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COMPUTED TOMOGRAPHY OF THE CORONARY ARTERIES

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It all seems so stupid
It makes me want to give up
But why should I give up
When it all seems so stupid

Martin L Gore

ABSTRACT

Non-invasive coronary computed tomography angiography (CCTA) has become an important tool for visualisation of coronary arteries since the introduction of 64-channel detector CCTA in 2004. It has been proved to be especially beneficial for ruling out coronary artery disease (CAD) in selected patient populations, due to the high negative predictive value (NPV).

The aim of this thesis was to study some aspects of the introduction, establishment and development of a new method, retrospectively ECG-gated CCTA with 64-channel detector, to evaluate coronary arteries.

In ***study I*** the diagnostic capacity and limitation of CCTA was compared to that of invasive coronary angiography (ICA) in a newly established CCTA team. CCTA had a very high NPV but the number of non-diagnostic scans was also high. The main limitations were motion artifacts and vessel calcifications, while short experience in reading CCTA did not affect image interpretation.
Study II described the learning-curve effect of the interpretation of 100 CCTA and also compared the diagnostic accuracy of both radiologists and radiographers, after a common introduction. The review time for novices was approximately halved during the first 100 cases, with maintained diagnostic accuracy. There was a learning-curve effect in positive predictive value (PPV) for radiologists, but not for the radiographers. However, the diagnostic accuracy of dedicated radiographers indicated that they might be considered as part of the evaluation team.
Study III compared the radiation exposure in retrospectively ECG-gated CCTA and ICA in the same population. Both mean estimated effective (ED) dose and organ doses (skin, breast, lung and oesophagus) were higher in CCTA when compared to ICA. The relatively high radiation dose to breast indicates that bismuth shielding should be used in women when performing CCTA. When using the updated tissue weighting factors provided in ICRP 103 the calculated ED from CCTA were significantly higher than those obtained using outdated ICRP 60.
In ***study IV*** the image quality and radiation doses were compared when decreasing X-ray tube peak kilovoltage (kVp) from 120 to 100 kVp in patients undergoing CCTA. By reduction of tube voltage the radiation dose was almost halved while the diagnostic image quality was kept at a clinically acceptable level.

In conclusion, CCTA is increasingly available throughout the world as an alternative to gold standard ICA, especially due to the excellent capability to rule out CAD. Still, retrospectively ECG-gated 64-channel detector CCTA has limitations such as motion artifacts and vessel calcifications. Another limitation is the high radiation doses required for CCTA compared to ICA. By lowering the kVp from traditionally 120 kVp to 100 kVp the radiation dose is halved while retaining diagnostic accuracy. There is a learning curve effect (regarded PPV and review time) of the interpretation of CCTA. However, more than 100 reviewed CCTA cases are necessary to reach a diagnostic accuracy that is acceptable.

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I. **Limitations of 64-detector-row computed tomography coronary angiography: calcium and motion but not short experience.**
Mir-Akbari H, Ripsweden J, Jensen J, Pichler P, Sylvén C, Cederlund K, Rück A.
Acta Radiol. 2009 Mar;50(2):174-80.

II. **Is training essential for interpreting cardiac computed tomography?**
Ripsweden J, Mir-Akbari H, Bacsovics Brolin E, Brismar T, Nilsson T, Rasmussen E, Rück A, Svensson A, Werner C, Winter R, Cederlund K.
Acta Radiol. 2009 Mar;50(2):194-200.

III. **Radiation exposure in retrospectively ECG-gated coronary CT angiography and invasive coronary angiography in the same population.**
Ripsweden J, Holm J, Aspelin P, Brismar TB, Mir-Akbari H, Rück A, Cederlund K.
In manuscript.

IV. **Impact on image quality and radiation exposure in coronary CT angiography: 100 kVp vs 120 kVp.**
Ripsweden J, Brismar TB, Holm J, Melinder A, Mir-Akbari H, Nilsson T, Nyman U, Rasmussen E, Rück A, Cederlund K.
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LIST OF ABBREVIATIONS

AA	Ascending aorta
ACCF	American College of Cardiology Foundation
ACR	American College of Radiology
AHA	American Heart Association
ALARA	As low as reasonably achievable
BMI	Body mass index
CAD	Coronary artery disease
CCTA	Coronary computed tomography angiography
CNR	Contrast-to-noise ratio
CT	Computed tomography
$CTDI_{vol}$	Volume computed tomography dose index
DAP	Dose area product
DLP	Dose length product
DSCT	Dual-source computed tomography
EBCT	Electron beam computed tomography
ECG	Electrocardiography
ED	Effective dose
ESAK	Entrance surface air kerma
ESD	Entrance skin dose
FFR	Fractional flow reserve
HDCT	High definition computed tomography
HU	Hounsfield units
ICA	Invasive coronary angiography
ICRP	International Commission on Radiological Protection
kVp	Tube peak voltage
LAD	Left anterior descending coronary artery
LCX	Left circumflex coronary artery
LMCA	Left main coronary artery
LV	Left ventricular
MDCT	Multi detector row computed tomography
MESD	Maximum entrance skin dose
MIP	Maximum intensity projection
MPR	Multiplanar reformatting
MRI	Magnetic resonance imaging

NPV	Negative predictive value
PCI	Percutaneous coronary intervention
PET	Positron emission tomography
PPV	Positive predictive value
RCA	Right coronary artery
ROI	Region of interest
SCCT	Society of Cardiovascular Computed Tomography
SD	Standard deviation
SNR	Signal-to-noise ratio
SPECT	Single photon emission computed tomography
US	Ultrasound
VR	Volume rendering

1 INTRODUCTION

1.1 BACKGROUND

Coronary artery disease (CAD) is the most common type of heart disease and is a major cause of morbidity and mortality in the Western world. The disease is reaching endemic proportions and will probably put an enormous strain on healthcare economics in the future (1, 2). Early detections and characterization of coronary atherosclerotic plaque could help prevent cardiac events.

CAD appears when the coronary arteries become hardened and narrowed. This can be attributed to atherosclerosis, a condition in which an artery wall thickens as the result of a build-up of plaque on the inner walls of coronary arteries. Coronary plaque is made up mainly of fat, cholesterol and calcium. As the plaques grow, less blood can flow through the arteries and the heart muscle can not get the oxygen it needs. This condition can lead to angina or a myocardial infarction. Myocardial infarction is most commonly attributed to occlusion of a coronary artery, which results in an ischemia in the myocardium.

Imaging of the coronary arteries is technically very demanding. Imaging a beating heart requires optimal spatial and temporal resolution. Excellent spatial resolution is necessary to evaluate the coronary branches, which can be very small (1-2 mm), and still contain plaque that is clinically significant. Sufficient temporal resolution, in combination with ECG-synchronization, is also necessary to visualize the coronary arteries without motion artifacts (3). In order to enable the characterisation of coronary plaque composition, which may influence patient prognosis and management, a high contrast resolution is required (4, 5).

The gold standard for assessing coronary artery stenoses is invasive coronary angiography (ICA), which has excellent spatial resolution and allows direct visualization of the coronary lumen. However, several disadvantages of the technique have led to the search and development of non-invasive imaging modalities to accurately detect or rule out the presence of CAD. Modalities that are traditionally used for this purpose are stress echocardiography, magnetic resonance imaging (MRI), single-photon emission computed tomography (SPECT) and positron emission tomography (PET). With these functional modalities, the hemodynamic consequences of coronary artery stenoses can be assessed by detecting the presence of perfusion abnormalities or left ventricular (LV) systolic dysfunction. Even though the presence of a significant flow-limiting stenosis can be adequately ruled out with these techniques, atherosclerosis cannot be visualized with functional techniques. Further more, since there is an increasing interest in early detection of CAD, the knowledge of pre-clinical CAD may be of great value for patient management and may substantially improve the outcome. Therefore, extensive research is currently being carried out in the field of non-invasive anatomical imaging and in the evaluation of coronary calcium burden or non-invasive coronary imaging with coronary computed tomography angiography (CCTA). The potential of CCTA with a high negative predictive value (NPV) to exclude CAD has been shown in several previous studies using CCTA (6, 7).

Two main focuses of imaging for diagnosis of CAD are anatomical imaging and functional imaging. The purpose of this chapter is to provide an overview of some of the currently used imaging modalities to detect CAD, with main focus on CCTA.

1.2 ANATOMICAL IMAGING OF CORONARY ARTERY DISEASE

By anatomical imaging of CAD it is simple to visualize the coronary artery tree and to look for plaque, significant or non-significant.

1.2.1 Invasive coronary angiography (ICA)

Selective ICA was introduced in 1960 by Sones (8) and has since then been the gold standard for evaluating coronary arteries. This technique requires the puncture of a peripheral artery (transradial or transfemoral approach) through which a long thin flexible catheter is advanced towards the heart and a selective injection of contrast media is introduced directly into the coronary arteries. During this procedure, conventional X-ray images are obtained which display the lumen and potential stenoses of the coronary arteries. Both spatial (0.2 mm) and temporal resolution (5 ms) of ICA is extremely high when compared to other methods such as CCTA. In addition to this the main advantage direct intervention is possible if, during the diagnostic procedure the presence of one or more significant lesions is confirmed. However, since there may be a discrepancy between anatomy and myocardial blood supply due to coronary collateral flow and vasomotor tone, the degree of stenosis might prove to be a weak descriptor of coronary resistance (9). Another big advantage of ICA is the possibility to measure fractional flow reserve (FFR), which can be used as a gatekeeper for percutaneous coronary intervention (PCI) (10).

One drawback of ICA is that it is costly, since it, for example, involves hospital admission and is a time-consuming procedure (11). Other drawbacks are that it is associated with a small, but not negligible risk of procedure related complications (12), as well as radiation to the staff when performing ICA. Furthermore, almost 50% of ICA examinations are not followed by any PCI procedure (13). However, the complication rates are too high to be neglected when applying it on patients with expected normal coronary arteries. In view of this and the growing numbers of purely diagnostic ICA, a non-invasive method has been searched for.

1.2.2 Coronary computed tomography angiography (CCTA)

The present feasibility of coronary artery imaging with computed tomography (CT) depends on several important developments in technology. The development has been rapid – and taken place in only one decade.

1.2.2.1 Development of CCTA

Before multi-detector row CT (MDCT) was developed in 1998, electron beam CT (EBCT) was used for imaging of the coronary arteries. The first examinations with EBCT were performed in the late 80s. EBCT is a tomographic imaging non-mechanical CT scanner with a high temporal resolution (50-100 ms) made possible by the absence of mechanically moving parts. Instead X-rays are created through a magnetically focused beam of electrons that is guided by a 210° arc ring of tungsten in the gantry and images are acquired in a step and shoot mode using prospective ECG-triggering. Despite the high temporal resolution, the technique is suboptimal to

visualize the coronary arteries. This is due to restrictions in non-spiral sequential scanning and ECG-triggering, a single breath-hold scan of the heart requires slices of 3 mm, which is not adequate for 3D visualization of the coronary arteries. Because of this, and low signal-to-noise ratio, the main clinical use of EBCT has become quantification of calcifications in the coronary artery, the so-called calcium score (14, 15).

In 1998, the 4-slice CT systems were introduced as the first generation of MDCT. Even though it offered many advances compared to earlier single-slice CT systems, the entire heart could still not be imaged with acceptable resolution. There were great limitations due to limited spatial resolutions (4 x 1 mm or 4 x 1.25 mm), a temporal resolution of 250-400 ms and the fact that the patients had to hold their breath for up to 40-50 seconds to get a single breath-hold scan (16-18). The second generation of MDCT was introduced in 2001, and consisted of 16-slice CT systems with sub-millimeter collimation (16 x 0.5 mm or 16 x 0.625 mm), gantry rotation times down to 375 ms and temporal resolution of 190-250 ms. These advancements resulted in better image quality and diagnostic accuracy, but the scanning time was still too long, around 20-30 s (18-22).

