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On the use of computed tomography in cardiac imaging

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“...even if it could be made to work as you suggest, we cannot imagine a significant market for such an expensive apparatus which would do nothing but make a radiographic cross-section of a head.”

Anonymous X-ray equipment manufacturer in rejection letter to CT pioneer W.H. Oldendorf, in 1963 (1).

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ABSTRACT

Background

Cardiac computed tomography in general and Cardiac Computed Tomography Angiography (CCTA) in particular, is becoming increasingly useful in the work-up of coronary artery disease (CAD). The main strength of CCTA is the high negative predictive value and thus the ability to exclude significant stenosis. When more extensive atheromatous change is seen, there is a tendency of overestimation of stenosis significance, leading to a number of unnecessary invasive procedures. Several potential methods for increasing the diagnostic yield of cardiac CT are available.

Purpose

Study I: To investigate whether the use of a 2-D, non-linear adaptive noise reduction filter can improve image quality in CCTA.

Study II: To evaluate the variation in adenosine stress dynamic Computed Tomography Perfusion (CTP) blood flow as compared to ^{99m}Tc Single Photon Emission Computed Tomography (SPECT). Secondly, to compare the perfusion results from manual and automatic myocardial segmentation.

Study III: To evaluate the accuracy of noninvasively computed fractional flow reserve (cFFR) derived from CCTA.

Study IV: To evaluate the prognostic value of CCTA in terms of major adverse cardiac events (MACE).

Materials and methods

Study I: Images from 36 consecutive CCTA exams performed with two different dose levels were used. Low-dose (20% of full dose) images were duplicated and one copy subjected to an external noise reduction filter. Image quality in full dose, low-dose and noise-reduced low-dose images were graded using visual grading analysis. Image noise was measured.

Study II: Stress CTP and stress SPECT were performed in 17 patients, and the variation in per segment blood flow was evaluated and compared. Also, both

manual and automated CTP image segmentation was performed and the results compared.

Study III: A total of 21 patients with CCTA and subsequent invasive coronary angiography (ICA) including measurement of FFR were selected. The CCTA datasets were processed using cFFR software and the results compared to the corresponding invasively measured FFR (invFFR).

Study IV: A cohort of 1205 patients with chest pain of unknown origin but without known CAD underwent CCTA. CCTA findings were classified as: 1) normal, 2) non-obstructive CAD or 3) obstructive CAD. Baseline data and data on subsequent MACE were retrieved from the SWEDEHEART/SCAAR medical quality registries and from the National Board of Health Patient and Cause-of-death registries. Survival, hazard ratios and three-year incidence in terms of MACE were calculated for each group. The three-year incidence for readmission due to stable angina pectoris or unspecific chest pain was also calculated.

Results

Study I: There was a significant improvement in perceived image quality for all quality criteria when the filter was applied to low-dose images. The image noise for the whole group, expressed as the average standard deviation of the mean HU-value, decreased from 70.5-59.5 ($p<0.001$) and from 67.2-55.8 ($p<0.001$) in the ascending and descending aorta respectively.

Study II: The analysis of variation (ANOVA) correlation coefficients for CTP vs. SPECT were 0.38 and 0.41 ($p<0.001$), for manual and automated segmentation respectively. Mean per patient CTP blood flow in normal segments varied between 94-183 ml/100 ml tissue/min for manual segmentation, and 104-196 ml/100 ml tissue/min for automated segmentation. The Spearman rank correlation coefficient for manual vs. automated segmentation CTP was $\rho=0.88$ ($p<0.001$) and the Intraclass Correlation Coefficient (ICC) was 0.93 ($p<0.001$).

Study III: The Spearman rank correlation coefficient for cFFR vs. invFFR was $\rho=0.77$ ($p<0.001$) and the ICC was 0.73 ($p<0.001$). Sensitivity, specificity, positive predictive value and negative predictive value for significant stenosis (FFR<0.80, per vessel) were 0.83, 0.76, 0.56 and 0.93 respectively.

Study IV: The hazard ratio for non-obstructive CAD vs. normal coronary arteries was 5.13 (95% C.I 1.03-25.43, $p<0.05$), and 151.40 (95% C.I 37.03-619.08, $p<0.001$) for obstructive CAD vs. normal coronary arteries. The three-year incidence of MACE was 1.1% for patients with normal coronary arteries on CCTA,

2.5% for patients with non-obstructive CAD and 42.7% for patients with obstructive CAD ($p<0.001$).

The three-year incidence of readmission for stable angina or chest pain after CCTA was 8.6%, 15.4% and 46.3% for normal coronary arteries, non-obstructive CAD and obstructive CAD respectively.

Conclusions

Study I: The perceived image quality and image noise in low dose images were significantly improved with the application of a 2-D, non-linear adaptive noise reduction filter, even though the improvement was small compared to the image quality of the corresponding full-dose images.

Study II: Correlation between dynamic CTP and SPECT was positive but weak. There were large variations in CTP blood flow in normal segments on SPECT, rendering the definition of an absolute cut-off value for normal vs. ischemic myocardium difficult. Manual and automatic segmentation were equally useful.

Study III: The correlation between cFFR and invFFR was good, indicating that noninvasively estimated cFFR performs on a similar level as invasively measured FFR.

Study IV: The long-term risk for MACE was very low in patients with non-obstructive CAD on CCTA, even though there seemed to be a substantial increase in the risk for MACE in patients with non-obstructive CAD as compared to normal coronary arteries. In addition, even patients with normal coronary arteries or non-obstructive CAD continued to have a substantial number of readmissions for chest pain or angina pectoris.

LIST OF PAPERS

This thesis is based on the following original papers, referred to in the text by their Roman numerals:

- I Jakob De Geer**, Michael Sandborg, Örjan Smedby, Anders Persson:
The efficacy of 2-D, non-linear adaptive noise reduction filtering in cardiac imaging: a pilot study
Acta Radiol 2011; 52: 716–722.
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- II Jakob De Geer**, Marcus Gjerde, Lars Brudin, Eva Olsson, Anders Persson, Jan Engvall:
Large variation in blood flow between left ventricular segments, as detected by Adenosine stress dynamic CT perfusion
Clin Physiol Funct Imaging 2015 Jul;35(4):291-300.
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- III Jakob De Geer**, Mårten Sandstedt, Anders Björkholm, Joakim Alfredsson Magnus Janzon, Jan Engvall, Anders Persson:
Software-based in-house estimation of fractional flow reserve using standard coronary CT angiography data
Acta Radiol 2015; doi:10.1177/0284185115622075
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- IV Mårten Sandstedt, Jakob De Geer**, Jan Engvall, Anders Persson, Joakim Alfredsson:
Long-term outcome of real-life patients with chest pain of unknown origin undergoing coronary computed tomography angiography (manuscript)

ABBREVIATIONS

2-D	Two-dimensional
3-D	Three-dimensional
AEC	Automatic Exposure Control
AHA	American Heart Association
ALARA	As Low As Reasonably Achievable
ANOVA	ANalysis Of Variance
AP	Angina Pectoris
BPM	Beats Per Minute
CAD	Coronary Artery Disease
CAT	Computed Axial Tomography
CCTA	Coronary Computed Tomography Angiography
cFFR	CT-based Fractional Flow Reserve
cMR	cardiac Magnetic Resonance tomography
CT	Computed Tomography
CTDI	Computed Tomography Dose Index
CTP	Computed Tomography Perfusion
Cx	Circumflex coronary artery
DAP	Dose Area Product
DNA	DeoxyriboNucleic Acid
DLP	Dose Length Product
DECT	Dual Energy Computed Tomography
DeFACTO	Determination of Fractional Flow Reserve by Anatomic Computed Tomographic Angiography (study)
DSCT	Dual Source Computed Tomography
EMI	Electric and Musical Industries Ltd
FAME	Fractional Flow Reserve Versus Angiography in Multivessel Evaluation (study)
FFR	Fractional Flow Reserve
Gy	Gray
HR	Hazard Ratio
HU	Hounsfield Unit
ICA	Invasive Coronary Angiography
ICC	Intraclass Correlation Coefficient

invFFR	Invasively measured Fractional Flow Reserve
kV	kiloVolt
LAD	Left Anterior Descending coronary artery
mA	milliAmpere
mAs	milliAmpere x seconds
mL	milliLitre
mSv	milliSievert
MACE	Major Adverse Cardiac Event
MI	Myocardial Infarction
MPR	MultiPlanar Reconstruction (or Reformatting)
MRT	Magnetic Resonance Tomography
mSv	milliSievert
NXT	Analysis of Coronary Blood Flow Using CT Angiography: Next Steps (study)
PCI	Percutaneous Coronary Intervention
PET	Positron Emission Tomography
PLATFORM	Prospective Longitudinal Trial of FFRct: Outcome and Resource IMpacts (study)
PTP	Pre-Test Probability
QCA	Quantitative Coronary Angiography
RCA	Right Coronary Artery
ROC	Receiver Operating Characteristic
ROI	Region Of Interest
SCAAR	Swedish Coronary Angiography and Angioplasty Registry
SCAPIS	The Swedish CARDioPulmonary BioImage Study
SCCT	Society of Cardiovascular Computed Tomography
SPECT	Single-Photon Emission Tomography
STEMI	ST-Elevation Myocardial Infarction
Sv	Sievert
SWEDEHEART	Swedish Web-based system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (registry)
TAG	Transluminal Attenuation Gradient
VGA	Visual Grading Analysis

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BACKGROUND

Historical background

X-ray tomography, the word itself derived from the Greek word “*tomos*” (slice or plane), refers to the sectional imaging of a plane, as opposed to conventional x-ray imaging where all structures between the x-ray tube and the detector are superimposed upon each other. The concept of x-ray tomography is almost as old as the discovery of x-rays itself, with the basic principles being developed during the 1910s and early 1920s. The first patent was registered in 1921 by the French physician André-Edmund-Marie Bocard but it was not until the 1930s that the technique came into more widespread clinical use, most notably in the hands of Italian radiologist Alessandro Vallebona (2). The technique was further developed during the following decades, eventually paving the way for the development of computed axial tomography (CT or CAT). The concept of CT was developed during the 1960s by, among others, William H. Oldendorf, Alan Cormack and Godfrey Hounsfield and culminated with the introduction of the first commercial CT-scanner, the so-called "EMI-scanner" (Fig. 1), in 1971 (3).

Fig. 1 EMI-scanner no.1 on display at the Science Museum, London, England. Photo by Jakob De Geer.

