Radiol*. 2006;16(5):1165-1176. doi:10.1007/s00330-005-0117-x
37. Huda W, Ogden KM, Khorasani MR. Converting Dose-Length Product to Effective Dose at CT. *Radiology*. 2008;248(3):995-1003. doi:10.1148/radiol.2483071964
38. Huda W, Scalzetti EM, Levin G. Technique Factors and Image Quality as Functions of Patient Weight at Abdominal CT. *Radiology*. 2000;217(2):430-435. doi:10.1148/radiology.217.2.r00nv35430
39. Jensen CT, Liu X, Tamm EP, et al. Image Quality Assessment of Abdominal CT by Use of New Deep Learning Image Reconstruction: Initial Experience. *Am J Roentgenol*. 2020;215(1):50-57. doi:10.2214/AJR.19.22332

40. Jensen CT, Wagner-Bartak NA, Vu LN, et al. Detection of Colorectal Hepatic Metastases Is Superior at Standard Radiation Dose CT versus Reduced Dose CT. *Radiology*. 2019;290(2):400-409. doi:10.1148/radiol.2018181657
41. Jensen K, Martinsen ACT, Tingberg A, Aaløkken TM, Fosse E. Comparing five different iterative reconstruction algorithms for computed tomography in an ROC study. *Eur Radiol*. 2014;24(12):2989-3002. doi:10.1007/s00330-014-3333-4
42. Johnson PT, Naidich D, Fishman EK. MDCT for suspected pulmonary embolism: multi-institutional survey of 16-MDCT data acquisition protocols. *Emerg Radiol*. 2007;13(5):243-249. doi:10.1007/s10140-006-0547-z
43. Jones SE, Wittram C. The Indeterminate CT Pulmonary Angiogram: Imaging Characteristics and Patient Clinical Outcome. *Radiology*. 2005;237(1):329-337. doi:10.1148/radiol.2371041520
44. Kalender W. *Computed Tomography: Fundamentals, System Technology, Image Quality, Applications*. MCD Verlag; 2000.
45. Karlsberg RP, Dohad SY, Sheng R. Contrast Medium–Induced Acute Kidney Injury: Comparison of Intravenous and Intraarterial Administration of Iodinated Contrast Medium. *J Vasc Interv Radiol*. 2011;22(8):1159-1165. doi:10.1016/j.jvir.2011.03.020
46. Kim B, Han M, Shim H, Baek J. A performance comparison of convolutional neural network-based image denoising methods: The effect of loss functions on low-dose CT images. *Med Phys*. 2019;46(9):3906-3923. doi:https://doi.org/10.1002/mp.13713
47. Kooiman J, Le Haen PA, Gezgin G, et al. Contrast-induced acute kidney injury and clinical outcomes after intra-arterial and intravenous contrast administration: Risk comparison adjusted for patient characteristics by design. *Am Heart J*. 2013;165(5):793-799.e1. doi:10.1016/j.ahj.2013.02.013
48. Kormano M, Dean PB. Extravascular contrast material: the major component of contrast enhancement. *Radiology*. 1976;121(2):379-382. doi:10.1148/121.2.379
49. Kormano M, Partanen K, Soimakallio S, Kivimäki T. Dynamic Contrast Enhancement of the Upper Abdomen: Effect of Contrast Medium and Body Weight. *Invest Radiol*. 1983;18(18):364-367.