In 2004, the 64-slice CT systems were introduced. Further improvements regarding gantry rotation time (330-400 ms) and 64 slices with 0.5-0.75 mm collimated slices, resulted in scan times as low as 6 to 12 s. All together MDCT with 64 slices resulted in further improvement in diagnostic accuracy for visualising the coronary arteries by CT, with temporal resolution of 165 ms and isotropic resolution down to 0.4 mm (23-25). But still, diagnostic accuracy at higher heart rates and in calcified segments remained limited (26). Since 2004 continuing improvements to MDCT scanners have continued at an extremely high pace. Different vendors have chosen different directions to solve the remaining problems, for example, dual-source CT (2006), 256-MDCT (2007), 320-MDCT (2008) and high definition CT (2009).

1.2.2.2 Basic principles of CCTA

In 1998, 4-slice CT systems were introduced as the first generation of *MDCT*. Instead of a single-detector row, MDCT scanners have several parallel detector rows, which allow simultaneous acquisition of several slices. As a result larger sections can be scanned in a shorter time. The z-axis coverage has increased from 2 cm (4-slice) to 2.4 cm (16-slice) to 4 cm (64-slice) and finally up to 16 cm (320-slice) (18).

The *spatial resolution* refers to the degree of blurring in the image and the ability to discern objects and structures of small size. With higher spatial resolution, more details can be distinguished. Since the coronary arteries have small dimensions, a high spatial resolution is required to visualize and detect lesions. Most 64-slice CT scanners can provide an isotropic resolution down to 0.4 mm. Further improved spatial resolution, at best to a level of 0.2-0.25, is desirable for a reliable evaluation of stent patency, severely calcified arteries and for better plaque characterization.

The *temporal resolution* is crucial when imaging moving organs; and is defined as the required time for data acquisition per slice. Temporal resolution should be as short as possible to avoid motion artifacts. The temporal resolution is influenced by scanner characteristics such as, the rotation time as well as the reconstruction algorithm. The 64-slice CT scanners can provide temporal resolution down to about 165 ms, but a reduction of temporal resolution to less than 100 ms is desirable to eliminate the need for heart rate control.

Despite the fact that image quality at higher heart rates is significantly improved with 64-slice CT, most studies still propose the administration of beta-blockers for patients with higher heart rates > 60-65 beats/min (27-29). The rapid, constant motion of the heart might cause significant image motion artifacts. *ECG-synchronization* is performed to obtain motion-free images of the coronary arteries despite scan duration of several heartbeats. The time between two consecutive heartbeats is defined by the RR-interval. There are two types of ECG synchronization: retrospective ECG-gating and prospective ECG-triggering. With *retrospective ECG-gating* a continuous scan throughout the RR-interval is performed with simultaneous ECG-recording. After scanning, data reconstruction can be performed of the complete scanned volume in different data sets based on phases of the RR-interval. The phases are normally defined by percentage of the RR-interval or by time in ms from the R-peak. The data set at the most optimal time point due to motion artifact can be chosen after the scanning. Since it allows reconstruction at any time point of the RR-interval, cardiac function such as ejection fraction can be evaluated. With *prospective ECG-triggering* the scanner performs a single rotation at a defined point in the RR-interval (usually mid-diastole, phase 70-80%). Before the next single rotation the table moves the distance of the used scanner collimation (example 64 x 0.625 mm = 40 mm). This prospective technique (step-and-shot) is sensitive to motion artifacts and need a slow heart rate (below 65 bpm) and regular rhythm.

Optimal visualization of the coronary arteries demands sufficient *contrast concentration* in the vessels during the relative short scan time. Dual-injection, i.e. iodinated contrast media followed by saline, with high flow rate of at least 5 ml/s is recommended at CCTA. Using saline is helpful to avoid artifacts from dense opacification of the right cardiac chambers, which might limit the interpretation of the right coronary artery (RCA). Two major techniques are available to synchronize the arrival of contrast media in the coronary arteries: test bolus and bolus tracking. The *test bolus* technique is based on a separate contrast media injection during the acquisition of a series of dynamic low-dose scans at the level of interest. To determine the optimal scan delay, the time to peak enhancement within a region of interest (ROI) in the ascending aorta is measured. In *bolus tracking*, a real time monitoring of the main bolus injection is performed within a ROI in ascending aorta. Once contrast media enhancement reaches a preset attenuation threshold, the patient is instructed to hold their breath and then the scan is initiated. During this interval the optimal enhancement in the coronary arteries is normally reached. It is also possible to start the scanning manually when the contrast enhancement in the ROI is good enough (29). The Society of Cardiovascular Computed Tomography (SCCT) prefers the test bolus strategy, since it is more reliable than the simpler bolus tracking strategy. The risk of false start is decreased and contrast dilution problems as well as the adequacy of the intravenous line can be noticed before the real scan (30).

The *radiation dose* from 64-slice CCTA is dependent upon the ECG-synchronization technique used. With *prospective* ECG-triggering the radiation dose is considerably lower (radiation only during a short period of the RR-interval) than with *retrospective* ECG-gating (radiation during the complete RR-interval). A typically mean effective dose (ED) from retrospectively ECG-gated CCTA is 8-18 mSv (depending on with or without ECG-based tube current modulation) and from prospectively ECG-triggered CCTA is 2-4 mSv (Figure 1, Table 1) (31).

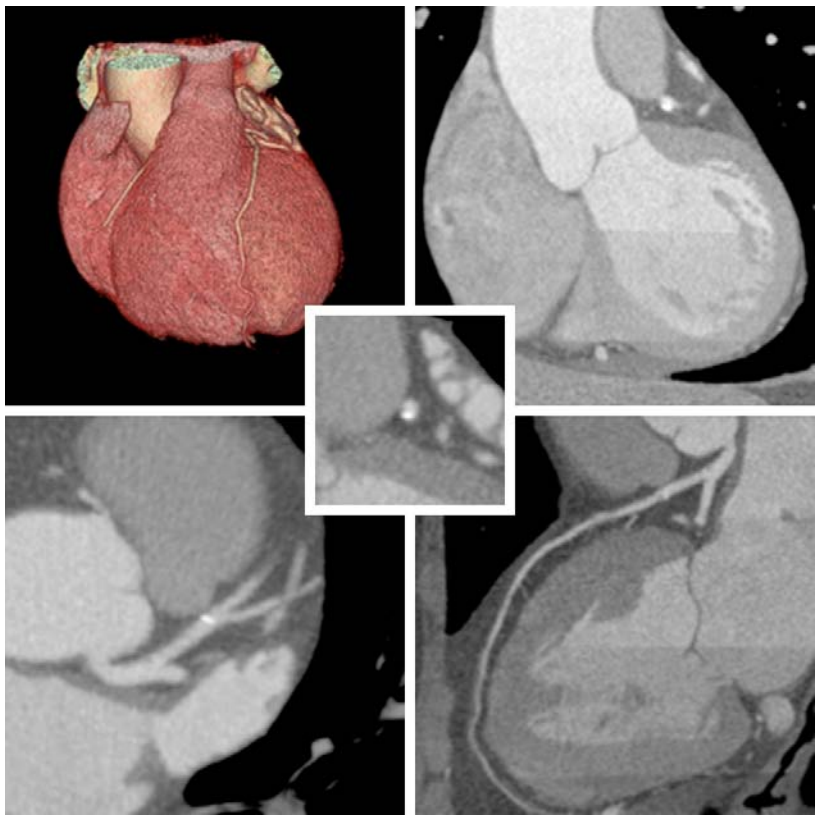

Figure 1. Example of prospectively ECG-triggered CCTA with an effective dose below 2 mSv. This case was not included in study I-IV, and illustrates a non-significant calcified plaque in proximal left anterior descending artery (LAD).

The clinical acceptability of CCTA is closely related to radiation dose exposure in routine use. One condition for a larger acceptance of this technique is a mean ED lower than that of ICA, which typically is around 7 mSv (31). However, radiation doses from 64-slice CCTAs vary a lot between different centres and different vendors (32). *ECG-based tube current modulation* lowers the radiation dose from retrospective ECG-gated scan. The maximum tube current is only used during pre-determined time intervals of the RR-cycle, e.g. mid-diastole. During the rest of the RR-cycle a lower tube current is used and dose savings over 40% have been reported using this technique (33).

Table 1. Mean values and range of effective dose estimates reported in literature (31).

Type of examination	Mean effective dose (mSv)	Range (mSv)
Retrospectively ECG-gated 64-slice CCTA without tube current modulation	15	12-18
Retrospectively ECG-gated 64-slice CCTA with tube current modulation	9	8-18
Prospectively ECG-triggered 64-slice CCTA	3	2-4
Invasive coronary angiography	7	2-16

Because of the complexity of coronary anatomy, the frequency of motion- and calcium-related image artifacts and the morphologic subleties of lesions, interpreters must review CCTA interactively on workstations capable of 2- and 3-dimensional displays in all conventional *reconstruction formats* (Figure 2). These include axial image stacks, multiplanar refomations (MPR), curved MPR, maximum intensity projections (MIP) and volume rendering (VR). According to the guidelines for interpretation from SCCT the recommend the use of axial image, MPR and MIP, while curved MPR are optional and VR not recommended for interpretation of the coronary arteries (93).

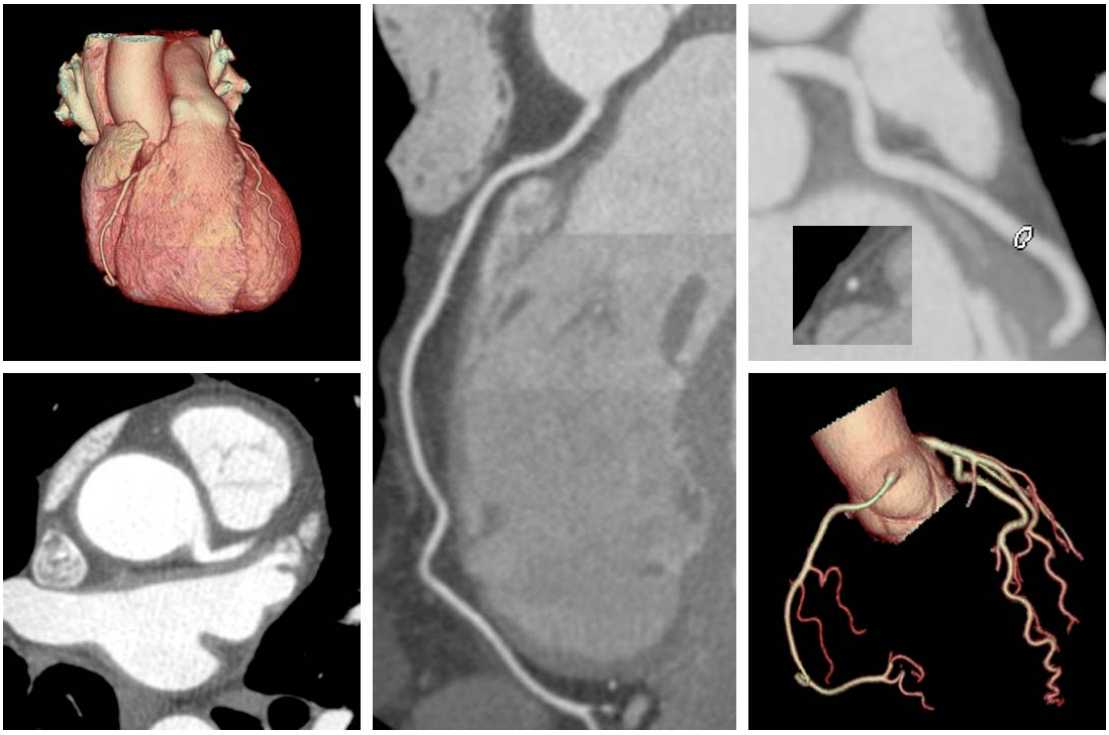

Figure 2. Examples of some conventional reconstruction formats: VR (upper left and bottom right corner), axial (bottom left corner), MIP with infolded cross-section image (upper right corner) and curved MPR (middle).