The EMI-scanner was limited to scanning of the head only, but body scanning was introduced soon after by dr. Robert S. Ledley, with the so-called Automated, Computerized, Transverse Axial (ACTA) scanner in 1973 (4). These early scanners were single-step scanners and far too slow for imaging of moving organs such as the heart (although the EMI-scanner was actually designed with dual detector rows). However, the introduction of spiral CT in general (in the early 1990s), and multi-slice spiral CT in particular (late 1990s) provided the technological basis for the development of scanners that were fast enough for accurate imaging of the heart and, more importantly, the coronary arteries. The first description of coronary CT angiography (CCTA) was published in 1995 (5), although in the beginning only the proximal parts of the coronary arteries were possible to visualise as both temporal and spatial resolution were still too low.

Since then, CT technology has evolved rapidly, but even with modern scanners it has been necessary to compensate for the lack of temporal resolution by decreasing the heart rate through the use of beta-blockers. However, today's fastest scanners have a temporal resolution of 66 milliseconds which in many cases makes it possible to visualise the coronary arteries without the use of beta blockers.

Methods for visualising coronary arteries

Invasive Coronary Angiography (ICA)

Invasive coronary angiography (ICA) has for a long time been the method of choice for visualising the lumen of the coronary arteries, in order to assess the need for surgical or intravascular intervention. A small catheter is introduced via the femoral or radial artery and placed in the ostium of the relevant coronary artery. An iodine-containing contrast agent is injected in order to visualise the coronary arteries and evaluate the presence or absence of significant stenosis. Conventional ICA only depicts the lumen of the coronary artery in two dimensions at a time, although different projections are used, and sometimes simultaneously acquired using biplane systems. There is little information about intra-mural atherosclerotic plaques or their composition, and there is also no detailed information about the surrounding tissues. If a significant stenosis is found, there is usually an option to perform percutaneous coronary intervention (PCI), where a catheter is introduced into the coronary artery and a small balloon is used to dilate the vessel. In most cases, a stent is inserted into the stenotic area after dilatation, to ensure that the artery remains patent.

However, research has shown that visual assessment of coronary artery stenoses of intermediate severity during ICA may not always be accurate and the concordance between different interventionists may also be poor (6,7). More recent data from the FAME study also showed that the functional severity of a stenosis was difficult to judge from angiographic images alone (8).

An additional technique for the evaluation of coronary stenoses is the use of Quantitative Coronary Angiography (QCA), where a quantitative component is added to the visual evaluation of a stenosis. However, like conventional coronary angiography, QCA is still limited by the 2-D-representation of a 3-D structure (9).

ICA is an invasive technique and apart from the use of contrast agent, it also carries a small but not negligible risk of adverse effects such as arterial wall dissection and arrhythmias (10,11). The reported average radiation dose is 7 milliSievert (mSv) for diagnostic ICA, but average doses of up to 15.8 mSv have been reported (12).

Cardiac Computed Tomography Angiography (CCTA)

The heart is one of the most difficult organs to visualise with CT because of its constant movement. This is especially true for the systolic phase when the ventricles with a rapid movement eject the blood into the receiving blood vessels. The heart moves the least during the middle and end of the diastolic phase and previous studies have shown that optimal overall image quality is obtained at approximately 60-65% of the R-R-interval (13), when heart motion is at its minimum (14). Also, contrary to most body tissues, perfusion of the myocardium takes place primarily during the diastolic phase, at which time the flow in the coronary arteries is at its maximum (15). Thus, CT imaging of the heart and the coronary arteries is best performed during diastole, but the short time available makes rapid image acquisition essential in order to obtain acceptable image quality. Image acquisition is usually ECG-modulated, with either prospective or retrospective gating. Prospective gating utilises sequential radiation with image acquisition during a pre-determined phase only. This facilitates a low radiation dose but the method also becomes more sensitive to irregular cardiac rhythm. Retrospective ECG-gating utilises continuous radiation, usually with ECG-modulated dose levels during different phases of the cardiac cycle, and is thus a more robust method. Apart from the coronary arteries, the use of continuous radiation also facilitates the evaluation of ventricular and valvular movement throughout the cardiac cycle, although it also increases the radiation dose manifold

(16). Although native images can be used for calcium scoring (17), iodine contrast agent is required for the visualisation of the coronary arteries.

During the last decade, CCTA has become a viable alternative to conventional angiography for diagnostic imaging of the coronary arteries (18). Current guidelines recommend that CCTA is to be used primarily in cases with low-to intermediate pre-test probability (PTP) of coronary artery disease (CAD). When performed with the appropriate indication, it is a clinically useful tool with high sensitivity and high negative predictive value (19,20). However, CCTA is currently not recommended in cases with a high PTP, as this patient category may have more to gain from conventional ICA (21-23). Despite several studies, the long-term prognostic value is not entirely clear, although a normal result on CCTA seems to indicate a good prognosis (24-28).

Compared to conventional angiography, CCTA has a number of advantages such as its non-invasive nature and the possibility to extract additional anatomical and physiological information from the image material. Also, the use of multiplanar reconstruction (MPR) enables image evaluation in three dimensions. More recent advances include the possibility to perform dynamic perfusion scans (CTP) as well as estimating the fractional flow reserve (FFR), i.e. the flow/pressure drop over a stenosis, thereby estimating stenosis significance.

Effective patient dose has steadily decreased with the emergence of better scanners and in optimal conditions, the effective patient dose can stay well below 1 mSv (29-31). However, with retrospective gating the dose is generally in the range of 8-10 mSv (16,32).

The main draw-back as compared to conventional angiography is the inherent inability to perform intervention. Hitherto, there has also been a tendency for stenosis overestimation as compared to conventional coronary angiography (18,33).

Functional methods for evaluating coronary artery disease

Fractional Flow Reserve (FFR)

Apart from the methods described above, additional information on stenosis significance can be obtained by measuring the pre-and post-stenotic intracoronary pressure during maximum vasodilatation, the quotient of which is referred to as the

fractional flow reserve (FFR). In practice, the pre-stenotic pressure is measured in the aorta.

The concept of FFR was first described in 1993 (34,35) and subsequent studies have shown that a stenosis with $FFR \leq 0.75$ almost always induces ischemia, while a stenosis with $FFR 0.75 - 0.80$ is in more of a “grey zone” area in terms of significance (36-38). Stenoses with FFR of 0.80 or more rarely induce myocardial ischemia. It has also been shown that atheromatous changes in the arterial wall can induce a significant reduction of FFR, even in the absence of a discrete stenosis (39). Thus FFR provides the interventionist with additional information on stenosis significance and a relatively clear cut-off value, thus aiding in the decision-making on whether to perform PCI.

Measuring FFR is an invasive procedure which requires an additional passage with a special pressure sensor-equipped guide wire, and also the use of additional radiation, contrast agent and intracoronary or intravenous Adenosine.

Basic theory

FFR is defined as the as the ratio of maximal myocardial blood flow in a diseased artery as compared to the flow as it would be in the same artery if it was normal (34,36). Although difficult to measure in practice, it has been shown that the blood flow can be approximated by measuring the intravascular pressure, according to the formulas below (40). The basic assumption that has to be made is that the coronary resistance is constant and minimal, allowing for the resistance to be taken out of the equation, as described below :

$$FFR = \frac{Q_S^{\max}}{Q_N^{\max}}$$

where $Q_S^{\max}$ is the maximum flow in the stenotic area, and $Q_N^{\max}$ is the maximum flow in the normal artery.

Flow (Q) can be expressed as the quotient between the pressure difference and resistance, yielding the formula:

$$FFR = \frac{[(P_d - P_v)/R_S^{\max}]}{[(P_a - P_v)/R_N^{\max}]}$$

where P_d is the pressure in the coronary artery distal to the stenosis, P_a is the pressure in the aorta and P_v is the venous pressure. At maximum vasodilatation, the resistances are assumed to be equal, and thus cancel out:

$$\text{FFR} = \frac{(P_d - P_v)_S^{\max}}{(P_a - P_v)_N^{\max}}$$

Venous pressure is considered to be negligible as compared to arterial pressure.

Thus:

$$\text{FFR} = \frac{P_d}{P_a}$$

CCTA-based FFR estimation (cFFR)

In fluid dynamics, the so-called Navier-Stokes equations are used to calculate the flow of fluids and gases (41,42). The Navier-Stokes equations are derivatives of Newtons second law of motion (“The acceleration of an object as produced by a net force is directly proportional to the magnitude of the net force, in the same direction as the net force, and inversely proportional to the mass of the object”) and hence relate to the conservation of mass and momentum. Their use is widespread and applications can be found in as disparate areas as aeronautical design and, as in this case, intra-arterial blood flow. However, the Navier-Stokes equations can be solved analytically only when under ideal circumstances such as in steady flow or in an ideal vessel. In more realistic circumstances, the equations must be solved numerically (i.e. computationally), in order to approximate velocity and pressure. This is done by simultaneous, time-resolved computation of a huge number of differential equations, typically requiring equally vast computer power (42,43).

The CCTA-based computation of blood flow requires that a domain of interest is defined and that boundary conditions, or mathematical relationships between the variables of interest at the boundaries of that domain, are established. The domain of interest when computing coronary artery flow is the arterial lumen and the relevant boundaries are the vessel walls, the inlet (aortic root) and the outlets (the distal end of the coronary arteries and the ascending aorta) (42-44). The hyperemic state induced by adenosine in invFFR must also be simulated.

Single Photon-Emission Computed Tomography (SPECT)

In spite of other emerging technologies, SPECT is still the most widely used method for visualising myocardial perfusion. SPECT is a nuclear medicine method combining a gamma camera with tomographic imaging, allowing for a 3-D presentation of the results. It is performed by injecting a radionuclide labeled carrier molecule into the bloodstream, which is subsequently deposited in the target organ. The gamma rays emitted by the radionuclide are detected, with imaging taking place approximately 30-60 minutes after radionuclide administration (45,46). The most common radionuclide used for myocardial perfusion imaging today is ^{99m}Tc Technetium (^{99m}Tc), although older radionuclides such as Thallium (^{201}Tl) may also be used. Commonly used carrier molecules are ^{99m}Tc -2-methoxyisobutylisonitrile (Sestamibi/Cardiolite®) or ^{99m}Tc -1,2-bis[bis(2-ethoxyethyl) phosphino]ethane (Tetrofosmin/Myoview®). These substances are transported over the cell membrane and deposited in the mitochondria (47,48). The relationship between myocardial blood flow and tracer uptake has been shown to be fairly linear within the range of normal resting coronary flow, although with a flat gradient which makes quantitative differentiation difficult. Uptake rolls off when flow exceeds approximately 200 ml/100 ml tissue /min. Thus, at higher flow SPECT tends to underestimate the uptake in relation to the blood flow. Conversely, at very low flow (<20 ml/100g tissue/min) SPECT is reported to overestimate the uptake in relation to the blood flow, possibly because of a more effective tissue extraction (48,49). Also, in damaged but still viable myocardium, SPECT with tetrofosmin has been reported to overestimate perfusion deficits in relation to blood flow as measured by quantitative ^{15}O -water PET, probably due to reduced viability of the ion pumps (Na^+/H^+) in the cell membrane (50).