50. Lehti L, Nyman U, Söderberg M, Björres K, Gottsäter A, Wassélius J. 80-kVp CT angiography for endovascular aneurysm repair follow-up with halved contrast medium dose and preserved diagnostic quality. *Acta Radiol.* 2016;57(3):279-286. doi:10.1177/0284185115577251
51. Lell MM, Kachelrieß M. Recent and Upcoming Technological Developments in Computed Tomography: High Speed, Low Dose, Deep Learning, Multienergy. *Invest Radiol.* 2020;55(1):8-19. doi:10.1097/RLI.0000000000000601
52. Leng S, Bruesewitz M, Tao S, et al. Photon-counting Detector CT: System Design and Clinical Applications of an Emerging Technology. *RadioGraphics.* 2019;39(3):729-743. doi:10.1148/rg.2019180115
53. Li B, Toth TL, Hsieh J, Tang X. Simulation and analysis of image quality impacts from single source, ultra-wide coverage CT scanner. *J X-Ray Sci Technol.* 2012;20(4):395-404. doi:10.3233/XST-2012-00347
54. Lubbers MM, Kock M, Niezen A, et al. Iodixanol versus Iopromide at Coronary CT Angiography: Lumen Opacification and Effect on Heart Rhythm—the Randomized IsoCOR Trial. *Radiology.* 2018;286(1):71-80. doi:10.1148/radiol.2017162779
55. Masuda T, Nakaura T, Funama Y, et al. Aortic and Hepatic Contrast Enhancement During Hepatic-Arterial and Portal Venous Phase Computed Tomography Scanning: Multivariate Linear Regression Analysis Using Age, Sex, Total Body Weight, Height, and Cardiac Output. *J Comput Assist Tomogr.* Published online October 2016:1. doi:10.1097/RCT.0000000000000513
56. Masuda T, Nakaura T, Funama Y, et al. Aortic and Hepatic Contrast Enhancement During Hepatic-Arterial and Portal Venous Phase Computed Tomography Scanning: Multivariate Linear Regression Analysis Using Age, Sex, Total Body Weight, Height, and Cardiac Output. *J Comput Assist Tomogr.* 2017;41(2):309-314. doi:10.1097/RCT.0000000000000513
57. McCollough CH, Yu L, Kofler JM, et al. Degradation of CT Low-Contrast Spatial Resolution Due to the Use of Iterative Reconstruction and Reduced Dose Levels. *Radiology.* Published online March 26, 2015:142047. doi:10.1148/radiol.15142047
58. McDonald JS, Leake CB, McDonald RJ, et al. Acute Kidney Injury After Intravenous Versus Intra-Arterial Contrast Material Administration in a Paired Cohort. *Invest Radiol.* 2016;51(12):804–809. doi:10.1097/RLI.0000000000000298

59. McDonald JS, McDonald RJ, Carter RE, Katzberg RW, Kallmes DF, Williamson EE. Risk of Intravenous Contrast Material–mediated Acute Kidney Injury: A Propensity Score–matched Study Stratified by Baseline-estimated Glomerular Filtration Rate. *Radiology*. 2014;271(1):65-73. doi:10.1148/radiol.13130775
60. Mehran R, Aymong ED, Nikolsky E, et al. A simple risk score for prediction of contrast-induced nephropathy after percutaneous coronary intervention. *J Am Coll Cardiol*. 2004;44(7):1393-1399. doi:10.1016/j.jacc.2004.06.068
61. Mehran R, Dangas GD, Weisbord SD. Contrast-Associated Acute Kidney Injury. *N Engl J Med*. Published online 2019:10.
62. Mileto A, Guimaraes LS, McCollough CH, Fletcher JG, Yu L. State of the Art in Abdominal CT: The Limits of Iterative Reconstruction Algorithms. *Radiology*. 2019;293(3):491-503. doi:10.1148/radiol.2019191422
63. Mileto A, Zamora DA, Alessio AM, et al. CT Detectability of Small Low-Contrast Hypoattenuating Focal Lesions: Iterative Reconstructions versus Filtered Back Projection. *Radiology*. 2018;289(2):443-454. doi:10.1148/radiol.2018180137
64. van der Molen AJ, Reimer P, Dekkers IA, et al. Post-contrast acute kidney injury – Part 1: Definition, clinical features, incidence, role of contrast medium and risk factors: Recommendations for updated ESUR Contrast Medium Safety Committee guidelines. *Eur Radiol*. 2018;28(7):2845-2855. doi:10.1007/s00330-017-5246-5
65. van der Molen AJ, Reimer P, Dekkers IA, et al. Post-contrast acute kidney injury. Part 2: risk stratification, role of hydration and other prophylactic measures, patients taking metformin and chronic dialysis patients: Recommendations for updated ESUR Contrast Medium Safety Committee guidelines. *Eur Radiol*. 2018;28(7):2856-2869. doi:10.1007/s00330-017-5247-4
66. Nagel HD, Galanski M, Hidajat N, Maier W, Schmidt T. Radiation exposure in computed tomography. Fundamentals, influencing parameters, dose assessment, optimization, scanner data, terminology. 4th revised and updated revision. In: Vol 2002. CTB Publications, D-21073 Hamburg; 2002:31-32.