1.2.2.3 Post 64-era

Despite acceptable image quality and diagnostic accuracy in 64-detector row CCTA, the technique is still not fully developed, especially due to moving artifacts and limited plaque diagnostic. The different vendors have chosen different ways to solve these remaining problems. For example, by larger z-axis coverage (320-row volume CT, high pitch spiral acquisition), improved temporal resolution (dual-source CT, adaptive multi-segment reconstruction) and improved spatial resolution (high-definition detectors).

Dual-source CT (DSCT) was introduced in 2006 mainly to overcome the occurrence of motion artifacts at heart rates over 65 bpm. In several studies DSCT has been shown to provide stable image quality even for higher heart rates. DSCT uses two orthogonally placed X-ray tubes and two corresponding detector units in a single gantry. The key benefit of DSCT for cardiac scanning is improved temporal resolution (75-83 ms), equivalent to a quarter of the gantry rotation time (34, 35).

Several clinical studies have shown that DSCT can provide diagnostic acceptable results irrespective of the patients' heart rate (36-38).
The development of *area-detector technology* and related cone beam reconstruction techniques allows covering of the whole cardiac anatomy in a single heartbeat without table movement. This approach makes CCTA less susceptible to arrhythmias, and will potentially reduce radiation dose, especially if prospective ECG-triggering technique is used. Both 256- and 320-row single source systems and 128-row DSCT scanners have been developed. The 320-detector scanner can cover 16 cm (320 x 0.5mm) with a gantry rotation speed of 350 ms (18). The first 320-detector CCTA studies have shown high diagnostic accuracy across all coronary segments, regardless of size, cardiac rhythm or image quality (39-41).
High definition CT (HDCT) introduce a new detector material (gemstone), which is faster than older detector materials and might give greater details due to improved spatial resolution (0.23 x 0.23 mm). It also includes the possibility to use multi energy by fast kV switching in the single tube system. Significant radiation dose reduction has been shown compared to prospectively ECG-triggered CCTA, by use of iterative reconstruction technique, which allows lowering of mAs (42). Further studies are expected.

1.3 FUNCTIONAL IMAGING OF CORONARY ARTERY DISEASE

The main subject of a functional imaging modality is to assess the hemodynamic consequences of CAD instead of directly visualize the coronary arteries. For this purpose, regional perfusion or wall motion abnormalities are induced during stress, reflecting the presence of stress-induced ischemia. Normally perfusion abnormalities are more sensitive than wall motion dysfunction. The sensitivity and specificity for some different modalities are summarized in Table 2 (43, 44).

1.3.1 Stress echocardiography

Echocardiography is the first-line non-invasive imaging method in cardiology and routinely used in daily clinical practice for the analysis of cardiac function, as it is relatively easy to perform. Other advantages include the low costs of the examination, no radiation exposure and minimal patient discomfort. During stress echo-cardiography, the occurrence of wall motion abnormalities indicates the presence of myocardial ischemia. Stress can be induced by exercise or by dobutamine. Limitations of stress echocardiography mainly include operator dependency and suboptimal image quality due to a poor acoustic window. The use of intravenous ultrasound (US) microbubbles, allows the assessment of myocardial perfusion with echocardiography. After administration, the microbubbles will reside in the vascular space until they dissolve and can, therefore, be used for evaluation of the micro-vascular circulation. Similar to other methods resting perfusion defects suggest infarced myocardium, whereas stress induced perfusion defects indicates ischemia (43).

1.3.2 Magnetic resonance imaging (MRI)

MRI is a non-invasive method that can evaluate suspect CAD both by perfusion and wall motion abnormalities with the absence of radiation burden. When evaluating myocardial perfusion, short axis images are performed over a suspect area during the first pass of a bolus of contrast media. Thereafter, imaging is repeated during

pharmacological stress. The applied contrast media increases the signal intensity of the perfused myocardium and ischemic areas are identified as areas with reduced signal intensity. The spatial resolution of MRI enables distinction between sub-endocardial and transmural perfusion detects, which may indicate compromised blood flow at an early stage. In addition to myocardial perfusion, wall motion abnormalities can be obtained, by global and regional LV function at rest or during stress. The main limitation of MRI imaging of suspected CAD is that it is time consuming, despite this, it is still considered to be the gold standard for assessment of cardiac function (45).

Table 2. Diagnostic accuracy of some different modalities on per-patient level for detection of significant CAD (43, 44). ICA considered gold standard.

Modality	Sensitivity	Specificity
Stress echocardiography (systolic function - exercise)	84%	82%
Stress echocardiography (systolic function - dobutamine)	80%	84%
Magnetic resonance imaging (perfusion)	84%	85%
Magnetic resonance imaging (systolic function)	89%	84%
SPECT (perfusion)	86%	74%
PET	92%	85%

1.3.3 Single-photon emission computed tomography (SPECT)

Evaluation of myocardial perfusion with stress and rest myocardial perfusion SPECT has become a useful clinical practice in the management of patients with known or suspected CAD. For myocardial perfusion two sets of images are obtained: after stress and at rest. The presence of reversible (indicating ischemia) and irreversible (indicating infarced myocardium) perfusion defects is considered to be indicative of CAD. The introduction of ECG-gated SPECT imaging has allowed assessment of global and regional LV function in addition to perfusion. Direct comparisons between ECG-gated SPECT and MRI showed excellent correlations for assessment of LV volumes and regional wall motions (46). The main limitation for the patient is the radiation burden, which typically is about 10 mSv (47).

1.3.4 Positron emission tomography/CT (PET/CT)

Imaging of myocardial perfusion with PET has several important benefits over ECG-gated SPECT imaging. In contrast to SPECT, which measures relative perfusion, PET has the ability to quantify myocardial perfusion in absolute terms (millilitres per gram per minute), which may be important in patients with homogeneous reduced perfusion. With the use of hybrid PET/CT scanners, the location, severity and composition of plaques and stenoses can be correlated with their significance (9, 48). Another important advantage of PET is the quantification of coronary flow reserve, which allows evaluation of endothelial function. The main limitations of PET/CT imaging are the need of a nearby cyclotron and the radiation burden of 9-22 mSv depending on prospective or retrospective ECG synchronization (49).

2 AIMS OF THE THESIS

The overall purpose of this thesis was to study some aspects of establishing a new method to evaluate coronary arteries.

For each paper the specific aims were:

I. To evaluate the diagnostic capacity and limitations of a newly established 64-slice CCTA service.

II. To describe the learning-curve effect of interpretation of CCTA examinations for both radiologists and radiographers.

III. To compare the radiation dose between 64-slice retrospectively ECG-gated CCTA and conventional ICA in the same population.

IV. To compare image quality and radiation doses when decreasing X-ray tube peak kilovoltage (kVp) from 120 to 100 kVp in patients undergoing 64-slice retrospectively ECG-gated CCTA.

3 MATERIAL AND METHODS

3.1 PATIENTS

Between November 2005 and June 2007, 198 patients underwent both CCTA and ICA at Karolinska University Hospital, Huddinge. All patients were referred and scheduled for a clinical routine ICA. No patient had a cardiac event or clinical instability between CTA and ICA. Exclusion criteria included known adverse reactions to iodine contrast media, renal dysfunction with an estimated creatinine clearance <50 ml/min according to the Cockcroft-Gault equation based on adjusted body weight (50), atrial fibrillation, age < 50 years and previous coronary artery bypass surgery. Patients' age, gender, height, body weight, and heart rate were recorded, and body mass index (BMI) was calculated.

The local ethical committee at Karolinska Institutet approved the study. Written informed consent was obtained from all study participants.

Study I: In this study 101 consecutive patients with stable angina were included between November 2005 and May 2006. Mean age were 63 years (range 50-82), 37 women and 64 male. The mean heart rate during CCTA was 61 beats per minute (range 38-80). ICA revealed CAD in 51 of the patients (23 with one-vessel disease, 17 with two-vessel disease and 11 with three-vessel disease), whereas 50 patients had no significant stenosis. Per protocol, 538 of 1818 potential segments were excluded from the study by ICA (proximal diameter less than 2 mm, non-interpretable or stents). ICA detected 121 significant stenosed segments in the remaining 1280 segments.

Study II: The same patients as in *study I* were included. According to our study design, we wanted 10 sessions with the same number of cases in each session. Since the numbers of patients in *study I* were 101, we excluded one patient to get 10 patients in each session. We decided to exclude the last consecutive included patient without knowing which case it was. The final 100 patients mean age were 63 (range 50-82), 37 % were women and mean BMI was 27 (range 19-38). The indication for coronary investigation was typical angina pectoris in 71%, atypical angina pectoris in 21%, and valvular disease in 8%. After excluding segments with stents, a proximal diameter less than 2 mm, and segments not interpretable by ICA (e.g., segments distal to chronic total occlusions), a total of 1277 segments were evaluable at ICA. ICA showed significant CAD in 49 out of 100 patients (one-vessel disease, n=21; two-vessel disease, n=17; three-vessel disease, n=11) and, in total, 138 significant obstructive lesions were detected.

Study III: Of the 101 included consecutive patients in this study (same as *study I*), 14 patients had incomplete data recorded from CCTA and another 16 patients had incomplete data recorded from the ICA. Four patients were not scanned according to the study protocol and were therefore excluded. Finally 2 patients were excluded because their recorded data from ICA included data from intervention procedure and left ventricular angiography. Consequently 65 patients (40 men and 25 women) had proper radiation data recorded for further measurements in both CCTA and ICA. The mean age was 63 year and BMI 27 kg/m^2.

Study IV: This study included 198 patients with suspected or known CAD between November 2005 and June 2007. Twenty-eight patients were excluded due to missing proper radiation data. Another 42 examinations were excluded because they were performed with different contrast media at CCTA, due to another study (51). The final number of patients in the study was 128. Of the included 128 patients, 46 patients were examined at 120 kVp and 82 patients at 100 kVp, while all other scanning parameters were kept unchanged. There were no differences in body weight, BMI, and heart rate between the two cohorts, while there were differences in age ($p<0.05$) and height ($p<0.05$).

3.2 METHODS

All CCTA were performed on a 64-channel detector scanner (LightSpeed VCT; GE Healthcare, Milwaukee, Wisc., USA) with ECG-gated retrospectively technique. The rotation time was 350 ms, collimation 64 x 0.625 mm, pitch 0.16 - 0.24, matrix 512 x 512, and a standard reconstruction algorithm was used. The peak kilovoltage used in study I-III was 120 kVp. In study IV both 100- and 120 kVp was used. All examinations used ECG-gated tube current modulation with the maximum set to 650 mA (70-80% phases) and the minimum tube current set to 250 mA.
Contrast media was injected a rate of 5 ml/s using a dual-head injector (Medrad, Stellant Dual Head Injector, Pittsburgh, Pa., USA). The contrast media used were iodixanol (Visipaque 320 mg/ml; GE Healthcare, Little Chalfont, UK) or iomeprol (Iomeron 400 mg/ml; Bracco, Milan, Italy). First a test bolus (15 ml contrast media mixed with 15 ml saline) was used to establish the individual circulation time for optimal timing of the diagnostic acquisition. A triple-phase contrast media protocol was used for the coronary scanning: initially 50 ml contrast media followed by a 50 ml mixture of 40% contrast media and 60% saline, and finally a 50 ml saline chaser. All CCTA was performed at least 3 days (range 3-60) prior to ICA. In order to minimize motion artifacts, patients with a heart rate above 75 beats per minute received intravenous metoprolol (2.5-10 mg) before scanning if there were no contraindications. As we sought a non-selected population, scans were performed irrespective of coronary calcium score.

In study I, II and IV, images in 10 phases of the cardiac cycle were reconstructed, using retrospective ECG gating. These data sets were transferred to a dedicated workstation (Advantage Workstation 4.3; GE Healthcare, Milwaukee, Wisc., USA) for further processing and analyses.

ICA was performed by experienced operators according to standard techniques with two different monoplane fluoroscopy systems (Philips Integris Allura and Philips Integris H; both Philips Medical Systems, Eindhoven, The Netherlands). Standard projections were used with additional projections if needed. All lesions obstructing more than 50% of the lumen diameter at ICA were considered clinically significant. We excluded segments with stents or a proximal diameter less than 2 mm, segment s with stents and segments not interpretable by ICA. The coronary artery angiograms were independently analyzed with visual assessment by two board-certified interventional cardiologists, without knowledge of the CCTA or clinical data. If no consensus was reached, the advice of a third observer was sought.