Since a stenosis of 80-85% is required for the detection of significant perfusion deficiency at rest (51,52), myocardial SPECT usually needs to be performed as a stress exam, using either pharmacological stress or exercise testing. If the stress exam is normal, no further imaging is necessary. However, if uptake deficiencies are visualised in the myocardium during stress, further imaging under resting conditions is needed in order to differentiate between CAD-induced hypoperfusion and manifest infarction. In Sweden and many other countries, it is common practice to perform myocardial SPECT as a 2-day protocol, but under certain conditions it is also possible to perform both exams in one day (45).

The evaluation of myocardial SPECT is most frequently visual, although computers are used for display of various cut planes as well as polar maps. A semi-quantitative approach is also possible, with segmental perfusion being expressed as a percentage of the highest recorded uptake in that particular exam. The lack of

quantitative data means that extensive three-vessel disease, with so-called balanced ischemia in the entire myocardium, might go unnoticed (53).

Perfusion imaging CT (CTP)

A number of different methods for evaluating myocardial perfusion using CT have been proposed (54). These include the use of so-called late enhancement, where imaging is performed after a pre-determined time delay, usually 5-15 minutes (55) after contrast injection. At this time point, most of the contrast agent has been washed out from healthy myocardium whereas the decreased vascularity in infarcted areas causes pooling of the contrast agent. Another proposed method is single shot, first-pass image acquisition during the contrast inflow phase, where hypoperfused areas will show less attenuation than the surrounding, normally perfused myocardium. With this method, timing is essential as the time window for optimal contrast between normal and ischemic myocardium only lasts for approximately 8 seconds (56).

A third method, which has become feasible with the emergence of scanners with higher temporal resolution and more advanced acquisition protocols, is dynamic CTP imaging. With dynamic CTP, myocardial perfusion is visualised through repeated imaging during the first pass contrast inflow in the myocardium. The change in myocardial attenuation during this period is detected and forms the basis for a quantitative estimation of myocardial blood flow (57-61). There are a number of critical pre-requisites for this approach: the scanning of the left ventricle must be fast to be able to detect the short-lived phase of increase in attenuation that comes with the wash-in of contrast, and the x-ray detector has to be large enough to allow coverage of the entire heart.

CT-based methods have a number of advantages when compared to MR and SPECT. The short acquisition time reduces the risk of motion artefacts, and there are no restrictions or contra-indications to the method in itself (although there may be to the use of iodinated contrast agent and Adenosine). The rapid image acquisition in combination with a short and comparatively wide gantry is useful when examining patients with claustrophobia. It is also possible to combine CT perfusion imaging with other types of exams, such as a standard CCTA scan.

Perfusion imaging MR

In analogy with CT perfusion imaging, Cardiac MR (cMR) perfusion imaging can be performed using either a Gadolinium-enhanced first-pass imaging protocol, or a late enhancement protocol with image acquisition at approximately 10-20 minutes after Gadolinium administration. MR imaging with ECG-gating also allows for extensive evaluation of ventricular movement throughout the cardiac cycle. Apart from general MR-related restrictions regarding pacemakers and metallic implants, the main drawbacks are the long exam times which increases the risk of motion artefacts and patient claustrophobia.

Exercise testing

Although not an imaging method, the use of exercise testing is still a clinically important method when evaluating coronary artery disease. The reproducibility of symptoms during exercise in combination with other parameters, such as ECG-reaction, work capacity, heart rate and blood pressure, yield important information about the presence and extent of coronary artery disease, and also about its functional impact.

Basic X-ray theory

X-rays are a form of electromagnetic radiation, with wavelengths in the range 0,01-10 nanometers (nm) and a frequency between 3×10^{16} and 3×10^{19} hertz, placing them in between ultraviolet light and γ -radiation in the electromagnetic spectrum. The production of x-rays, for CT as well as conventional X-ray imaging, relies on the conversion of the kinetic energy attained by electrons being accelerated under the influence of a potential difference, to electromagnetic radiation. This process takes place in the x-ray tube where an electron cloud is built up through intense heating of a negatively charged cathode. During exposure, a high voltage ("tube voltage"), typically ranging between 50 and 150 kilovolt (kV) for CT, is applied and the electrons are accelerated towards the positive anode. The number of electrons that travel between the cathode and the anode defines the tube current, with 6.24×10^{15} electrons per second equaling 1 milliAmpere (mA). The formation of x-rays occur when the electrons to a variable degree decelerates in the vicinity of the positively charged nuclei of the anode material (usually tungsten). The kinetic energy of the electrons is converted to electromagnetic radiation through a process

known as “bremsstrahlung”, the resulting energy for each electron being dependent on the distance to the nucleus at the point of interaction. Thus, the resulting x-ray energies are all different and are presented as a spectrum (62).

Medical aspects of X-rays

X-rays belong, alongside α -, β - and γ -radiation, to the ionising kind of electromagnetic radiation. This means they have the capability to alter the electron layers of an atom, thereby converting it into an ion. When this happens in a cell, the result may be alterations in the cell DNA. Usually, these damages will be repaired but in a small number of cases they might lead to more pronounced biological damage. This damage can be either deterministic, where the damage is foreseeable and proportional to the degree of exposure, or stochastic, where exposure may or may not lead to biological damage such as cancer. The risk of biological changes is the main reason for minimising patient dose in any x-ray-based exam, and the basic principle of “As Low As Reasonably Achievable” (ALARA) is generally applied every time an x-ray-based exam is considered.

The generally accepted theory of the relationship between low-dose radiation (<100 mSv) and adverse health effects is the so-called linear, no-threshold model, which states that the relationship between dose and the risk of cancer is linear and without threshold. Thus, even a very low dose is considered to be potentially harmful (63,64). However this model is debated and several authors question its legitimacy (65,66).

Dose estimation on CT and conventional X-ray

For the individual patient, there is no practical way of determining the exact dose deposited during a particular exam. Instead, all clinically obtained dose data are estimates, although partially based on different kinds of measurements (67).

For CT, the basic unit for estimation of dose (D) is the Computed Tomography Dose Index (CTDI, mGy). CTDI is established for every CT scanner through the use of dosimeter-equipped phantoms and is, through a series of steps, used to calculate the dose length product (DLP) (68). The total DLP (DLP_{tot}) is the sum of the DLP of all series in one exam. The effective patient dose (E) is then estimated by multiplying DLP_{tot} with a body-part specific coefficient E_{DLP} (mSv/mGy×cm) using the formula:

$$E = E_{DLP} \times DLP_{tot} \text{ (mSv)}$$

The value of E_{DLP} has varied over time but is generally estimated to 0,014 or 0.018 for the thorax (69,70), although some authors consider a significantly higher value of 0.030 to be appropriate for CCTA (71). Hence, the effective dose E is an estimate which takes into account the location and radiosensitivity of the irradiated tissue. Effective dose (E) is measured in joules per kilogram (J/kg), and the SI unit in this particular case is named Sievert (Sv).

For conventional x-ray, including angiography, the stated dose is an estimate based on the so-called Dose-Area Product (DAP, $Gycm^2$) which is the dose as measured by an ionisation chamber at the level of the x-ray tube. This value is multiplied by an organ-specific coefficient (E_{DAP} , $mSv/Gycm^2$) to yield the estimated dose deposited in that particular organ. For coronary artery angiography, $E_{DAP} = 0,18 Gycm^2$ (72).

Image quality and strategies for reducing dose in CT

In technical terms, CT image quality is based on four different factors: image contrast, image spatial resolution, image noise and artefacts (73,74).

Image noise is due to random fluctuations around the average measured CT value (or Hounsfield Unit-value, HU), and is hence proportional to the standard deviation of this value. Its magnitude is dependent on the number of photons that contribute to the formation of the image and is thus affected by the tube current, the scan time, the slice thickness and the tube voltage. Thus, for any reduction of image noise, there is usually a trade-off in the form of increased dose.

However, the radiation dose necessary for adequate image quality has steadily decreased with the introduction of different dose reduction measures and more sophisticated detectors which generate less noise. A number of different technical solutions are presented below. Although not the focus of this thesis, patient positioning also plays a crucial role (75,76).

Automatic exposure control

Automatic exposure control (AEC) is a standard feature on most modern CT scanners. AEC can be performed in an angular and/or longitudinal fashion and usually involves adjustment of the tube current in order to compensate for irregular patient size and shape, and for the variable density/attenuation of the human body.

Background

It has been shown that AEC can reduce the necessary dose with 20-30% while retaining sufficient image quality for diagnosis (77).

Detector development

The dose efficiency of a detector depends on the ability to capture and detect as large a proportion as possible of the primary x-rays exiting the patient. To achieve this, both the geometric efficiency of the scanner/detector and the absorption efficiency of the detector elements need to be considered. Electrical noise also needs to be addressed and kept at a minimum (73).

Dual source CT (DSCT) and High-pitch protocols

The introduction of dual source CT scanners in 2005 (78), allowed for a much higher temporal resolution (79) and paved the way for the use of high-pitch protocols which were able to cover the entire heart in just one heartbeat. Before that, a typical CCTA would yield an average effective dose of up to approximately 16 mSv dose (12). However, with a high pitch of >3 it has been possible to reduce the dose to sub-mSv levels when the circumstances are optimal (30,31).

Iterative reconstruction

Iterative reconstruction is based on repetitive comparisons between estimated and measured image data, which results in decreased image noise and less artefacts as compared to the more commonly used filtered back projection technique (80-82). Reconstruction can be performed on raw data, on image data, or on both, with a potential dose reduction of approximately 30-70% depending on the technique (83-85). Since the process requires more computer power than filtered back projection, it has not reached clinical use until relatively recently. However, simplified algorithms in conjunction with advances in computer technology have led to a more widespread use.

Noise reduction filters

Filtering solutions include 2-dimensional and 3-dimensional adaptive noise reduction filters, which have been shown to be able to facilitate a significant dose reduction for a number of different applications. In essence, adaptive non-linear filters work by estimating the local orientation in each pixel (2-D) or voxel (3-D), and letting this determine the degree of smoothing applied in that particular pixel/voxel.

Methods for evaluating image quality

There are several methods available for the assessment and quantification of image quality. Perhaps the most accurate form is Receiver Operating Characteristic (ROC) analysis. ROC analysis has its roots in signal detection analysis where the detection of low contrast signals against a noisy background is described (86). In the image quality context, this is translated into the measurement of the observers' ability to detect a certain lesion in the image. However, the images can only be categorised as normal or abnormal, and there are also difficulties in handling multiple lesions in the same image. Thus, the image data set has to be carefully selected accordingly.