67. Nijssen EC, Rennenberg RJ, Nelemans PJ, et al. Prophylactic hydration to protect renal function from intravascular iodinated contrast material in patients at high risk of contrast-induced nephropathy (AMACING): a prospective, randomised, phase 3, controlled, open-label, non-inferiority trial. *The Lancet*. 2017;389(10076):1312-1322. doi:10.1016/S0140-6736(17)30057-0
68. Nowak T, Hupfer M, Brauweiler R, Eisa F, Kalender WA. Potential of high-Z contrast agents in clinical contrast-enhanced computed tomography. *Med Phys*. 2011;38(12):6469-6482. doi:10.1118/1.3658738
69. Nyman U, Ahl TL, Kristiansson M, Nilsson L, Wettemark S. Patient-circumference-adapted dose regulation in body computed tomography. a practical and flexible formula. *Acta Radiol*. 2005;46(4):396-406. doi:10.1080/02841850510021193
70. Nyman U, Ahlkvist J, Aspelin P, et al. Preventing contrast medium-induced acute kidney injury: Side-by-side comparison of Swedish-ESUR guidelines. *Eur Radiol*. 2018;28(12):5384-5395. doi:10.1007/s00330-018-5678-6
71. Nyman U, Almén T, Jacobsson B, Aspelin P. Are intravenous injections of contrast media really less nephrotoxic than intra-arterial injections? *Eur Radiol*. 2012;22(6):1366-1371. doi:10.1007/s00330-011-2371-4
72. Nyman U, Björkdahl P, Olsson M-L, Gunnarsson M, Goldman B. Low-dose radiation with 80-kVp computed tomography to diagnose pulmonary embolism: a feasibility study. *Acta Radiol*. 2012;53(9):1004-1013. doi:10.1258/ar.2012.120327
73. Nyman U, Elmståhl B, Geijer H, Leander P, Almén T, Nilsson M. Iodine contrast iso-attenuating with diagnostic gadolinium doses in CTA and angiography results in ultra-low iodine doses. A way to avoid both CIN and NSF in azotemic patients? *Eur Radiol*. 2010;21(2):326-336. doi:10.1007/s00330-010-1924-2
74. Nyman U, Leitz W, Kristiansson M, Pålshörp PÅ. Statens strålskyddsinstitut rapport 2004:12 - Stråldosreglering vid kroppsdatortomografi - bakgrund till dosregleringsprogrammet Omnimas. stralsakerhetsmyndigheten.se/publikationer/rapporter/stralskydd/2004/200412/. Published November 2004.
75. Olsson B, Aulie A, Sveen K, Andrew E. Human pharmacokinetics of iohexol. A new nonionic contrast medium. *Invest Radiol*. 1983;18(2):177-182. doi:10.1097/00004424-198303000-00015

76. Pickhardt PJ, Lubner MG, Kim DH, et al. Abdominal CT with model-based iterative reconstruction (MBIR): initial results of a prospective trial comparing ultralow-dose with standard-dose imaging. *AJR Am J Roentgenol.* 2012;199(6):1266-1274. doi:10.2214/AJR.12.9382
77. Pooler BD, Lubner MG, Kim DH, et al. Prospective Evaluation of Reduced Dose Computed Tomography for the Detection of Low-Contrast Liver Lesions: Direct Comparison with Concurrent Standard Dose Imaging. *Eur Radiol.* 2017;27(5):2055-2066. doi:10.1007/s00330-016-4571-4
78. Radiological Society of the Netherlands. Guideline Safe Use of Contrast Media Part 1. Published November 1, 2017. <https://www.radiologen.nl/kwaliteit/richtlijnen-veilig-gebruik-van-contrastmiddelen-guidelines-safe-use-contrast-media>
79. Radon J. Uber die bestimmung von funktionen durch ihre integralwerte langs gewisser mannigfaltigkeiten. *Berichte Uber Verhandlungen Gesellschaft Wiss Zu Leipz.* 1917;(69):262-277.
80. Ronco C, Haapio M, House AA, Anavekar N, Bellomo R. Cardiorenal Syndrome. *J Am Coll Cardiol.* 2008;52(19):1527-1539. doi:10.1016/j.jacc.2008.07.051
81. Sauter AP, Kopp FK, Bippus R, et al. Sparse sampling computed tomography (SpSCT) for detection of pulmonary embolism: a feasibility study. *Eur Radiol.* 2019;29(11):5950-5960. doi:10.1007/s00330-019-06217-5
82. Schindera ST, Odedra D, Raza SA, et al. Iterative Reconstruction Algorithm for CT: Can Radiation Dose Be Decreased While Low- Contrast Detectability Is Preserved? *Med Phys.* 2013;269(2):8.
83. Singh R, Digumarthy SR, Muse VV, et al. Image Quality and Lesion Detection on Deep Learning Reconstruction and Iterative Reconstruction of Submillisievert Chest and Abdominal CT. Published online 2020:8.
84. Son JH, Kim SH, Yoon J-H, Lee Y, Lim Y-J, Kim S-J. Comparison of Model-Based Iterative Reconstruction, Adaptive Statistical Iterative Reconstruction, and Filtered Back Projection for Detecting Hepatic Metastases on Submillisievert Low-Dose Computed Tomography. *J Comput Assist Tomogr.* 2017;41(4):644–650. doi:10.1097/RCT.0000000000000577
85. Stacul F, Molen AJ van der, Reimer P, et al. Contrast induced nephropathy: updated ESUR Contrast Media Safety Committee guidelines. *Eur Radiol.* 2011;21(12):2527-2541. doi:10.1007/s00330-011-2225-0