3.2.1 Study I

All CCTA examinations were analyzed independently, and without knowledge of the ICA or clinical data, by two local radiologists. Each coronary *segment* was analyzed visually, and the degree of stenosis was defined by consensus between the radiologists. Lesions with a visually estimated lumen diameter reduction of more than 50% were defined as "significant stenosis", otherwise the segment was classified as "no stenosis" or "non-diagnostic". At the *vessel* and *patient* level, CCTA was interpreted as:

- no stenosis - all segments interpretable and no stenosis detected
- significant stenosis - at least one stenosis, despite of non-diagnostic segments
- non-diagnostic - no stenosis but at least one segment non-interpretable

Image quality was classified in each segment as:

- excellent - no artifacts, unrestricted interpretation
- adequate - moderate artifacts, acceptable for clinical diagnosis
- poor/non-interpretable - severe artifacts impairing accurate evaluation

If the image quality was "poor/non-interpretable", one or more reasons were listed (calcification, motion artifact, inadequate contrast attenuation or other reason).

The two local radiologists were experienced in chest CT and had received CCTA training at visit to one highly experienced centre abroad, equivalent to level 1 competence (52, 53). Before including the study patients, a pilot phase with nine other patients was completed. As an external validation, a cardiologist with experience of more than 500 CCTA examinations made an independent evaluation of all segments using the same grading system.

The number of existing coronary segments and type was defined for each patient on ICA and was then also used for the comparison with the CCTA results. The 18-segment model of the American Heart Association (AHA) was used (54). The segment classifications of CCTA were compared to ICA (gold standard) and eventual corrections on different segment classification (not stenosis classification) were decided in concensus with the two cardiologist. ICA and CCTA were compared on three levels: per segment, per vessel, and per patient. In addition, segments were grouped into proximal, mid, distal, and side branches.

3.2.2 Study II

Four observers, two radiologists and two radiographers, independently evaluated 100 CCTA examinations regarding significant CAD (obstruction more than 50% of the lumen diameter). The observers had no prior experience in evaluation of CCTA. One radiologist (observer 1) sub-specialized in thoracic radiology, with more than 5 years' experience of performing ICA and more than 10 years' experience of thoracic CT. The other radiologist (observer 2) had no previous experience in performing ICA but more than 8 years' experience of general CT. The radiographers (observers 3 and 4) had 20 and 5 years of experience, respectively, in the full-time performance of general CT examinations, but neither had any prior experience in the evaluation of CT examinations. All observers had experience in working with general CT image reconstructions, but the radiographers were more practiced.

Each observer underwent a dedicated training program during a 2-week period (80 hours in total). The program started with a 2-hour anatomy lecture (using both CT images and a cardiac phantom), followed by instructions in how to use the workstation. Thereafter, the rest of the first day was spent analyzing 5-8 pre-study examinations, with the main objective to be comfortable with the workstation.

After the introduction, the evaluation of the 100 examinations started (day 2-10). These were divided into 10 blocks (sessions), with 10 randomized examinations in each session. All observers were blinded to all clinical findings as well as the ICA results, and they made their interpretations individually. All observers made their own reconstructions (maximum intensity projection (MIP), multiplanar reformatting (MPR), and curved MPR) that they thought would be necessary to find obstructions. The coronary arteries were analyzed segment per segment according to AHA classifications (54). After every session, the 10 corresponding ICAs were shown, and personal feedback with explanations and analysis together with an experienced reader was given individually, without any time limit. For every observer and session, the reading time, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were analyzed. To evaluate early and late effects, the same parameters were compared for the first 50 (sessions 1-5) and last 50 examinations (sessions 6-10).

3.2.3 Study III

For estimation of CCTA radiation doses, the ED and organ doses (breast, lung and oesophagus) were calculated for each patient using a CT dosimetry spreadsheet (ImPACT CT Patient Dosimetry Calculator v1.0.1a). The tube current was adjusted in the spreadsheet so that the resulting $CTDI_{vol}$ was in agreement with the reported from the CT scanner. The $CTDI_{vol}$ from the scanner was calibrated with a pencil ion chamber (DCT10, Wellhöfer, Germany), which is calibrated each year against a reference ion chamber (Model 550-4-T, Victoreen, Cleveland, Ohio, USA) calibrated at the secondary standard dosimetry laboratory in Sweden. In order to simplify comparison to previously published studies, ED was calculated using both the ICRP 103 tissue weighting factors (55) and the ICRP 60 weighting factors (56).

The entrance surface air kerma (ESAK), including backscatter, was measured using a previously described method (57). A solid-state CT dosimeter (Dose profiler, RTI Electronics AB, Sweden) was positioned over an anthropomorphic Alderson-Rando phantom (The Phantom Laboratory, Salem, New York, USA) that was scanned using the same clinical scanning protocol as used for the patients. The ESAK including the backscatter were measured for both the main and the bolus scanning series and were multiplied with an f-factor (the mass-energy absorption coefficient ratio for tissue and air) of 1.07, acquired from the CT dosimetry spreadsheet, to get the entrance skin dose (ESD). This was done for different levels of tube currents (i.e. with tube current modulation turned off) so that the ESD as a function of the computed $CTDI_{vol}$ could be acquired. The obtained functions were then used to convert $CTDI_{vol}$ to ESD. The $CTDI_{vol}$, which is automatically obtained by the CT scanner, is reported by the equipment as an average value. Therefore, to estimate the maximum ESD (MESD) for the examination, the $CTDI_{vol}$ over the same position as the bolus scan was calculated.

The estimations of ED and organ doses at ICA were calculated with a Monte Carlo software (PCXMC 2.0, STUK, Radiation and Nuclear Safety Authority in Finland) (58). For every patient, all exposure parameters (tube voltage, size of image intensifier, beam projection angles, distance from focal spot to image intensifier and dose area product (DAP)) were retrieved from the dose recording system of the angiography X-ray system and together with information about height and weight of the patient were used as input to the software. A focus–skin distance of 60 cm was assumed for all patients (59). The internal DAP meter of the angiography x-ray systems were calibrated with a reference DAP meter (Doseguard 100, RTI Electronics AB, Sweden), which was calibrated each year with a reference ion chamber (Model 550-4-T, Victoreen, Cleveland, Ohio, USA), that had been calibrated at the secondary standard dosimetry laboratory in Sweden. The total filtration of the x-ray beam was obtained for both angiography x-ray systems after passing through the patient couch by using a solid-state dosimeter (MPD, RTI Electronics AB, Sweden) to 4.8 mm Al. The obtained values were used as input to the PCXMC software. The MESD was estimated using the mean of two conversion factors (4.3 and 3.5 mGy/(Gy*cm^2)) reported for a similar angiography x-ray system (Philips Integris H 5000 C) in a previous study (59). When calculating the ED and organ doses the DAP readings were corrected for the absorption in the patient couch, but not when estimating the MESD, because those conversion factors are only valid for uncorrected readings. The absorption (30 %) was obtained by using a solid-state dosimeter (R100, RTI Electronics AB, Sweden).

3.2.4 Study IV

Two board-certified senior radiologists, with level II competence (53, 60), subjectively classified image quality on a per-patient basis regarding vascular density and noise in the coronary vessels. Classifications were made according to a four-point Likert scale (61):

4 - excellent
3 - good
2 - adequate
1 - not evaluable

In case of disagreement between the two readers, a final decision was reached by consensus. The readers, who were blinded to clinical and scan parameters, used axial views (0.6 mm) and made their own reconstructed MPR, mainly curved MPR (0.6-3.0 mm). They used individualized window settings, generally a window width between 800 and 1200 Hounsfield units (HU) and a window level between 100 and 200 HU.

To calculate signal-to-noise ratio (SNR), mean vascular density was measured in a circular region of interest (ROI) in the ascending aorta (AA) at the level of the origin of the left main coronary artery (LMCA) and another ROI in the LMCA. The ROI in the AA was defined as large as possible and the ROI in the LMCA had an area of at least 5 mm^2, both with the aim of avoiding calcifications, artifacts, and partial volume effects (Figure 3). Image noise was defined as one standard deviation (SD) from the mean pixel values in HU within the ROI in the AA on axial view with the thinnest slice (0.6 mm). To calculate contrast-to-noise ratio (CNR) we also measured the mean attenuation in the adjacent perivascular tissue in the area close to the LMCA.

SNR and CNR were calculated accordingly:

SNR = vascular density/image noise,
CNR = (vascular density-perivascular density)/image noise.

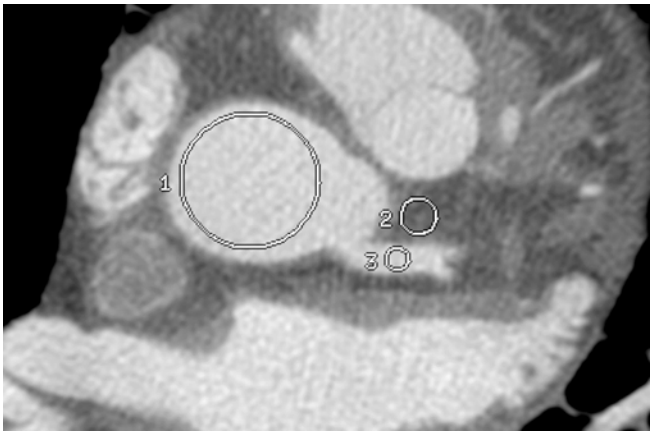

Figure 3. Determination of density and image noise within the region of interest (ROI) placed in the ascending aorta (1), perivascular tissue (2) and left main coronar artery (3).

Volume CT dose index ($CTDI_{vol}$) and dose length product (DLP) presented by the CT equipment were registered excluding topograms and bolus tracking scans. The effective dose per unit DLP (ED/DLP) conversion factor of 0.018 mSv x mGy^{-1} x cm^{-1}, specific for the chest region with a LightSpeed VCT scanner, was used to estimate the effective dose at 120 kVp. At 100 kVp an ED/DLP of 0.0166 mSv x mGy^{-1} x cm^{-1} was used since the ED/DLP conversion factor increases with 4.2% for each 10 kVp increase in X-ray tube potential (62).

ICA and CCTA were compared on a per-segment level using the 18-segment model of AHA (54). ICA was considered the gold standard. In four patients in the 100 kVp cohort, image data could not completely be retrieved and comparison between ICA and CCTA could not be done, and the final number of patients for comparing the accuracy was 46 in the 120 kVp cohort and 78 in the 100 kVp cohort. The total number of segments were 577 (120 kVp cohort) and 956 (100 kVp cohort).

3.2.5 Statistical analysis

In study I statistical analysis was conducted using Microsoft Excel 2003.

In study II-IV the statistical analyses were carried out using the SAS for Windows software, version 9.1 (SAS Institute Inc., Cary, N.C., USA). Probability values (*p*-values) < 0.05 were considered statistically significant.

Study I: With ICA as the standard of reference, the diagnostic accuracy of CCTA for the detection of significant lesions in coronary arteries is expressed in terms of the sensitivity, specificity, PPV and NPV.

The diagnostic performance was calculated on a per-segment, per-vessel (presence or absence of at least one significant lesion along each of the major coronary arteries) and per-patient (presence or absence of any lesions in each patient) basis.

Study II: Multiple comparisons of continuous data were performed by analysis of variance (ANOVA). In the case of a statistically significant result in the ANOVA, statistical comparisons were made by use of the post hoc test proposed by Fisher to control for multiplicity (63, 64). The study employed multiple hypotheses testing, where each hypothesis was analyzed separately and the existence of patterns in and the consistency of the results were considered in the analysis. Statistical comparisons in order to test differences between two groups were made by use of the Student's t test for uncorrelated means, after validation for normal distribution by use of the Shapiro-Wilk test. The Pearson correlation coefficient was used in order to test independence between variables. All trend analyses were performed by means of regression analysis. In order to evaluate hypotheses of variables in contingency tables, the chi-square test was used or, in the case of small, expected frequencies, Fisher's exact test. In addition, descriptive statistics was used to characterize the data. The mean, standard deviation, and range are given.