A more convenient way is the use of visual grading analysis (VGA), which is based on the assessment of important anatomical structures, either with (relative VGA) or without (absolute VGA) a reference image. Image quality is graded depending on the extent to which a particular anatomical structure is evaluable, and assessment is often based on an established standard such as the European Guidelines for Image quality (70). The basic assumption that has to be made is that the visibility of normal anatomical structures correlates with the detectability of pathological lesions (86,87).

HYPOTHESES AND AIMS

The overall focus of this thesis has been the exploration of potential methods of improving the diagnostic yield of CCTA. These include image quality improvement and different functional applications, but also evaluation of the long-term prognostic value of CCTA. The specific hypotheses and aims for each study are presented below.

Hypotheses

- I That the image quality of low-dose CCTA images can be improved by the use of a 2-dimensional, non-linear adaptive noise reduction filter.
- II That adenosine stress dynamic CT perfusion blood flow values correlate to myocardial blood flow as visualised by ^{99m}Tc SPECT. Secondly, that automated segmentation of the myocardium according to the AHA 17-segment model corresponds to manual segmentation, in terms of CTP blood flow.
- III That noninvasive computed fractional flow reserve (cFFR) values correspond to invasively obtained measurements.
- IV That patient prognosis in terms of major adverse cardiac events (MACE) varies depending on the presence or absence of atheromatosis as well as of obstructive CAD on CCTA.

Aims

- I To investigate whether the use of a 2-D, non-linear adaptive noise reduction filter can improve image quality in cardiac computed tomography angiography.
- II To evaluate the variation in adenosine stress dynamic CTP blood flow as compared to ^{99m}Tc SPECT. Secondly, to compare per-segment CTP perfusion results from manual and automatic myocardial segmentation.

Hypotheses and Aims

- III** To evaluate the degree to which noninvasive cFFR derived from CCTA agrees with invasively obtained FFR.
- IV** To evaluate the prognostic value of CCTA in terms of MACE, depending on the presence or absence of atheromatosis and/or obstructive CAD.

MATERIALS AND METHODS

All studies were performed at Linköping University Hospital, using image data collected at CMIV/Department of Radiology. Additional clinical data, when required, was acquired from the Radiology Information System (RIS), the patient medical records, the SWEDEHEART/SCAAR medical quality registry (88), and from the Patient- and Cause-of-death-registries of the National Board of Health and Welfare (Socialstyrelsen).

Ethical aspects

All studies in this thesis were conducted according to the principles set forward in the declaration of Helsinki, and according to Swedish law and Good Clinical Practice. Permission was obtained from the regional ethical review board in study II-IV.

Study I was conducted as a dedicated image quality study, using anonymised single images from previously performed clinical exams. No extra radiation was added, and no further diagnostic evaluation was performed. Thus, no ethical permit was required according to the standard procedure at the time.

Study II (ethical permit Dnr M207-08) involved exposure to rather high radiation doses from both CT and SPECT. Radiation dose was kept at a minimum, but the patients were still exposed to approximately twice the amount of radiation required for clinical purposes. They also received additional iodinated contrast agent, Adenosine and radionuclides. Informed consent was obtained from the patients at inclusion, and they were free to withdraw from the study at any time.

Study III (ethical permit Dnr M6-09 with amendment 2013/278-32), utilised image data from previously performed, clinical CCTA exams. There was no additional imaging and all included patients had already been examined using the relevant gold standard. All patients were included in the SWEDEHEART registry and had thus agreed in general to their image and clinical data being used in future studies. Hence, informed consent for this study was waived.

Study IV (Dnr M6-09 with amendments Dnr 2013/278-32 and 2015/112-32) was conducted using registry data from a large number of patients, some of which was anonymised. All patients were included in the SWEDEHEART medical quality registry and had agreed in general to their data being used for research. Thus, informed consent was waived.

Study design

Study I is a retrospective experimental image quality study, using image data from consecutive CCTA exams performed during a period of one month..

Study II is a prospective experimental study on specifically selected patients, evaluating the novel technology of dynamic CT perfusion imaging.

Study III is a retrospective experimental study, evaluating the performance of CCTA-based FFR estimation.

Study IV is a retrospective, large scale observational study on prospectively collected data, evaluating the prognostic value of CCTA in relation to cardiac-related morbidity, mortality, intervention and hospital admission.

Patient populations

Patients included in study I and III-IV come from a cohort of 3038 clinical CCTA performed at CMIV and Linköping University Hospital between July 1 2007 and December 14 2014. Patients in study II were examined for research purposes only. Some patients may appear in two or more of the included studies, although no attempt has been made to further explore to what extent this is the case. Study I, III and IV were retrospective and used only already available image data from clinical exams. Thus, no further radiation or contrast agent was given to the patients included in these studies.

Study I

In study I, 47 consecutive CCTA exams, performed during one particular month in early 2008, were evaluated for inclusion. A total of eleven cases were excluded due

to the image material not conforming with the study protocol, leaving 36 cases in the study (Fig. 2).

Fig. 2. Patient selection, study I

Study II

In study II, the participating patients were carefully selected from a post infarction population attending the cardiac out-patient clinic at Linköping University Hospital. The relevant exams were performed between May 2009 and March 2011.

The participants were included specifically for having a history of at least one ST-elevation myocardial infarction (STEMI) with subsequent PCI, where at least one significant stenosis had been left untreated. A total of 17 patients with these particular prerequisites were identified and examined but due to technical and methodological difficulties, only eight exams were deemed readable. The exclusion process is described in Fig. 3.

Fig. 3. Patient selection, study II

Study III

In study III all CCTA examinations performed on one particular CT scanner between September 2009 and March 2012 (n=1396) were surveyed for inclusion. Eligible patients were those who had been referred to invasive angiography within 120 days of a CCTA, and where invFFR had been measured in one or more of the main epicardial arteries (except in the left main artery). In all, 63 patients with invasive FFR measurements in 71 vessels were identified. A total of 42 patients/48 vessels were excluded, the most common reason being the lack of angiographic images depicting the pressure guide wire position (21 patients/22 vessels). After further exclusions (Fig. 4), the final sample consisted of 23 FFR measurements in 21 patients.

Fig. 4. Patient selection, study III.

LAD = Left anterior descending coronary artery. Cx = Circumflex coronary artery, RCA = Right coronary artery.

Study IV

All CCTA exams in the study performed at CMIV/Linköping University Hospital between July 1 2007 and December 31 2014 (N=3038) were evaluated for participation in the study.

Patients with a known previous history of coronary heart disease and/or intervention were excluded, as well as all patients where CCTA was performed with other cardiac-related indications, such as valvular disease or arrhythmia (n=1668). All exams where image quality was deemed inadequate were also excluded (n=144). Since the aim was to investigate patients with no known previous history of coronary artery disease, exams where the patient had been through a previous CCTA were also excluded, except when a second exam was performed due to inadequate image quality at the first attempt. Thus, the final study population consisted of 1205 previously not examined patients, who were all referred for examination due to chest pain of unknown origin (Fig. 5).

Fig. 5. Patient selection, study IV.

Image acquisition

Four different CT scanners were used throughout the study period: one 64-slice dual source CT (Somatom Definition, Siemens, Forchheim, Germany, 2007-2009) and two 128-slice dual source scanners (SOMATOM Definition FLASH and Definition FLASH with Stellar detector, Siemens, Forchheim, Germany, 2009-2012 and 2012-2014 respectively). The last few months of the study period, a 192-slice dual source scanner was used (SOMATOM Force, Siemens, Forchheim Germany).

However, only study IV contains results from different scanners. In study II, patients also underwent a SPECT-exam and a dedicated dynamic CTP exam.

Study I

For the 64-slice dual source CT-scanner used in study I, the standard protocol included ECG-modulated tube current and retrospective ECG-gating, with different settings depending on body mass (ref. mAs 380, 100 kV, pitch 0.29 for patients < 90 kg and ref. mAs 310, 120 kV, pitch 0.25 for patients > 90kg; rotation time 0.33 s). Due to the clinical nature of the material, protocol selection was somewhat inconsistent, with the 120 kV protocol being used in six patients weighing less than 90 kg. Thus, a total of 24 patients were examined with a 120 kV protocol (mean 87.8 kg, range 65-108 kg) and 12 with a 100 kV protocol (mean 68.5 kg, range 51-87 kg).

Study II

Although a CCTA was performed on all patients in study II, focus was on dynamic stress CT perfusion imaging. In order to obtain reference perfusion imaging alongside CTP, a stress and rest SPECT exam was also performed. No rest CTP imaging was performed. No beta blockers or Nitroglycerin were administered.

Image acquisition: CTP

CTP images were acquired using a dual source/dual energy CT scanner (Definition Flash, Siemens, Forchheim, Germany) in mono-energetic dynamic perfusion mode (ref. mAs 300, 100kV, rotation time 0.285 s).

A test bolus was used to determine the appropriate scan delay in relation to the contrast infusion (Fig. 6). The delay was initially set at 5 seconds less than the time needed for the bolus to reach the ascending aorta, but was changed to 8 seconds halfway through the study.

Fig. 6. Time-attenuation curves depicting the myocardial contrast inflow. Left: Imaging commences too late, and thus no baseline is visualised before contrast inflow. Right: Correct timing.

After the test bolus, a 5-minute Adenosine infusion ($140 \mu\text{g/kg/min}$) was started, with injection of $^{99\text{m}}\text{Tc}$ -tetrofosmin and iodinated contrast media, and subsequent CTP imaging commencing approximately 3 minutes later (Fig. 7).

Fig. 7. Graphic description of the stress CTP image acquisition process.

CTP data was obtained through alternate imaging of two 3.8 cm thick, slightly overlapping axial slabs every 2 seconds for at least 30 seconds, resulting in a total coverage over the heart of 7.3 cm.

Image acquisition: SPECT

After completion of the CTP scan, and approximately one hour after the injection of ^{99m}Tc -tetrofosmin and Adenosine, the patients underwent a standard-of-care stress SPECT scan in a 90° (“L-mode”) dual-head SPECT camera (Infinia Hawkeye, GE Healthcare, United Kingdom), as a part of a standard 2-day-protocol as described in the European Association of Nuclear Medicine guidelines (45). Projection data were collected at 30 angles/head (in total 180°), and 30 seconds per angle for both the stress and rest studies. The rest studies were performed 4-7 days after the stress studies

Study III

All exams included in study III were standard of care CCTA exams obtained with a 128-slice dual source CT scanner (Definition Flash, Siemens, Forchheim, Germany) in mono-energetic dual source mode. The standard protocol was either a prospectively ECG-gated common spiral protocol (ref. mAs 306, 100kV, pitch 0.17, rotation time 0.285 s), a prospectively ECG-gated high-pitch protocol (ref. mAs 324, 100kV, pitch 3.4, rotation time 0.285 s) or a retrospectively ECG-gated protocol (ref. mAs 306, 100 kV, pitch 0.17-0.38 depending on the heart rate, rotation time 0.28 s). Nitroglycerin was routinely administered, as were beta blockers to patients with a heart rate > 65 beats per minute (bpm).