86. Svensson A, Thor D, Fischer MA, Brismar T. Dual source abdominal computed tomography: the effect of reduced X-ray tube voltage and intravenous contrast media dosage in patients with reduced renal function. *Acta Radiol*. Published online June 22, 2018;028418511878321. doi:10.1177/0284185118783213
87. Swick M. Darstellung der Niere und Harnwege im Röntgenbild durch Intravenöse Einbringung eines Neuen Kontraststoffes, des Uroselectans. *Klin Wochenschr*. 1929;8(45):2087-2089. doi:10.1007/BF01875121
88. Teuffenbach M von, Koehler T, Fehringer A, et al. Grating-based phase-contrast and dark-field computed tomography: a single-shot method. *Sci Rep*. 2017;7. doi:10.1038/s41598-017-06729-4
89. Thomas KE, Wang B. Age-specific effective doses for pediatric MSCT examinations at a large children's hospital using DLP conversion coefficients: a simple estimation method. *Pediatr Radiol*. 2008;38(6):645-656. doi:10.1007/s00247-008-0794-0
90. Tong GE, Kumar S, Chong KC, et al. Risk of contrast-induced nephropathy for patients receiving intravenous vs. intra-arterial iodixanol administration. *Abdom Radiol*. 2016;41(1):91-99. doi:10.1007/s00261-015-0611-9
91. Tsapaki V, Aldrich JE, Sharma R, et al. Dose reduction in CT while maintaining diagnostic confidence: diagnostic reference levels at routine head, chest, and abdominal CT--IAEA-coordinated research project. *Radiology*. 2006;240(3):828-834. doi:10.1148/radiol.2403050993
92. Willemink MJ, Jong PA de, Leiner T, et al. Iterative reconstruction techniques for computed tomography Part 1: Technical principles. *Eur Radiol*. 2013;23(6):1623-1631. doi:10.1007/s00330-012-2765-y
93. Willemink MJ, de Jong PA, Leiner T, et al. Iterative reconstruction techniques for computed tomography Part 1: technical principles. *Eur Radiol*. 2013;23(6):1623-1631. doi:10.1007/s00330-012-2765-y
94. Willemink MJ, Leiner T, Jong PA de, et al. Iterative reconstruction techniques for computed tomography part 2: initial results in dose reduction and image quality. *Eur Radiol*. 2013;23(6):1632-1642. doi:10.1007/s00330-012-2764-z
95. Winklehner A, Karlo C, Puippe G, et al. Raw data-based iterative reconstruction in body CTA: evaluation of radiation dose saving potential. *Eur Radiol*. 2011;21(12):2521-2526. doi:10.1007/s00330-011-2227-y

96. Wolterink JM, Leiner T, Viergever MA, Išgum I. Generative Adversarial Networks for Noise Reduction in Low-Dose CT. *IEEE Trans Med Imaging*. 2017;36(12):2536-2545. doi:10.1109/TMI.2017.2708987
97. Yanaga Y, Awai K, Nakaura T, et al. Effect of Contrast Injection Protocols with Dose Adjusted to the Estimated Lean Patient Body Weight on Aortic Enhancement at CT Angiography. *Am J Roentgenol*. 2009;192(4):1071-1078. doi:10.2214/AJR.08.1407







**FACULTY OF  
MEDICINE**

Department of Medical Imaging and Physiology  
Clinical Sciences Lund

Lund University, Faculty of Medicine  
Doctoral Dissertation Series 2021:13  
ISBN 978-91-8021-019-5  
ISSN 1652-8220