Study III: Statistical comparisons in order to test differences between the two methods were made by use of paired Student's t-test for correlated variables. The Pearson correlation coefficient was used in order to test independence between variables (63, 64). The study employs multiple hypotheses testing, where each hypothesis was analyzed separately and the existence of patterns in and the consistency of the results were considered in the analysis.

Study IV: The protocol with the use of a 120 kVp tube voltage was defined as the standard protocol and all of the parameters obtained with the 100 kVp protocol were compared with the parameters of the standard protocol. The quantitative variables were expressed as mean, median, and 2.5-97.5 percentiles and the categorical variables as frequencies and/or percentages. Statistical comparisons to test differences in the continuous variables between the two cohorts were made by use of the Student's *t* test for uncorrelated means, after validation for normal distribution by use of the Shapiro Wilk test (63, 64). To evaluate hypotheses of variables in contingency tables, the chi-square test was used or, in the case of small expected frequencies, Fisher's exact test.

4 MAIN RESULTS

The principal findings were:

Study I: In accordance with other studies, CCTA had a very high NPV, although we were a newly establish centre. The number of non-diagnostic scans was also high, with motion artifacts and vessel calcifications as main limitations. Short experience did not influence the interpretation.

Study II: There was a learning-curve effect in PPV for radiologists but not for radiographers. The review time of interpreting CCTA for novices decreased by approximately half during the first 100 cases while accuracy was maintained. The diagnostic accuracy of dedicated radiographers indicated that they might be considered to be included as part of the evaluation team.

Study III: Both mean estimated dose and organ doses (skin, breast, lung and oesophagus) were higher in CCTA compared to ICA. The relatively high radiation dose to breast indicates that bismuth shielding should be used in women when performing CCTA. When using the updated tissue weighting factors provided in ICRP 103 the calculated ED from CCTA were significantly higher than those obtained using outdated ICRP 60.

Study IV: By reduction of tube voltage from 120 to 100 kVp in CCTA, the radiation dose was almost halved while the diagnostic image quality was kept at a clinically acceptable level.

5 RESULTS AND COMMENTS

5.1 STUDY I

5.1.1 Results

At CCTA, 79% of the segments were assessable with excellent or adequate image quality. Thus, interpretation was not possible in 274 of 1280 segments (21%). The cause of inadequate image quality was mainly: severe calcifications (49%) and motion artifacts (45%) (Figure 4). The main local reason for poor image quality was motion artifacts in the RCA and calcification in the LAD. Patients and vessels were classified as "non-diagnostic" if they had no significant stenosis, but at least one segment that was classified as non-interpretable. The 274 non-diagnostic segments resulted in 105 of 400 vessels and 29 of 101 patients being non-diagnostic by CCTA.

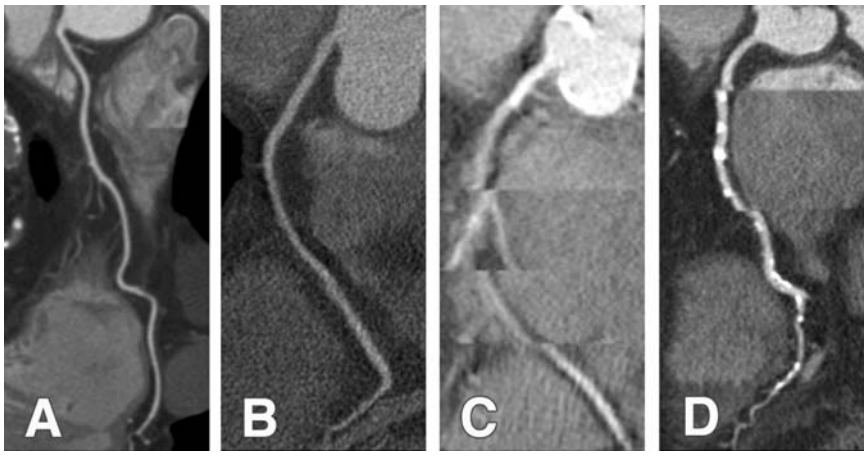

Figure 4. Four patients illustrating different technical limitations of CCTA. A. Excellent image quality. B. Low contrast attenuation and high degree of image noise (obese patient, BMI 37 kg/m^2). C. Motion artifacts. D. Multiple calcifications and some motion artifacts.

Patients with a non-diagnostic CCTA had a higher mean heart rate (64 vs. 59 beats/min, $p<0.005$). A heart rate above 60 beats/min was associated with more non-diagnostic patients (38% vs. 18%, $p<0.05$) (Figure 5). There was no significant difference depending on mean age and BMI, but female sex was more common in non-diagnostic patients (43% of women had non-diagnostic scans compared to 20% of men, $p<0.05$). Female sex was not correlated to higher age, BMI, or heart rate ($p>0.8$).

On per-patient basis (72 patient with diagnostic scans), CCTA had a sensitivity of 100%, specificity of 65%, PPV of 79%, and NPV of 100%. On per-segment basis (1006 segment with adequate or excellent image quality), CCTA had a sensitivity of 78%, specificity of 95%, PPV of 54%, and NPV of 98%.

By including non-diagnostic segments (all 274 non-diagnostic segments with poor image quality at CCTA were added as potentially stenosed, thus increasing the false-positive counts), CCTA had a sensitivity of 88%, specificity of 77%, PPV of 28%, and NPV of 98% on per segment basis. On the per-patient basis (101 patients), using

the same logic (all patients with non-diagnostic scans were counted as potentially stenosed), sensitivity was 100%, specificity 40%, PPV 63%, and NPV 100%.

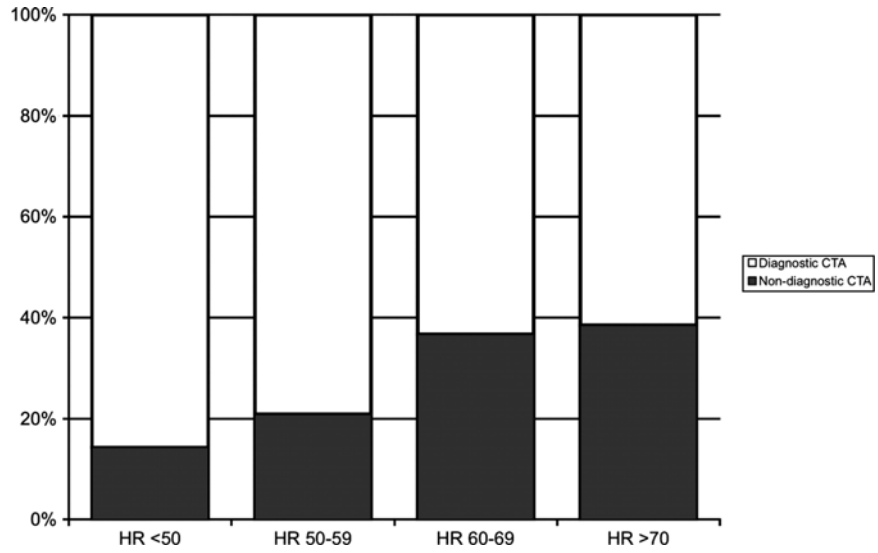

Figure 5. Proportion of non-diagnostic CTA scans depending on heart rate. The CCTA was rated as non-diagnostic on the patient level if no stenosis was found and at least one segment was non-diagnostic. Twenty-one patients had a heart rate (HR) below 50, 24 patients 50-59, 30 patients 60-69, and 26 patients had a HR above 70 beats/min.

The result of the more experienced observer compared to our (local radiologists) result is summarized in Table 3.

Table 3. Comparison of the result (on per-segment basis) from the more experienced observer and the local radiologists. In the all segment result, non-diagnostic segments counts as potentially stenosed.

	Local radiologists	The more experienced observer
Interpretable segments	1006/1280 (79%)	906/1280 (71%)
Sensitivity	78%	59%
Specificity	95%	99%
PPV	54%	74%
NPV	98%	97%
All segments (n=1280)		
Sensitivity	88%	82%
Specificity	77%	73%
PPV	28%	24%
NPV	98%	97%

5.1.2 Comments

We found a higher proportion of non-diagnostic segments (21%) compared to other studies (4%, range 0-15%) (65). The two most common factors for non-diagnostic quality were motion artifacts (associated with high or irregular heart rate) and severe calcifications. We identified heart rate over 60 beats/min as a significant cause of non-diagnostic segments, which is confirmed in other studies (66, 67). Eighty patients took oral beta-blockers regularly, four received intravenous beta-blockers at examination and seventeen patients did not have any beta-blockers. Thus, a more rigorous use of beta-blockers prior to the CCTA might have reduced the number of non-diagnostic scans.

Calcifications were the other main reason for non-diagnostic segments. Due to blooming artifacts from the calcification, calcified segments can be hard to interpret Figure 6). This factor is difficult to reduce, but some studies suggest that you should not perform a CCTA, when the initial calcium score is high (66).

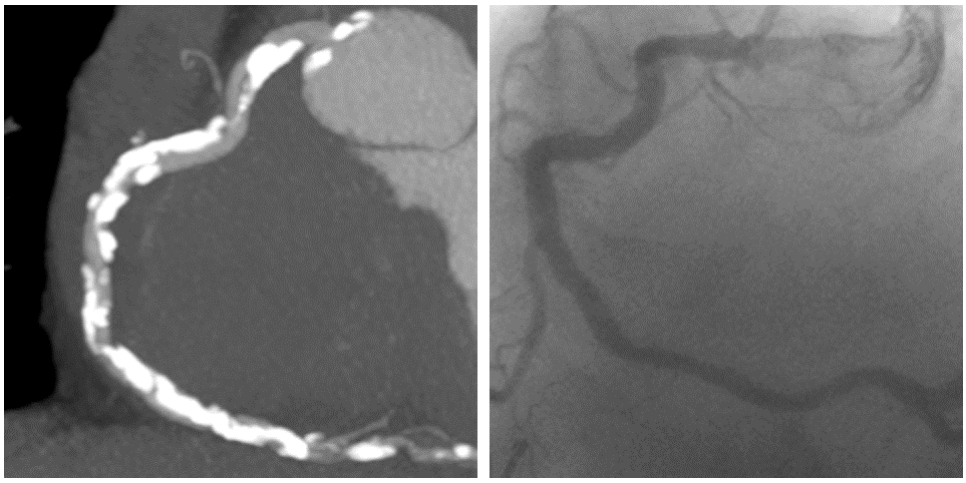

Figure 6. Severe calcifications in right coronary artery (RCA) at CCTA (left). Corresponding ICA revealed no significant stenosis.

Somewhat surprisingly, female patients were more than twice as likely as men to have non-diagnostic CCTA (43% vs. 20%). The reason for this is not clear. Another study found no difference in diagnostic of men and women (68), whereas another study found a lower PPV in women (69). But Meijboom et al also found that the sensitivity was lower in distal segments for women compared to men (56% vs. 85%) and also in side branches (54% vs. 89%) (69). It is likely to believe that women generally has smaller coronary arteries than men and this might lead to that the coronary arteries are more difficult to interpret. A possibility to overcome this problem might be to use nitro glycerine before scanning to dilate the coronary arteries (70). In our study we did not use nitro glycerine. Another explanation might be that female breast would give higher image noise, thereby be more difficult to interpret especially the distal segments.

As our CCTA service was recently established when this study was performed and the experience of CCTA interpreting of the two local radiologists was limited, we validated our data using an independent observer with experience of more than 500 CCTA scans. Overall, the experienced observer was not superior to the local

radiologists, suggesting that short experience did not influence the interpretation (Table 3). Not surprisingly, the mean review time was lower for the more experienced observer (5.8 minutes, range 2-18 minutes), compared to that of the novices (26 minutes, range 9-84). The review time included an upload time of 2-3 minutes to get images into the workstation.

5.2 STUDY II

5.2.1 Results

There was a successive improvement ($p<0.05$) in PPV during the 10 sessions for the radiologists, but not for the radiographers. Otherwise, there was no significant improvement in sensitivity, specificity, or NPV for any of the observers or together as a group (Table 4).