Study IV

Four different CT-scanners were used in study IV. Standard protocols for the 64-slice DSCT and 128 slice DSCT scanners have been described above. For the 192-slice scanner, the standard protocol was a prospectively ECG-gated high-pitch protocol (ref. mAs 290, 100kV, pitch 3.2, rotation time 0.25 s) for patients with a stable heart rate below 60 bpm. A retrospectively ECG-gated spiral protocol (ref. mAs 276, 100kV, pitch 0.15-0.34, rotation time 0.25 s) was used for patients with heart rate > 60 bpm or irregular heart rhythm.

Image analysis***Study I***

From each exam, two single 0.75 mm images covering parts of the left main coronary artery were selected: one from the systolic, low-dose phase at 35% of the

Materials and Methods

R-R-interval, and one from the diastolic, full dose phase at 70% of the R-R-interval. The low-dose systolic image was duplicated and one copy subjected to post processing using a hardware based 2-D, non-linear adaptive noise reduction filter (SharpView™ CT, Sharpview AB, Linköping, Sweden), resulting in three images per patient and a total of 108 images.

The quality of the selected images were evaluated using absolute VGA in a visual grading software package (ViewDEX 1.0, University of Gothenburg, Sweden) (89). Image quality was independently assessed by nine radiologists evaluating five different parameters, resulting in 972 image assessments and 4860 different parameter evaluations (Fig. 8). Prior to assessing the actual study material, each participating radiologist assessed 21 images for the purpose of training and calibration. The perceived image quality was graded using a five-point scale for five different criteria, three of which were applicable parts of the European Guidelines for assessment of image quality (70). Another two criteria were constructed along similar lines for the purpose of this study.

Fig. 8. Example from Viewdex 1.0 visual grading software package. Grading of each image quality criteria was performed using a 5-grade scale.

Image noise was quantitatively evaluated by measuring the HU-value and its standard deviation (SD) in the ascending and descending aorta (Fig. 9).

Fig. 9. Attenuation and noise level/SD measured in ascending aorta, with full-dose (left), reduced dose (mid) and reduced dose with applied noise reduction filter (right) respectively. The region of interest is enhanced for the purpose of clarity.

Study II

Image analysis: CTP

CT images were manually post-processed in order to align them as closely as possible with the AHA 17-segment model (90) and the corresponding SPECT, and to extract per segment blood flow values (Fig. 10).

Fig. 10. Example of manual segmentation in one slice, with data on min/max/mean CTP blood flow. The left ventricular myocardium was manually divided into 10 similar slices and perfusion data was extracted for each AHA-segment in every slice.

Eventually, a dedicated software was made available (Syngo Cardiac Function Analysis, prototype 2012-07-12, Siemens Healthcare, Germany), providing automated segmentation according to the AHA 17-segment model (Fig. 11). Calculation of per segment blood flow was based on the same image data as the manual method previously described.

Image analysis SPECT

The dataset of the SPECT scan was reconstructed using filtered back projection and the images were evaluated according to clinical routine, including the creation of an AHA 17-segment polar map image for comparison (Fig. 12). The stress SPECT results were stratified, with intensity values of $\geq 70\%$ of maximum regarded as normal, values of 50-69% regarded as indeterminate and values of $< 50\%$ of the maximum intensity value regarded as pathological, in analogy with previously suggested stratification (45).

Fig. 11. Example of automated CT perfusion segmentation in the same patient as in Fig. 10.

Fig. 12. Stress SPECT polar map in the same patient as in Fig. 10 and Fig. 11.

Study III

In study III, standard 0.75 mm CCTA data sets were transferred to a standalone workstation equipped with a research prototype software (Siemens cFFR, versions 1.4 and 1.7; Siemens Healthcare, not commercially available). Vessel centerlines and luminal contours were automatically generated by the software but had to be manually adjusted in most cases. Atherosclerotic/stenotic vascular segments were identified and their extent manually defined. Based on this input, a patient-specific 3-dimensional mesh was constructed by the software (Fig. 13).

Applying the principles of computational fluid dynamics, the cFFR algorithm simulated the coronary blood flow, including the hyperemic state usually induced by adenosine in invasive FFR measurements. Additional data incorporated into the algorithm included blood pressure, heart rate and left ventricular mass. The result was presented as a colour map of the coronary vascular tree, with the points of cFFR estimation being freely adjustable.

The cFFR colour map was compared to the corresponding ICA pressure guide wire image. The exact point of invFR-cFFR comparison was determined by an expert cardiac interventionist (>5000 interventions), who was blinded to the cFFR segmentation process (Fig. 14).

Fig. 13. Overview of segmentation process, with the left anterior descending artery (LAD) in cross-sectional and curved MPR view, and the 3-D coronary tree mesh. Stenotic segments are manually defined. Vessel contours are automatically outlined but can be manually adjusted.

Fig. 14. Left: Angiographic image from the same patient as in Fig. 13, with pressure guide wire in the left anterior descending coronary artery (LAD). FFR = 0.81. Right: Corresponding cFFR colour map with cFFR = 0.82.

The time needed for the cFFR post-processing procedure was evaluated in a series of 11 additional cases.

Study IV

The basis for study IV was the clinical CCTA results, as reported to the SWEDEHEART registry. However, as the SWEDEHEART registry does not record the presence or absence of non-significant atherosclerotic changes in the coronary arteries, all 1370 CCTA studies initially included were re-evaluated by a qualified thoracic radiologist and the presence of non-obstructive CAD was confirmed or negated (Fig.15). No re-evaluation of already reported obstructive CAD was made.

Fig. 15. Left anterior descending coronary artery (LAD) in three different patients. Left: Normal vessel. Mid: Mild atheromatosis. Right: Proximal stenosis

Statistical analysis

Study I

Basic biometrical data on age and body weight was presented with mean and min/max values. The results of the visual grading were analysed using ordinal logistic regression (91), controlling for patient and observer identity. HU-values in the ascending and descending aorta were evaluated with Student's T-test.

Study II

Biometrical data on age, sex, body weight, body length and body mass index (BMI) were presented individually for each of the participating patients, and the mean and min/max values for the whole group were also reported. CTP for each segment was normalised according to the mean blood flow in the segments that were considered normal on SPECT (signal intensity $\geq 70\%$) for each particular patient. The correlation between SPECT intensity values and the manually and automatically obtained CTP percentages was calculated for each patient using repeated measures analysis of variance (ANOVA). The results were presented as a correlation coefficient based on the average result obtained in all 8 patients, with a confidence interval of 0.95.

The correlation between manually and automatically obtained per segment blood flow values was also calculated using ANOVA, followed by Duncan's post hoc test. The difference was further tested using Wilcoxon's matched pair test. In addition, the average all-segment global blood flow (taken as the sum of all segment blood flow values divided by 17) was calculated for both manually and automatically obtained values for each patient, and compared using Student's T-test.

For this thesis, Spearman's rank correlation and the Intraclass Correlation Coefficient (ICC) were also calculated for the comparison between manual and automated segmentation.

Study III

Biometrical data was presented with mean, median and min/max values. The agreement between cFFR and invFFR was expressed as an ICC, and the correlation as a Spearman's Rank correlation coefficient. A Bland-Altman plot displaying bias and limits of agreement was constructed. Sensitivity, specificity, positive predictive value, negative predictive value and accuracy of cFFR in predicting significant

stenosis (defined from the invasive procedure as both $\text{FFR} \leq 0.80$ and $\text{FFR} \leq 0.75$) were calculated per-vessel as well as per-patient, using invFFR as the reference. Inter- and intraobserver reproducibility measurements on the severity of the stenosis in terms of the smallest diameter was performed in a total of 10 cases. The results were expressed as an ICC.

Study IV

Continuous variables were presented as median and inter-quartile range (IQR). Categorical variables were presented as numbers and percentages. Differences between the three groups (normal coronary arteries, non-obstructive CAD or obstructive CAD) were evaluated with Kruskal-Wallis one-way ANOVA by ranks as appropriate for continuous variables, and χ^2 -test for categorical variables. Fischer's exact test was used in case of very few ($n < 5$) outcome values.

A time-to-event curve for obstructive CAD vs. non-obstructive CAD and normal coronary arteries were drawn using the Kaplan-Meier method and further analysed with the log rank test. A separate analysis was also performed for normal coronary arteries vs. non-obstructive CAD. Multivariate analysis for classical risk factors and CCTA findings was performed using Cox proportional hazard regression with backward elimination.

The three-year incidence of MACE and readmission due to stable angina pectoris or chest pain was calculated for patients with a follow up period of three years or more ($n=655$). Differences between groups were calculated with the combined groups of normal vessels and non-obstructive CAD versus the group with obstructive CAD, using the χ^2 -test and Fischer's exact test.

RESULTS

Study I

The results of the visual grading are summarised for each criterion in Fig. 16. For all five criteria, there was a significant improvement in perceived image quality when comparing post-processed low-dose images with low-dose images without post-processing ($p < 0.001$ except criterion 1 where $p < 0.01$). However, comparing full dose images with post-processed low-dose images resulted in a considerably larger, more significant ($p < 0.001$) difference for all image criteria.

Fig. 16. Results for reproduction of the thoracic aorta, thoracic aortic wall, the heart and the left main coronary artery respectively. Criterion 5 pertains to the overall image quality

Applying the 2-D noise reduction filter to the low-dose images reduced the average standard deviation of the mean HU-value from 70.5 to 59.5 in the ascending aorta ($p < 0.001$), and from 67.2 to 55.8 in the descending aorta ($p < 0.001$). The average standard deviation in the full-dose images was 35.2 in the ascending aorta and 34.6 in the descending aorta.

Study II

Of the eight patients to be analysed, five had a total of 21 segments where, due to limited coverage, less than 50% of the estimated volume was within the imaging slab. These segments, which mainly involved the anterior and antero-lateral walls, were excluded from the analysis. However, 115 out of 136 segments (85%) were still deemed available for analysis on both CTP and SPECT. Of these 115 segments, 50 were considered “normal”, with a signal intensity of $\geq 70\%$ of the max intensity value for each respective patient. The number of segments classified as “normal” varied between 1 and 8 per patient.

CTP showed a positive correlation with SPECT data with both manual and automated segmentation, with correlation coefficients of 0.38 and 0.41 respectively ($p < 0.001$). There was no significant difference between the correlation coefficients of the manual and automated segmentation.

The mean, manually obtained global CTP blood flow value was 127 ± 39 mL/100 ml tissue/min and the mean, automatically obtained global blood flow value was 132 ± 43 mL/100 mL tissue/min. The mean CTP value for all normal (on SPECT) segments in the study group was 131 ± 38 and 141 ± 40 mL /100 ml tissue/min for manual and automatic segmentation respectively. The mean per patient CTP blood flow in normal segments on SPECT ranged from 94-183 mL/100 ml tissue/min for manual segmentation, and 104-196 mL/100 ml tissue/min for automated segmentation. Further data on the mean and range for normal segments in each individual patient (with automatic segmentation) are presented in Fig 17.