Table 4. Diagnostic accuracy and predictive value in 10 successive sessions (each with 10 cases) for detecting significant obstructive lesions. The *p*-value indicates the successive improvement during the 10 sessions. The total number of significant stenoses per session is also presented.

	Session	1	2	3	4	5	6	7	8	9	10	*p*-value
All observers	Sensitivity	0.50	0.66	0.75	0.43	0.54	0.72	0.62	0.36	0.61	0.89	NS
	Specificity	0.92	0.95	0.93	0.96	0.97	0.92	0.97	0.99	0.94	0.94	NS
	PPV	0.48	0.54	0.65	0.53	0.30	0.60	0.68	0.90	0.51	0.61	NS
	NPV	0.95	0.98	0.97	0.94	0.99	0.96	0.96	0.93	0.96	0.99	NS
Radiologists	Sensitivity	0.50	0.61	0.76	0.36	0.75	0.80	0.72	0.42	0.74	0.96	NS
	Specificity	0.88	0.95	0.88	0.95	0.97	0.89	0.96	0.98	0.95	0.94	NS
	PPV	0.38	0.55	0.40	0.40	0.40	0.54	0.63	0.79	0.60	0.60	<0.05
	NPV	0.93	0.97	0.97	0.93	1.00	0.97	0.97	0.92	0.97	0.99	NS
Radiographers	Sensitivity	0.50	0.70	0.74	0.50	0.33	0.65	0.51	0.30	0.49	0.83	NS
	Specificity	0.96	0.95	0.99	0.97	0.98	0.95	0.98	1.00	0.94	0.94	NS
	PPV	0.58	0.54	0.91	0.66	0.20	0.67	0.73	1.00	0.41	0.61	NS
	NPV	0.96	0.98	0.97	0.94	0.99	0.94	0.95	0.94	0.95	0.98	NS
Number of stenoses		15	10	20	14	5	16	16	17	10	15	-
Number of segments		122	128	131	125	128	126	125	132	129	131	-

The radiographers had a better total specificity than the radiologists (0.96 vs. 0.93, $P<0.01$), but there was no significant difference in sensitivity (0.55 vs. 0.66), PPV (0.63 vs. 0.53), or NPV (0.96 vs. 0.96) between radiographers and radiologists. When the first and last 50 cases (sessions 1-5 vs. sessions 6-10) were compared, the radiologists improved in PPV from 0.43 to 0.63 ($p<0.01$), but for the radiographers the increase (from 0.58 to 0.69) was not statistically significant.

The mean review time per examination was 21.6 (range 4-60) min. There was no difference in mean review time between radiographers (21.8 min) and radiologists

(21.5 min). There was a significant decrease in average review time during the 10 sessions for all reviewers except for one radiologist. The mean review time per examination during the first session was 32.4 min, and during the last session 15.7 min (Figure 7).

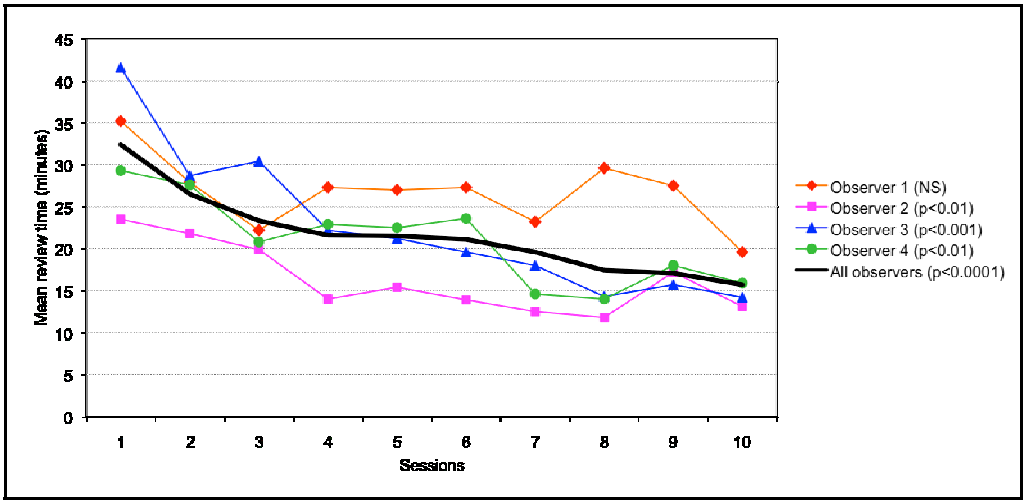

Figure 7. Mean review time in minutes per session for each observer and for all observers combined. The *p*-value indicates the successive improvement during the 10 sessions.

5.2.2 Comments

We wanted to study the learning curve effect for the interpretation of CCTA and to investigate whether it is possible to train radiographers to interpret CCTA. To our knowledge this was the first study of this kind. Since our CCTA service was newly established, we had to use the CCTA examinations we had at the time for the study start. These cases were consecutively included in another study (*study I*) with relatively high prevalence of CAD. The patient selection was thus not representative of the low-risk group that is more suitable for CCTA interpretation, which we believe had major impact on for the results.

We found a learning-curve effect regarding PPV for the radiologists, but, rather surprisingly, there was no observed significant improvement in sensitivity and specificity for either the radiologists or the radiographers during the 10 consecutive sessions. This finding is contradictory to the learning effect assumed in the recommendations from the American College of Radiology (ACR) (71) and the American College of Cardiology Foundation together with American Heart Association (ACCF/AHA) (52, 53), in which our 100 reviewed cases exceed the requirements of the former and almost meet the requirements for level 2 proficiency of the latter (Tables 5 and 6).

The most plausible explanation is that 100 cases are too few to obtain a learning-curve effect. Some sessions may also have been more complicated to evaluate than others due to technical imperfections, and this difference might have concealed the learning curve. These two assumptions are supported by the lack of statistical significance despite the rather great increases in sensitivity for the radiologists, when comparing the first and last 50 cases.

Table 5. Overview of the ACR guidelines from 2006 (71).

	Prior experience of CT	No prior experience of CT
Education in cardiac anatomy, physiology, pathology and cardiac CT imaging	≥ 30 h	≥ 30 h
Interpretation, reporting and/or supervised review of contrast-enhanced cardiac CT	≥ 50 cases	≥ 50 cases
Completion of an approved cardiac CT training program	No	Yes
Interpretation and performance of general CT	No	200 h
Supervised interpretation and reporting CT examinations	No	500 cases

Table 6. Overview of the ACCF/AHA recommendations from 2005 (52, 53).

	Level 1	Level 2	Level 3
Cumulative duration of training	1 month	2 months	6 months
Minimum number of mentored examinations present during performance	-	35	100
Minimum number of mentored examinations interpreted	50	150	300

Previously, other centres have reported a sensitivity of 86%, specificity 96%, PPV 83% and NPV 96.5% for CCTA (65). However, it has not been reported how many cases these reviewers experienced in order to reach this diagnostic level. Our relatively low values, particularly for sensitivity, even in the second half of the study (73% sensitivity for the radiologist and 56% sensitivity for the radiographers, on a per-segment basis), might also be due to the selection of cases/segments. Since we did not exclude segments with calcifications and artifacts, our examinations were technically complicated to evaluate.

In this study, each of the observers spent approximately 2 weeks of effective work to evaluate all cases. This relatively short and intensive learning period may have had a negative impact on the learning curve. However, it is not clear whether the learning conditions would have been improved if the training had been spread out over a longer period. On the contrary, the training period was similar to that of a training course, e.g., CT training courses endorsed by the Society of Cardiovascular Computed Tomography (www.scct.org). After the publication of our study, Pugliesi et al showed that acquiring expertise in CCTA was slow and might take more than one year (72).

Three of four observers improved their review time significantly with maintained accuracy. This improvement may be explained by increased confidence both in workstation handling and in anatomy. Interestingly, the most experienced radiologist did not improve review time significantly and also required the longest time for the evaluations. Probably due to less experience at the particular workstation used, but it could be speculated that the psychological pressure, of being compared with radiographers, might have influenced this result.
The training program in our study included personal feedback with tutored

comparison of the corresponding ICA in all cases. Theoretically, a merging of different imaging modalities for the same anatomical region should be a valuable educational tool. However, the main reason for including comparison with ICA was to give feedback based on the gold-standard reference rather than on personal experience alone. Strangely, nothing about the necessary of using corresponding ICA as feedback is mentioned in the recommendations from ACR and ACCF/AHA (52, 53)

In contrast to our expectations, the radiographers had a higher specificity at the start of the training program compared to the radiologists. This difference was no longer significant after 50 reviewed cases. The reason for the improved specificity among the radiographers is difficult to explain, but might be that the previous experience in image post-processing may have assisted in ruling out artifacts. Though there was no significant difference between radiologists and radiographer (except PPV), there was a tendency towards better performance by the radiologists (Figure 8). Further studies of learning curve effect with an increased number of examinations would be of great interest. However, to start a follow-up study demands observers with no former experience in CCTA.

The results for the radiographers, especially NPV, indicate that radiographers might be considered to participate in an interpretation situation. Though, the radiographers in our study may have been more motivated than the average radiographer. Both have great interest and knowledge in the post-processing of general CT examinations, acquired over several years. The dedication of the radiographers was probably an essential element in their good performance. Their experience in workstation handling may also have positively influenced their interpretation of the images.

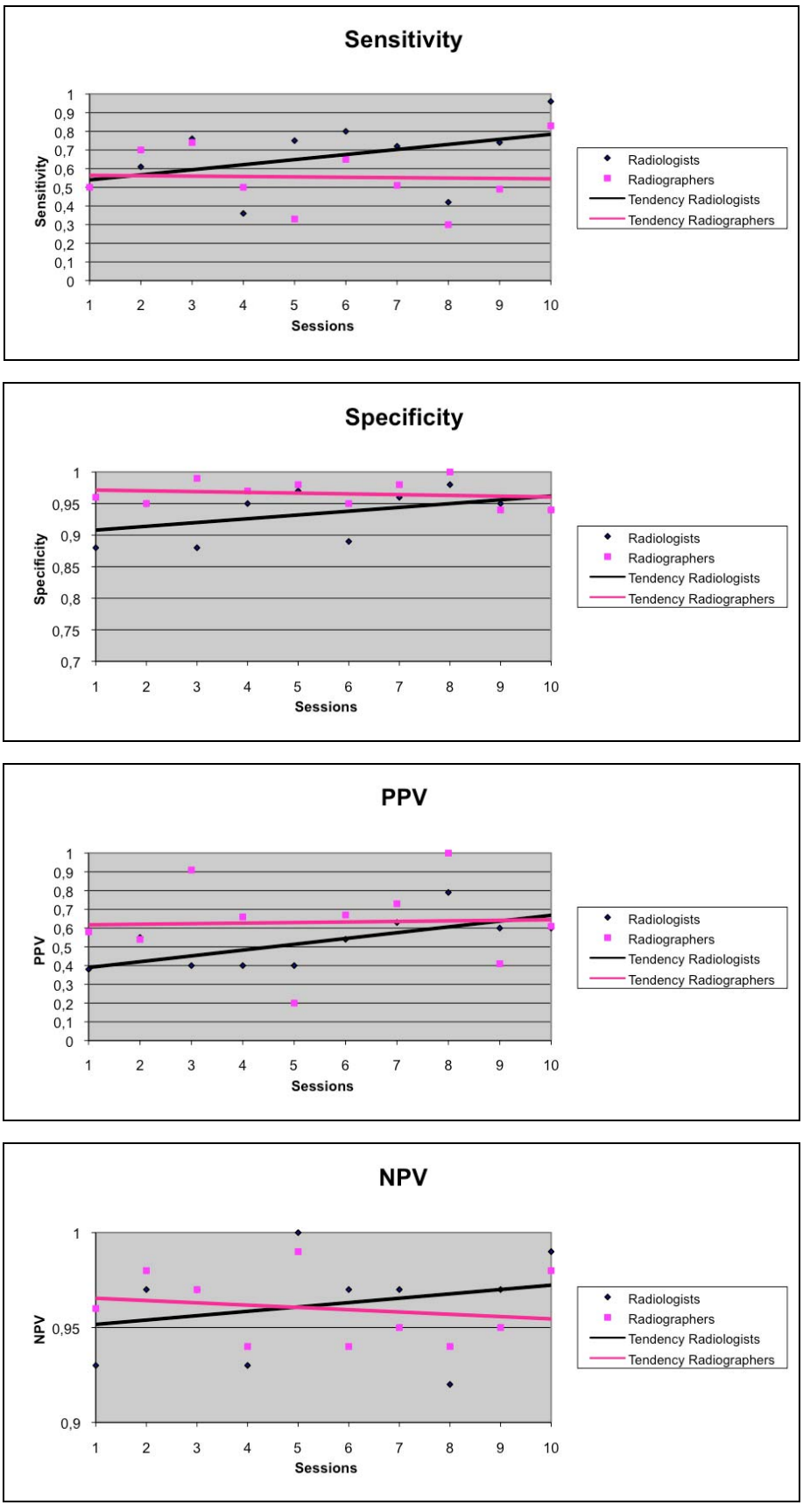

Figure 8. Tendencies for radiologists and radiographer regarding sensitivity, specificity, PPV and NPV during the 10 sessions.