The Spearman rank correlation coefficient between manual and automatic segmentation was $\rho = 0.88$ ($p < 0.001$) and the ICC was 0.93.

The global variation in blood flow between all segments (with automatic segmentation) is illustrated in Fig. 18. The total variation is similar for both segmentation methods.

Fig. 17. Stress CTP blood flow values (mean/max/min) in the normal segments ($\geq 70\%$ uptake on stress SPECT) for each individual patient. Automatic segmentation.

Fig. 18. CTP blood flow values presented as a percentage of the average CTP blood flow value of all segments with normal SPECT, and divided into normal ($\geq 70\%$ uptake on stress SPECT), indeterminate ($50-70\%$) or pathological ($\leq 50\%$) categories depending on the SPECT result for each respective segment.

Study III

The mean cFFR value for the whole group was 0.81, and the corresponding mean invFFR value was 0.84. The agreement between invFFR and cFFR expressed as an ICC was 0.73 ($p < 0.001$). The Spearman's correlation coefficient was $\rho = 0.77$ ($p < 0.001$) (Fig. 19).

Fig. 19. Scatterplot showing the relation between cFFR and InvFFR values. Spearman’s rank correlation $\rho = 0.77$.

The Bland-Altman analysis, as presented in Fig. 20, showed a low systemic bias and relatively tight limits of agreement.

Fig. 20 Bland-Altman plot comparing invasively obtained fractional flow reserve (invFFR) and CT-based fractional flow reserve (cFFR) on a per-lesion basis. The systematic bias is relatively low (95% limits of agreement are -0.18 to 0.12).

The cFFR sensitivity, specificity and the positive and negative predictive values for significant stenosis as defined by $\text{invFFR} \leq 0.80$ and $\text{invFFR} \leq 0.75$ are presented in table 1.

	FFR ≤ 0.80 per lesion (n = 23)	FFR ≤ 0.80 per pat. (n = 21)	FFR ≤ 0.75 per lesion (n = 23)	FFR ≤ 0.75 per pat. (n = 21)
Sensitivity	0.83	0.83	0.80	0.80
Specificity	0.76	0.80	0.89	0.88
Positive predictive value (PPV)	0.56	0.63	0.67	0.67
Negative predictive value (NPV)	0.93	0.93	0.94	0.93
Accuracy	0.78	0.81	0.81	0.86

Table 1: Results for CT-based fractional flow reserve (cFFR) in detecting significant stenosis, defined as both $\text{FFR} \leq 0.80$ and $\text{FFR} \leq 0.75$.

The mean and median time required for the complete cFFR post processing procedure was 45 and 46 minutes respectively (range 34-61 minutes). The mean and median time required for cFFR computation once the semi-automated segmentation process was completed was 4 min and 16 sec, and 3 min 28 sec respectively (range 2 min 10 sec – 12 min and 30 sec).

Study IV

The final study population consisted of 1205 patients (693 women and 512 men, 57.5% and 42.5% respectively) with a median age of 56 years and BMI of 26.0 kg/m². Maximum follow-up was 2724 days (7.5 years), with a median follow-up of 1121 (IQR 415-1793) days/3.1 years. Obstructive CAD was found in 177 patients (14.7%), non-obstructive CAD in 360 patients (29.9%) and normal coronary arteries in 668 patients (55.4%). A total of 84 MACE (47.5%) were recorded in the group with obstructive CAD on CCTA. The corresponding numbers for non-obstructive CAD and normal vessels were 9 MACE (2.5%) and 5 MACE (0.75%) respectively.

A total of 655 patients had a follow-up period of three years or more after CCTA. The incidence of a MACE during the three-year follow-up was 1.1% for patients with normal vessels on CCTA, 2.5% for patients with non-obstructive CAD and 42.7% for patients with obstructive CAD ($p < 0.001$).

Results

Kaplan-Meier survival curves over 7.5 years for MACE in obstructive CAD vs. normal coronary arteries and non-obstructive CAD, and for normal coronary arteries vs. non-obstructive CAD are shown in Fig. 21. The log rank test for differences between groups showed a χ^2 -value of 282.487 ($p < 0.001$) for obstructive CAD vs. normal coronary arteries and non-obstructive CAD, and 3.052 ($p = 0.081$) for normal coronary arteries vs. non-obstructive CAD.

Fig. 21: Kaplan-Meier plots for MACE-free survival over 7.5 years.

Left: Normal coronary vessels + non-obstructive CAD vs. obstructive CAD. Log rank: $\chi^2 = 282.487$, $p < 0.001$. Right: Normal coronary vessels vs. non-obstructive CAD. Log rank: $\chi^2 = 3.052$, $p = 0.081$. MACE = Major adverse cardiac event, CAD = Coronary artery disease.

Multivariate Cox regression analysis showed a hazard ratio (HR) of 5.13 (95% C.I 1.03-25.43, $p < 0.05$) for MACE among patients with non-obstructive CAD vs. normal coronary arteries and a HR of 151.40 (95% C.I 37.03-619.08, $p < 0.001$) for obstructive CAD vs. normal arteries. Beside CCTA findings, only male sex (HR 2.2, 95% C.I 1.33-3.57, $p < 0.05$) and BMI (HR 1.1, 95% C.I 1.33-3.57, $p < 0.05$) were associated with MACE.

The three-year incidence of readmission for stable angina or chest pain after CCTA was 101/655 (15.4%) for the whole group, and 32/372 (8.6%), 31/201 (15.4%) and 38/82 (46.3%) for normal coronary arteries, non-obstructive CAD and obstructive CAD respectively (Table 2).

Outcome 3 years	Total n=655	Normal vessels n=372	Non-obstructive CAD, n=201	Obstructive CAD, n=82	p-value
MACE	44 (6.7%)	4 (1.1%)	5 (2.5%)	35 (42.7%)	p<0.001
Cardiac death	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	-
MI	7 (1.1%)	2 (0.5%)	2 (1.0%)	3 (3.7%)	p <0.05*
Readm. UAP	15 (2.3%)	2 (0.5%)	2 (1.0%)	11(13.4%)	p <0.001*
Revasc.	34 (5.2%)	1 (0.3%)	2 (1.0%)	31 (37.8%)	p <0.001*
Re-adm, other					
Stable AP	31 (4.7%)	3 (0.8%)	10 (5.0%)	18 (22.0%)	p<0.001*
Chest pain	71 (10.8%)	29 (7.8%)	22 (10.9%)	20 (24.4%)	p<0.001

Table 2: Three-year incidence of major adverse cardiac events (MACE) and readmissions in patients with normal coronary arteries, non-obstructive CAD and obstructive CAD respectively. Some numerical overlap between the separate events and the compound MACE-parameter is present, since only one event per patient contributes to MACE. Differences between groups were calculated with the combined groups of normal vessels and non-obstructive CAD versus the group with obstructive CAD, using the χ^2 -test and Fischer's exact test (*).

MI = Myocardial infarction, UAP = Unstable angina pectoris, AP = Angina pectoris, CAD = Coronary artery disease, Readm.= Readmission, Revasc. = Revascularization.

All-cause death during the study period was limited to 12 cases (1.0%), with 5/668 (0.7%) in the group with normal vessels, 5/360 (1.4%) in the group with non-obstructive CAD and 2/177 (1.1%) in the group with obstructive coronary disease ($p = 0.558$). Only one death was cardiac-related, while the majority (eight deaths) were related to cancer. There was no significant difference in all-cause death between the different groups.

DISCUSSION

The core theme for this thesis has been the evaluation and improvement of the diagnostic capability of CCTA. Previous studies indicate that approximately 40% of all ICA in patients with suspected CAD show normal findings, thus leading to no further intervention (92,93). Data from the Swedish SCAAR registry indicate a similar percentage. This is unfortunate as ICA is an invasive, and thus expensive, technique that also carries with it a certain procedural risk. Hence, there are both medical and economical gain to be made by improving the diagnostic yield of CCTA and, where possible, reducing the number of unnecessary ICA.

Advanced CT applications such as CTP and cFFR might assist in the important triage process to invasive procedures by providing additional data beyond mere visualisation of the coronary arteries. One recent example is described in the PLATFORM study (94), where the use of cFFR (although from another vendor than used in study III) was shown to be able to reduce the number of unnecessary ICA by 83%, while retaining the same number of revascularisations and without increasing the 90-day risk of MACE.

Apart from CTP and cFFR, image improvement as outlined in study I may also play a role in improving CCTA diagnostic yield without increasing the radiation dose. Lastly, the epidemiological perspective of study IV contributes to the general knowledge on how to interpret CCTA results from a long-term prognostic point of view.

Aspects on patient selection

Study I

Patient selection in study I was uncontroversial as inclusion was consecutive during one randomly chosen month. Exclusions were only due to the fact that some image material did not conform to the study protocol. Since focus was on image quality only, the indication for the exam was not a concern.

Ethical aspects of Study I

Study I was performed without formal assessment in the Regional ethical review board. At the time, this was regarded as acceptable as the focus of the study was on

evaluation of image quality only. Only anonymised, single images were used, and there was no medical evaluation of the image material. The patient data needed was very limited. Today, in most situations an assessment from the Regional ethical review board provides evidence that an independent review of possible ethical problems has been performed.

Study II

In study II, patient selection was more complex, as the participating patients were selected specifically for their combination of previous myocardial infarction and PCI with at least one untreated significant stenosis, thus introducing significant selection bias. However, this was very early in the development of dynamic CTP and the intention was to maximise the number of potential ischemic lesions in a small pilot study, and to explore the possibility of differentiating between ischemic and infarcted myocardial tissue.

Study III

In study III, the main inclusion criterion was clinical CCTA with subsequent ICA and FFR-measurement within 120 days, and a total of 63 consecutive patients were identified. In order to avoid vendor- or model-specific variations, the inclusion time-frame was selected so that all CCTA were performed on one specific scanner.

All patients had findings on CCTA that warranted further investigation with ICA. Also, in a clinical setting FFR is mainly used on border-line stenoses as a tool for determining the need for revascularisation. Stenoses that are clearly significant, and light atheromatous changes are rarely investigated with this method. Hence, the risk of selection bias needs to be considered in relation to the study results.

Study IV

In study IV, the study cohort was chosen from a total of 3038 CCTA exams performed between 2007 and 2014. All exams in patients with known CAD or other cardiac disease were excluded, as were all exams with suboptimal image quality. Thus, the patient selection process was similar to several other studies with similar objectives (24-27,95-97).