5.3 STUDY III

5.3.1 Results

The radiation doses are summarized in Table 7. The mean ED based on ICRP 103 was 29.9±5.4 mSv for CCTA compared to 5.0±2.6 mSv for ICA (p<0.0001). The organ doses were 165.4±35.1 mGy (skin), 67.4±10.9 mGy (breast), 76.1±12.9 mGy (lung) and 97.0±17.8 mGy (oesophagus) for CCTA including the test bolus. For ICA the doses were 141.5±74.1 mGy (skin), 1.8±1.3 mGy (breast), 18.8±9.6 mGy (lung) and 14.9±7.4 mGy (oesophagus). The mean ED based on ICRP 60 was 24.2±4.5 mSv for CCTA compared to 29.9±5.4 mSv based on ICRP 103 (p<0.0001).

Table 7. Comparison of radiation doses between retrospectively ECG-gated coronary CT angiography (CCTA) and invasive coronary angiography (ICA). All calculations using ICRP 103 tissue weighting factors.

	CCTA	ICA	*p*-value
Effective dose (mSv)	29.9±5.4 (21-44)	5.0±2.6 (1.2-15)	<0.0001
Maximum skin dose (mGy)	165±35 (109-358)	141±74(32-408)	<0.05
Breast dose (mGy)	67±11 (55-99)	1.8±1.3 (0.4-9.2)	<0.0001
Lung dose (mGy)	76±13 (56-114)	19±9.6 (4-55)	<0.0001
Oesophagus dose (mGy)	97±18 (58-144)	15±7.4 (3.5-35)	<0.0001

Presented data are mean values, standard deviation (SD) and range in parenthesis.

5.3.2 Comments

When evaluating patients with suspected CAD retrospectively ECG-gated CCTA with 64-channel detector gives significantly higher ED and organ doses, including MESD, compared to ICA. When using the new ICRP 103 weighting factors the effective doses at CCTA were significantly higher than when using the outdated ICRP 60 weighting factors (29.9 mSv compared to 24.2 mSv, p<0.0001). This is in accordance with previously published data (73, 74). The large difference in calculated dose between the two protocols is probably due to the great increase in tissue weighting for breast, from 0.05 to 0.12, when updating the ICRP 60.

The radiation dose to all organs was higher at CCTA than at ICA. Of greatest concern is the breast dose, which from CCTA was approximately 40 times higher, compared to ICA (67 mGy respective 1.8 mGy). For comparison, a typical mean glandular radiation dose in a two-view digital mammography is approximately 3.7 mGy (75). A CCTA is therefore equivalent to 18 digital mammograms. The high doses to the breasts in our study is in line with the results from Nickoloff et al, who in a phantom study estimated the dose to breasts to 30-100 mGy (76).

In our study the MESD at ICA was rather roughly estimated by using the mean of two conversions factors obtained in a previous study for two other operators using a similar x-ray angiography unit (52). The obtained MESD at CCTA should therefore be regarded to be in the same range as ICA (165 mGy compared to 141 mGy), even if the difference was statistically significant (p<0.05). The relatively high MESD at

CCTA can be explained by the exposure during the test bolus (97 mGy). Techniques to reduce the radiation exposure during the test bolus should therefore have a great impact on the MESD. At ICA, MESD is heavily dependent on patient size and operator awareness of radiation protection measures. The greatest individual MESD was therefore observed in ICA (408 at ICA compared to 358 mGy at CCTA). However, when performing CCTA and ICA under controlled settings and by experienced operators MESD is normally safely below the threshold dose for transient skin injuries, which typically is 2 Gy (52).

5.4 STUDY IV

5.4.1 Results

The radiation dose parameters were lower (p<0.0001) in the 100 kVp cohort compared with the 120 kVp cohort (Table 8). The mean $CTDI_{vol}$, DLP and estimated effective dose were reduced by 40%, 49%, and 52%, respectively, at 100 kVp. The recorded scan length was shorter (p<0.001) in the 100 kVp cohort compared with the 120 kVp cohort (mean value 13.5 cm versus 16.0 cm).

Table 8. Results of vascular density, image noise, signal-to-noise ratio (SNR), contrast-to-noise ratio (CNR), subjective image quality, scan length and radiation dose parameters.

Parameter	Mean value (120 kVp)	Mean value (100 kVp)	p-value
Vascular density in the AA (HU)	434	496	<0.01
Vascular density in the LMCA (HU)	397	476	<0.0001
Density of perivascular tissue (HU)	-56	-65	0.05
Image noise in the AA	30	44	<0.0001
SNR AA	15.3	11.7	<0.0001
SNR LMCA	14.0	11.2	<0.0001
CNR AA	17.2	13.2	<0.0001
CNR LMCA	16.0	12.7	<0.0001
Subjective image quality	3.4	3.1	NS
Scan length (cm)	16.0	13.5	<0.0001
$CTDI_{vol}$ (mGy)	57.4	34.4	<0.0001
DLP (mGy×cm)	1125	578	<0.0001
Effective dose (mSv)	20.2	9.6	<0.0001

AA = ascending aorta. LMCA = left main coronary artery. HU = Hounsfield units. $CTDI_{vol}$ = volume computed tomography dose index. DLP = dose-length product. Subjective image quality is then mean and median values for the subjective image quality scores 1 to 4.

Measured image noise was lower and calculated SNR and CNR were higher (p<0.0001) in the 120 kVp cohort compared with the 100 kVp cohort (Table 8).
However, there was no statistically significant difference regarding subjective image quality between the two cohorts; mean 3.4 and 3.1 on the Likert scale in the 120 and 100 kVp cohorts, respectively.

ICA identified 59 (120 kVp) respective 160 (100 kVp) significant stenoses in the cohorts. In the two cohorts, CCTA had a sensitivity of 88% (120 kVp) and 84% (100 kVp). The specificity was 71% (120 kVp) respective 74% (100 kVp).

5.4.2 Comments

To estimate the effective dose (ED) we used the DLP-method. Instead of using traditionally used general conversion factors (77, 78) we used a conversion factor that is specific for the type of scanner we used (62), which might be more correct. By lowering the kVp from traditionally 120 kVp to 100 kVp, a reduction of 40% of the reduction dose was achieved, after adjusting for different scan length. Other studies have found reductions of 25-40% in similar studies (79-82).
Comparison of the two cohorts in this study showed shorter scan lengths used in the 100 kVp cohort (p<0.001). Since shorter scan length will give proportionally decreased radiation dose, the shorter scan length in the 100 kVp cohort will convey approximately 16% of the total DLP and estimated effective dose reductions. According to the $CTDI_{vol}$ values in the present study, shifting from 120 to 100 kVp implies a dose reduction of 40% for the same scan length. The importance of minimizing the scan length in CCTA is well known (83-85) and this study is a reminder that every extra unnecessary centimetre gives the patient about 1-2 mSv extra radiation dose, when the retrospective ECG-gated technique is used.

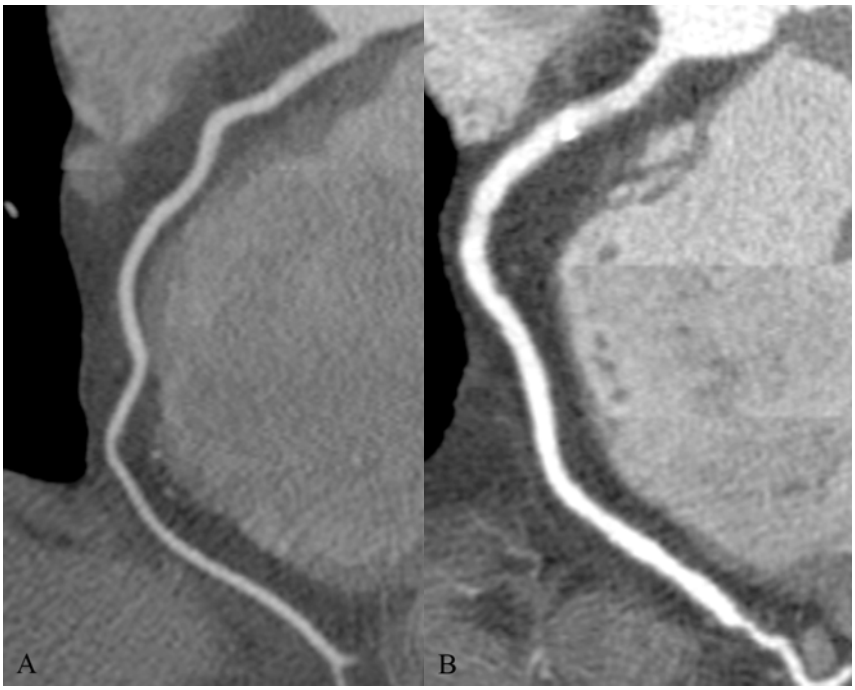

Figure 9. Curved multiplanar reconstruction of the right coronary artery demonstrating the image quality with different tube voltage (A, 120 kVp and B, 100 kVp) in two cases, both with BMI of 26 kg/m2 and CNR of 16. Both figures have window width 100 HU and window level 200 HU. Note the increased vascular density and image noise in figure B (100 kVp).

Despite the considerable radiation reduction in our study there was no statistically significant difference in subjective image quality between our two cohorts. Regarding objective image quality there was a difference with lower SNR and CNR in the 100 kVp cohort. In conformity with other studies (79-82), we observed an increase in

image noise at 100 kVp compared with 120 kVp, as well as an increase in vascular density between the two cohorts (Figure 9). Because of the latter, some other studies have showed no significant difference in CNR from examinations with 100 kVp compared to 120 kVp (79, 81, 82). Since we found a mean CNR in the LMCA of 12.7 and a mean subjective image quality score of 3.1 in the 100 kVp cohort, the optimal levels of CNR in CCTA might be discussed. To our knowledge there is no definition of the minimum values of CNR for acceptable quality in the literature, but different authors have suggested a variety of definitions. Leber et al. (86) set the level of CNR >3 for assessable vessels. Karaca et al. (87) defined CNR levels as follows: >8, high quality image; 4-8, moderate quality image; and <4, poor quality image. Similar definitions have been described for other anatomic regions, for example, for pulmonary arteries, where a CNR <5 resulted in suboptimal quality (88). In view of these definitions, our result for CNR in the 100 kVp cohort seems to be clearly acceptable for assessable examinations, even though it is lower than for the 120 kVp cohort.

6 DISCUSSION

6.1 CCTA FOR BEGINNERS (STUDY I)

Compared to other CT examinations, CCTA is more demanding regarding patient selection, patient preparations, scanning and interpretation. It is therefore a challenge for beginners to acquire the necessary expertise both for the scanning procedure and the interpretation.