Aspects on image acquisition and evaluation

Study I

Study I utilised high and low dose/quality images captured from the same clinical exam, which is a novel approach that we have not been able to find elsewhere. Through the use of retrospective ECG-gating, images covering the 35-75% segment of the cardiac R-R-interval were available. ECG-regulated dose modulation ensured that the 35% phase in most cases was captured with a reduced dose, and that the 40-75% phases were captured with the full dose. Thus the 35% phase and the 70% phases were selected for evaluation and comparison. Nine cases were excluded as the 35% phase was captured with full dose, possibly as a result of a slightly irregular heart rhythm.

However, comparison between systolic and diastolic images may be problematic as the flow in the coronary arteries (and probably also the vessel diameter) varies throughout the cardiac cycle (15). Thus, the fact that the full-dose images were acquired during the diastolic phase and the low-dose images during the systolic phase could affect the image quality rating, probably to the detriment of the low-dose images. Low-dose images obtained during the systolic phase might also be more prone to motion artefacts than the full-dose images obtained during the diastolic phase. This has not been compensated for and may thus constitute a systematic error. However, it does not affect the comparison between low-dose images with and without post-processing.

Due to limitations in the VGA software, only single images were assessed, thus creating an unrealistic evaluation situation. Later software releases have addressed this issue.

Study II

In study II a dynamic stress CTP image acquisition was performed and estimated quantitative CTP blood flow compared to semi-quantitative stress SPECT. In retrospect, had rest CTP been added, a better differentiation between ischemic and infarcted areas could have been facilitated. The reason for this omission was concern about radiation dose, as the study patients were already subjected to stress CTP and rest/stress SPECT. Except for Ho et al (58), most other studies on dynamic CTP have also abstained from rest CTP, for similar reasons.

The effective CTP scan length was only 7.3 cm along the long axis of the body, which in many cases proved inadequate for covering the whole heart. As previously

stated, four exams were excluded because of this, and several were partially affected. This seems to be a common problem, which is described by other authors as well (57,61). The use of Adenosine as an agent for vasodilatation and thus flow redistribution may have contributed to this problem by increasing respiratory drive (98), hence increasing chest motion and the risk of motion artefacts. Secondary effects such as tachycardia and increased blood flow velocity (99,100) may have contributed to a shortening of the time taken for the bolus front to reach the aorta as compared with the test bolus, thus possibly causing the timing errors that led to the exclusion of a further four cases. The use of receptor selective agents, such as regadenoson, could possibly have reduced the frequency of excessive respiratory drive and resulted in fewer exclusions due to motion artefacts (101,102). The timing problem was solved by shortening the estimated delay time from contrast infusion to image acquisition by three seconds.

The investigators were not blinded to the results from the SPECT, or from previous ICA/PCI. Although blinding would have been preferable, it was not regarded as essential in this early study on dynamic CTP, as the objective was to establish whether the use of dynamic CTP for myocardial perfusion imaging was at all feasible. The rather primitive and time-consuming manual segmentation process that was used initially was due to the lack of software able to present per-segment results according to the AHA 17-segment model (90), something that was considered essential when quantitatively evaluating estimated CTP blood flow values vs. relative SPECT signal intensity. At a later stage, the vendor made available a prototype software with this functionality, which greatly simplified the process. Thus, our focus was different to that of most other studies comparing dynamic CTP with SPECT or cMR, as the most common approach is that of visual detection of perfusion defects (58-60). However, a study by Wang et al (103) did a similar type of comparison albeit with a different patient group.

Study III

Study III used clinical, standard-of-care CCTA exams only, with 0.75 mm CCTA datasets being used for the cFFR segmentation process. At this early stage of cFFR stenosis evaluation, it was considered essential to use only ICA/FFR exams where the exact location of the pressure guide wire was depicted, as reference. Written descriptions or manual drawings, such as are commonly used in clinical routine, were not considered precise enough for exact comparison between cFFR and invFFR. Thus, the point of cFFR-invFFR comparison on the cFFR colour map was determined from the pressure guide wire position in the corresponding ICA.

The employment of an expert cardiac interventionist for this task minimised the risk of misinterpretation of the ICA images. A similar strategy seems to have been used by other early investigators (104,105).

Study IV

Study IV was not an experimental study, but rather conceived as an epidemiologic study on the prognostic value of clinical CCTA. Thus, the main focus was on risk and survival analysis.

Study patients were consecutively included in a clinical setting, thereby reflecting real-life patients. All exams were performed according to current guidelines, using a 64 slice DSCT or better. Unlike other similar studies, which to a large extent rely on telephone interviewing and patient files for follow-up, this study was based almost entirely on registry data (from the SWEDEHEART/SCAAR registries). However, all 1370 initially included exams were re-evaluated regarding the presence or absence of non-obstructive atheromatosis, since this information is not registered in the SWEDEHEART data base.

For outcome analysis, a MACE parameter was constructed, including cardiac death, myocardial infarction, admission due to unstable angina pectoris (UAP) and revascularisation. Unlike most other similar studies elective revascularisation was included in the MACE definition. The reasoning behind this decision was that, even though elective, most revascularisations were performed as a direct result of the CCTA findings. Also, in a clinical setting, it may be difficult to differentiate between elective, semi-elective and acute procedures.

Aspects on the results

Study I

The aim of study I was to investigate whether the use of a 2-D, non-linear adaptive noise reduction filter could improve image quality in CCTA. The results showed that there was a significant improvement of the perceived image quality of low-dose images when the filter was applied, even though the improvement was small compared to the image quality of the corresponding diastolic full-dose images. Thus, the filtering was not able to compensate for the large dose reduction. Also, image noise expressed as the average standard deviation of the HU-values in the

ascending and descending aorta was significantly reduced, thus providing a more quantitative indication of the value of additional image filtering.

In spite of the improvement in perceived image quality, the results did not actually show that the filter can be used to lower the dose while retaining image quality. Such proof would require a more systematic approach, with image acquisition at several different dose-levels for each subject. However, a later study, utilising the same patient material, statistically deduced that a more realistic dose reduction of 16-26% was feasible using this particular filter (106).

Clinical studies on adaptive filtering are scarce and presently, research interest seems to be more focused on iterative reconstruction techniques as a dose saving measure. As far as we know, there are no other studies performed on adaptive filters in cardiac imaging, but Borgen et al (107) used a comparable filter solution (among others) and a dose reduction of 50% in a prospective study on abdominal imaging, with similar results.

Study II

The primary aim of study II was to evaluate the variation in adenosine stress dynamic CTP blood flow as compared to ^{99m}Tc SPECT. The results showed a positive but weak correlation between quantitatively measured CTP and semi-quantitative SPECT of $r=0.38$ and $r=0.41$ for manual and automated CTP segmentation respectively, as compared to $r=0.64$ by Wang et al (103). There was also a surprisingly large variation in estimated stress CTP in segments that all could be considered normal with SPECT. As shown in fig. 18, the same absolute CTP blood flow value could be interpreted as normal, intermediate or pathological, depending on the patient. Based on these findings, we concluded that it is difficult to define a absolute cut-off value for normal vs. hypoperfused myocardium on the basis of comparison with SPECT.

There are several potential explanations for this result. One is the fundamentally different mechanisms utilised by each method, presumably making direct comparisons difficult. Another possible explanation is the presence of extensive CAD in the patient group. Although none of the patients were described as having three-vessel disease, the possibility of a general decrease in SPECT signal intensity due to extensive CAD must be taken into consideration. However, Wang et al (103) describe a mean CTP blood flow of 142.9 ± 30.6 mL/100 mL tissue/min in normal segments (on SPECT) in a population with suspected CAD, while Ho et al (58) describe 121 ± 31 mL/100 mL tissue/min and Kim et al (59) 113.2 ± 26 in normal segments, thus placing our corresponding results of 131 ± 38 and 141 ± 40 mL/100 mL tissue/min for manual and automated segmentation well

into the normal range as defined by these three studies. Also, in a relatively recent study by Bamberg et al (60), the cut-off point for differentiation between normal and ischemic myocardium was determined to be 0.88 mL/100 mL tissue/min.

All of these results are significantly lower than results in experimental studies using ^{15}O -water and ^{13}N - ammonia positron emission tomography (PET), where the average Adenosine stress blood flow was 263 and 273 mL/100 mL tissue/min respectively (108). The reason is not entirely clear but Rossi et al have shown that similar CTP blood flow values can be recorded in pigs by administering a much larger Adenosine dose than is used in clinical practice, thereby increasing regional myocardial blood flow (109).

Thus, quantitative comparison between dynamic CTP and SPECT is difficult to perform. Most other comparative studies (58-60,103) have used a qualitative approach, with focus on the visual detection of perfusion defects as compared to the reference method. The results of these studies have also been more encouraging, with sensitivity and specificity for perfusion defects in relation to SPECT of 0.83-0.85 and 0.78-0.92 respectively (58,103). In future studies this approach could possibly yield more clinically useful results.

The secondary aim of the study was to compare per segment myocardial blood flow values obtained by manual and automatic segmentation. For this comparison, the resulting between-segment difference in blood flow was small and non-significant. Calculation of Spearman rank correlation coefficient and Intraclass Correlation Coefficient showed excellent results, indicating that both methods were equally useful.

Study III

The aim of study III was to evaluate the accuracy of cFFR, as compared to invFFR.

The results showed a rather good concordance with invFFR, with a Spearman rank correlation coefficient of $\rho = 0.77$ ($p < 0.001$) and ICC = 0.73 ($p < 0.001$). Although a small study, these results are in the same range as the results obtained by other authors using the same software (104,105), and they are also similar to those obtained in the DeFACTO and NXT studies (110,111), where similar software from another vendor was used. Maybe most importantly, the high negative predictive value of 0.93-0.94 (depending on the cut-off limit for significant stenosis) suggests that cFFR has the potential to be very useful in the triage to invasive angiography, possibly reducing the need for further invasive investigation in a number of patients.

The average time of approximately 45 minutes required for the cFFR analysis was also in line with the results recorded by Coenen et al (105). Although the

comparatively short processing time in itself facilitates an efficient patient flow compared to other current solutions, newer algorithms and even faster hardware are expected to make the processing close to instantaneous in the near future.

Study IV

The aim of study IV was to evaluate the long-term outcome after CCTA in patients without known CAD. The maximum follow-up time of 7.5 years was unusually long in this context, although the median follow up time of 3.1 years was more in line with earlier studies. Only three patients (0.2%) were lost to follow-up, due to not having a Swedish personal identity number, as compared to approximately 5-15% in several other studies (25,27,28).

A total of 85.3% (n=1028) of the exams included did not indicate obstructive CAD, and the results for this group showed a very low risk for MACE. In fact, only nine cases (1.6%) of MACE were recorded during three-year follow-up in patients without obstructive CAD (n=573), and for the whole study period of up to 7.5 years the corresponding number was 14 cases (1.4%). However, even in patients without obstructive CAD, the differentiation between normal coronary arteries and non-obstructive atheromatosis on CCTA seems important as the multivariate Cox regression analysis showed a HR of 5.13 for non-obstructive CAD vs. normal coronary arteries. This is also supported by the approximately 2.5-fold increase in the 3-year incidence of MACE when non-obstructive atheromatosis was present at CCTA. The HR of 151.4 for obstructive CAD vs. normal arteries was considerably higher but also more expected.

All-cause mortality was low (n=12) and the cardiac-related death incidence was even lower (n=1). Cancer was, in fact, a far more common cause of death (n=8), and the possibility that cancer-related pain was erroneously interpreted as being cardiac-related cannot be entirely ignored. However, no further analysis of pre-CCTA, non-cardiac related morbidity was performed.

We also found a high rate of readmissions even in the groups with normal vessels or non-obstructive CAD. Again, this raises questions about alternative pathology causing the symptoms, but possibly also about patient-doctor communication. Even though earlier trials have indicated a high rate of readmission (112), and correspondingly high health care cost in chest pain patients, this has not been shown in a CCTA population. Thus, a conceivable future study would be to investigate the health care consumption before and after CCTA.

Limitations

Apart from the previously discussed limitations of each individual study, it must also be pointed out that all examinations included in this thesis were performed at CMIV/Linköping University Hospital. Although this ensures consistent image acquisition methodology, image quality control and clinical interpretation it also increases the risk of systematic errors in all of these processes.

FUTURE PERSPECTIVES

Ever since the introduction of the EMI-scanner in the early 1970s, CT technology has constantly improved at an amazing rate, allowing for ever faster image acquisition, higher resolution, larger field-of view, lower image noise and lower dose. During the last decade, CT has also gone from being a strictly morphological modality to becoming increasingly able to visualise physiological processes, and there is no reason to believe that this trend will not continue. A number of new technologies are on the verge of reaching clinical routine, both in terms of hardware and in terms of advanced software applications.

Among hardware innovations, the photon-counting detector warrants special mentioning. With a potentially unlimited number of spectra, tissue characterisation of coronary plaques and other structures can be expected to be much improved as compared to a conventional detector, thus adding important information in the triage to invasive procedures. In addition, lower noise levels, improved contrast-to-noise ratio, higher spatial resolution and a lower dose can also be expected.

Advanced software applications also continue to be developed, with cFFR presumably being just the beginning. Current research indicate that the application of computational fluid dynamics may also allow for visualisation and quantification of blood flow throughout the cardiac chambers and aorta, thus pushing CT firmly into what has hitherto been strictly MR territory. In addition, cFFR evaluation of coronary stenoses may be supplemented by other techniques such as advanced coronary artery plaque evaluation, measurement of the transluminal attenuation gradient (TAG) and improved versions of CT-based myocardial perfusion imaging.

Apart from technological advances, further knowledge on the value and diagnostic yield of CCTA will also be gained from large, prospective studies such as the Swedish CArdioPulmonary BioImage Study (SCAPIS) trial (113), which will include CCTA and various other imaging methods, physiological tests and laboratory parameters on 30000 randomly chosen persons, aged 50-64. Inclusion is expected to close in 2018.

In conclusion, one single innovative technology may not be sufficient, but the application of several different methods may contribute to a significant increase in diagnostic yield of CT, thereby potentially further reducing the number of unnecessary invasive procedures. Although the use of ionising radiation and iodinated contrast agent still has to be taken into account, CT has the potential to become a true “one-stop-shop” in terms of the cardiac work-up.

CONCLUSIONS

The studies included in this thesis have led to the following conclusions:

- I** There was a significant improvement of the perceived image quality and measured image noise of low-dose images with the application of a 2-D, non-linear adaptive noise reduction filter, even though the improvement was small compared to the image quality of the corresponding diastolic full-dose images.
- II** There were large variations in CTP blood flow in normal segments on SPECT, rendering the definition of an absolute cut-off value for normal vs. hypoperfused myocardium difficult. Correlation between dynamic CTP and SPECT was positive but weak. Manual and automatic segmentation were equally useful.
- III** The correlation between cFFR and invFFR was good, indicating that noninvasively estimated cFFR performs on a similar level as invFFR.
- IV** The long-term risk for MACE was very low in patients with normal coronary arteries or non-obstructive CAD on CCTA, even though there seemed to be a substantial increase in the risk for MACE in patients with non-obstructive CAD as compared to those with normal vessels. In addition, even if patients with non-obstructive coronary artery disease had very low risk of an acute coronary syndrome or revascularisation during extended long-term follow-up, they continued to have a substantial number of readmissions for chest pain or stable angina.

POPULÄRVETENSKAPLIG SAMMANFATTNING PÅ SVENSKA

Allmänt

Datortomografi (DT, CT, CAT-scan, skiktröntgen) är en metod som funnits sedan tidigt 70-tal, och som med hjälp av ett roterande röntgenrör kan avbilda kroppens inre delar. Den resulterande bilden presenteras i första hand som ett tvärsnitt genom den undersökta kroppsdelen, men dagens moderna datortomografer har en så pass god upplösning att bildmaterialet kan vinklas om och presenteras i vilket plan som helst. DT kunde länge endast statistiskt avbilda olika strukturer, men under det senaste åren har den tekniska utvecklingen medfört att man även kan använda metoden för att dynamiskt bedöma fysiologiska skeenden, såsom t.ex. genomblödning av hjärtmuskel och hjärna. Den tekniska utvecklingen har också ökat möjligheten att bearbeta ett i grunden statistiskt bildmaterial med avseende på fysiologiska frågeställningar.

Undersökning av hjärtats kranskärl med datortomografi (CCTA) har med tiden visat sig vara en enkelt genomförd och användbar undersökning vid misstänkt kranskärslssjukdom. Dock är metoden i många fall förknippad med en relativt hög stråldos, som det är önskvärt att i möjligaste mån sänka. Framförallt är metoden bra på att utesluta kranskärslssjukdom. Mer utbredda kärlförändringar överskattas lätt, och ofta måste patienten då även undersökas med konventionell, invasiv kranskärslsröntgen. I oklara fall kan graden av kärlförträngning då utvärderas genom en tryckmätning framför och bakom förträngningen, och om kvoten mellan dessa understiger 0.8 anses förträngningen vara signifikant. Påvisandet av en signifikant förträngning kan i sin tur leda till åtgärd i form av ballongvidgning (PCI) eller bypassoperation (CABG). Det har dock visat sig att ca 40% av alla invasiva kranskärslundersökningar inte visar på några förträngningar, och därmed har utförts i onödan. Då invasiva undersökningar är dyra och det även finns en viss risk för komplikationer är det således önskvärt att öka det diagnostiska utbytet av CCTA, för att på så vis minska antalet onödiga undersökningar.

Denna avhandling fokuserar på ett antal olika aspekter av hjärtundersökning med datortomografi. Delarbete I-III beskriver olika metoder för att förbättra

bildkvalitet och diagnostiskt utbyte, medan delarbete IV behandlar det prognostiska värdet av CCTA.

Delarbete I

I detta arbete, med bildmaterial från 36 patienter, undersöktes huruvida bildkvalitet och brusnivåer vid CCTA med låg strålningsdos (20% av normalhög dos) kunde förbättras med hjälp av ett brusreduceringsfilter, och i vilken utsträckning bilderna var jämförbara med bilder där normalhög dos utnyttjades. Utvärderingen visade på en viss förbättring av bildkvalitet och brusnivåer vid låg dos, men att förbättringen inte motsvarade bildkvaliteten vid normalhög dos.

Delarbete II

I denna pilotstudie med 17 deltagande patienter utvärderades en metod (dynamisk DT perfusion, CTP) att med CT dynamiskt avbilda och beräkna hjärtmuskeln genomblödning. Som referensmetod användes en allmänt använd nuklearmedicinsk metod (SPECT), med en annan verkansprincip än CTP. CTP visade sig vara tekniskt komplicerat att utföra, och resultatet visade relativt dålig överensstämmelse mellan de olika metoderna, samtidigt som stråldosen var hög. Med CTP varierade dessutom den beräknade genomsnittliga genomblödningen kraftigt mellan olika delar av hjärtat och mellan olika patienter, även i områden som på SPECT bedömdes som normala. Det var således svårt att med SPECT som referensmetod bestämma ett definitivt gränsvärde för normal genomblödning. Bildmaterialet från CTP-undersökningen hanterades med både en manuell och en automatiserad metod och resultaten jämfördes, utan att någon tydlig skillnad mellan dessa kunde påvisas.

Delarbete III

I denna studie, med bildmaterial från 21 patienter, utvärderades en programvara som utifrån en vanlig CCTA beräknar tryckfallet över en kärlförträngning, och således dess signifikans. Som referens användes invasiv tryckmätning utförd på samma patient.

Resultaten visade på en relativt god överensstämmelse mellan uppmätt och beräknat tryckfall, och metoden ansågs ha potential att användas i beslutsprocessen kring vidare utredning med invasiv kranskärlsröntgen.

Delarbete IV

Detta arbete var en epidemiologisk studie på 1205 patienter utan tidigare känd hjärtsjukdom, som genomgått CCTA pga oklara bröstsmärtor. Beroende på fynden på CCTA delades patienterna in i tre grupper: 1) normala kranskärl, 2) kärlförändringar men ingen signifikant förträngning, 3) signifikant förträngning. Med hjälp av registerdata från det medicinska kvalitetsregistret SWEDEHEART samt Socialstyrelsens patient- och dödsorsaksregister kunde efterföljande hjärtrelaterad sjukdom, död eller invasiv behandling kartläggas. Den längsta uppföljningstiden var 7.5 år och medianuppföljningstiden var 3.1 år.

Resultaten visade på en mycket låg risk för hjärtrelaterad sjukdom eller död i avsaknad av signifikant förträngning. Dock föreföll även icke signifikanta förträngningar ge en 5-faldigt ökad risk för hjärtrelaterad sjukdom eller invasiv åtgärd jämfört med normala kärl. Det visade sig också att många patienter, trots avsaknad av signifikant förträngning på CCTA, i hög utsträckning fortsatte att söka vård pga. bröstsmärtor av oklar orsak.

ERRATA

Paper	Page	Original	Corrected
II	2/292	...and ref. mAs at 165 A.	...and ref. mAs at 300.
II	5/295	p < 0.0001	p < 0.001
III	2	..., ref. mAs at 185 A.	..., ref. mAs at 306 or 324.
III	2	...in total 45 patients (71%) representing 49 vessels (68%).	...in total 42 patients (67%) representing 48 vessels (68%)
III	3	IBM SPSS, Chicago, IL., USA.	IBM SPSS, Armonk, NY, USA

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APPENDIX (PAPERS I - IV)

Papers

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