Compared to other studies, our results in *study I* showed somewhat lower accuracy and more non-diagnostic segments. In search for an explanation we involved an external and experienced colleague. The hypothesis that our limited experience was the explanation was ruled-out by the fact that the colleagues' result was in accordance with ours. Kolnes et al described a high sensitivity and a high NPV when introducing CCTA at a local hospital with observers that were beginners (89). However, specificity and in particular PPV were lower compared to results published by other centres, due to overestimation of CAD severity. They identified calcification to be the most important factor for false-positive results (80% compared to our study 55%).

An important finding about the scanning procedure from *study IV*, with partly the same patients in *study I*, was that the scan length in our early scans were significantly increased compared to later scans. This probably due to the radiographers was afraid to miss any part of the heart when scanning, which might be a typical result of inexperience. It was a reminder that every extra centimetre in the scan length gives the patient 1-2 mSv extra effective radiation dose, using retrospectively ECG-gated technique.

6.2 READER EXPERIENCE AND TRAINING (STUDY II)

An important factor affecting the quality of CCTA interpretation is readers' experience (72, 90-92). Expert guidelines recommend specific CCTA training courses at various levels to achieve the required skills. One guideline recommends the interpretation of at least 50 CCTAs (Table 5) and another at least 150 CCTAs (Table 6), but it appears to be no scientific evidence to support these guidelines (71, 52, 53).

Recently the Society of Cardiovascular Computed Tomography (SCCT) presented their guidelines for the interpretation and reporting of CCTA, with the aim to establish standards meant to ensure reliable practice methods and quality outcomes (93). The some what lack of standards for training and limited number of experienced readers are some factor that can influence the outcome of CCTA interpreting quality, which can lead to "a bad reputation" and could lead to that the development of the method may decrease. Therefore, efforts should be made to offer a standardized CCTA training program to radiologists or other readers, to achieve the required experience. One way to get this may be to establish a certification process.

6.3 RADIATION ASPECTS (STUDY III)

Comparison between the two imaging methods (CCTA and ICA) regarding radiation is problematic, since the CT scanner derived DLP and fluoroscopy system derived DAP do not allow direct comparisons. However by using a computer based anthropomorphic model the calculation of effective dose (ED) for both modalities can be done and thereby facilitate direct comparison.

There are mainly two different methods to calculate ED in CCTA. In the first method, called *the DLP method*, the ED is estimated from the product of the DLP and an ED conversing factor (E_{DLP}). The DLP is recorded directly from the CT-console at the time from the scan. The E_{DLP} is a conversing factor that is considered to be between 0.014-0.019 mSv x mGy^{-1} x cm^{-1} for the chest region (42, 77, 78). It has also been calculated as specific factors depending on type of scanner (62), as we used in study IV (0.018 for a GE LightSpeed VCT). The other method used is normally called *the phantom method*. In this method the ED is calculated as the sum of the measured absorbed organ doses, multiplied by individual tissue weighting factors published by ICRP using computational Monte Carlo modelling (94).

Most published studies have used the simpler DLP method instead of the more specific phantom method. The conversion factors used (0.014-0.019), are based on the outdated ICRP 60 tissue weighting factors. Other studies, which used the phantom method, are also mainly based on old ICRP 60 data. Since measurement based on ICRP 103 instead of the old ICRP 60 gives an increase of radiation dose of approximately 16-40%, it is of utmost importance to consider this difference when referring to older studies (73, 74). Depending on which calculation method adopted, the results in our study population should vary from 16.7 mSv to 29.9 mSv (Table 9).

Table 9. Estimated effective doses from CCTA using different calculation methods.

Effective dose calculation method	Effective dose (mSv)
DLP x 0.014	16.7
DLP x 0.017	20.3
DLP x 0.019	22.6
Phantom ICRP 60 (Monte Carlo)	24.2
Phantom ICRP 103 (Monte Carlo)	29.9

Breasts have been recorded to have the highest absorbed organ doses from CCTA. Of particular concern is the female breast, which may receive a dose up to 10-30 times higher than received in mammography screening (76). In fact, the lifetime risk for breast cancer in girls and young women undergoing a single ECG-gated CCTA may range from 1.7% to 5.5% (94). In order to reduce the radiation exposure to the breasts at CCTA, especially in younger women, a so-called bismuth shield can be used (95, 96). A technique to reduce the radiation exposure to the breasts in women by reducing the radiation when entering the anterior part of the body at CCTA has also been described (97).

6.4 RADIATION REDUCTION ASPECTS (STUDY IV)

Radiation dose has become a major safety issue in cardiac imaging. Since the introduction of 64-slice CCTA the radiation doses has successively decreased from initial up to 30 mSv to some cases reported below 1 mSv (94, 98). It seems that the mean radiation dose have decreased at least by approximately 50% every 2 years since 2005 (98). One plausible explanation for this great dose reduction is due to several new radiation dose techniques but could also be regarded as a learning curve effect and illustrates the importance being scrupulous in radiation exposure questions and to have close collaboration with physicists. A non-randomized, controlled, prospective, multicenter trial showed a mean reduction from 21 mSv to 10 mSv, in one year (July-August 2007 to May-June 2008). During the study time, the 15 different CCTA-centres (both doctors and radiographers) were educated in several dose reduction strategies such as minimizing z-axis coverage, tube current modulation and decreasing the kilovoltage in normal-weight patients (99).

During the last 5 years several techniques aiming at reduce radiation exposure in CCTA have been described. These include, for example, ECG-based tube current modulation, prospectively ECG-triggered CCTA, iterative reconstruction technique, high-pitch mode and helical prospective ECG-gating (6-12, 42, 100, 101). Some of these techniques is scanner specific and cannot be used by everyone and some requires a low and regular heart rate. However, in most hospitals, 64-slice CCTA with retrospective ECG-gating is still the standard technique (32) and whatever type of scanner is used it is important to be active in common dose saving strategies for every examination. The most important dose saving strategy is of course to only perform CCTA for appropriate indications. Other is to limit the z-axis coverage to a minimum required and frequently use as low kVp as possible.

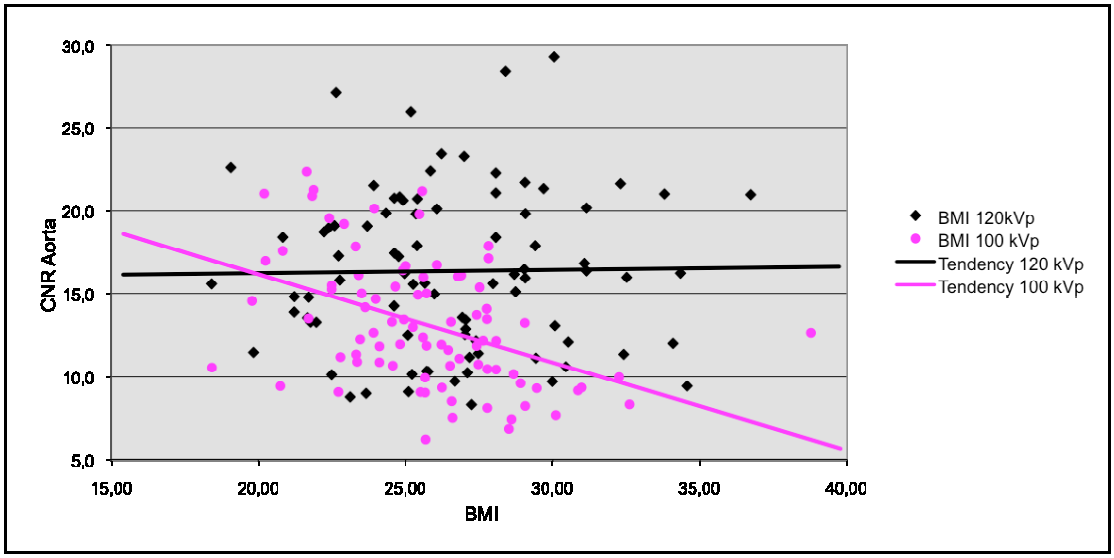

Figure 10. This diagram illustrates the proportion between contrast-to-noise ratio (CNR) in the ascending aorta and body mass index (BMI), for the 120- respective 100 kVp cohorts. The tendencies for each cohort are also illustrated.

By lowering the X-ray tube potential while keeping the other scanning parameters unchanged, the radiation dose to the patient will decrease by a factor roughly equal to the quotient between the final and initial peak kilovoltage (kVp) to the power of 2.0-

2.5 (102, 103). As the radiation intensity to the detectors also will decrease, an increased image noise will follow. At the same time the spectrum of photon energies will move closer to the k-edge of iodine (33.2 keV). This in turns results in an increased attenuation of photons by the iodine atoms (103, 104), which is why the final result may be a relatively unchanged CNR, an objective parameter to characterize image quality (105). Even if we found clinically acceptable image quality at 100 kVp, very small vessels might be difficult to analyze because of the increased noise. Other studies have recommended that 100 kVp should only be used at patients with BMI less than 25-30 30 (106, 107). In our study we had no BMI-limitation for be included, resulted in 48 patients with BMI>25 was scanned with 100 kVp (Figure 10).

The importance of radiation issues is emphasized by SCCT in their guidelines for performance of CCTA (30). They state that all examinations should be performed and interpreted by physicians adequately trained in CCTA, which include adequate knowledge of the ALARA (As Low As Reasonably Achievable) principle from the standpoint of radiation exposure.

7 CONCLUSIONS AND FINAL REMARKS

These four studies present some aspects when introducing a new method, 64-row detector CCTA with retrospective ECG-gating technique.

Study I:
CCTA seems to be well suited for the exclusion of CAD, due to its very high NPV. The main limitation was non-diagnostic scans due to motion artifacts and vessel calcifications. More aggressive heart rate lowering with pre-scan beta-blockers may reduce motion artifacts. Relatively inexperienced observers were not a limitation, as they had the same diagnostic ability as a more experienced observer. There were more non-diagnostic scans in women and in patients with a heart rate of 60 beats/min or higher. More research is warranted to explore the diagnostic limitations of CCTA in women.

Study II:
Although there was a learning-curve effect in PPV for the radiologists, this study indicates that 100 cases are probably too few to significantly improve diagnostic accuracy in CAD detection at CCTA and to reach diagnostic accuracy that is acceptable. The review time for novices in CCTA was halved during the first 100 cases, with maintained accuracy. This study also shows that the diagnostic accuracy of dedicated radiographers indicates that they might be considered to be included as part of the evaluation team.

Study III:
The mean ED for retrospectively ECG-gated CCTA was higher compared to ICA. The organ doses to skin, breast, lungs and oesophagus were also higher in CCTA. The relatively high radiation dose to breast indicates that bismuth shielding should be used in women when performing CCTA. When using the updated tissue weighting factors provided in ICRP 103 the calculated ED from CCTA were significantly higher than those obtained using outdated ICRP 60.

Study IV:
By reducing the X-ray tube voltage from 120 to 100 kVp at CCTA, while keeping all other scanning parameters unchanged, the radiation dose to the patient can be almost halved while keeping the diagnostic quality at a clinically acceptable level.

Several meta-analyses have shown that the NPV of the method is excellent, close to 100%, suggesting that CCTA can reliably rule out the presence of significant stenosis. PPV, however, has been less impressive. In most cases, this is due to overestimation of detected stenoses in MDCT (25, 65, 108-111). The false-positive stenosis has been shown to attribute the image artifacts (mainly calcifications) in 91-100% (27, 112). Of three multi-centre trials published, two was consistent with the results of the meta-analyses (7, 113) but the other showed only moderate NPV for CAD (114).

In order to establish CCTA as a clinically acceptable and complementary method for evaluation of CAD some critical issues (*indications, radiation* and *training*) should be considered for referring doctors as well as for the performing physicians. Although there is considerable enthusiasm, many doubts remain about the appropriate clinical

indications of CCTA. It is likely that outcome data will become available over time, with the increased clinical utilization. In the meantime, the high NPV make CCTA ideal for excluding CAD in patients with low-intermediate probability. CCTA may be an effective gatekeeper to ICA, in the work-up for diagnostic ICA and in patients presenting with chest pain in the emergency department (115, 116) by identifying patients without significant coronary artery stenosis thus eliminating their need for ICA and reserving ICA for those patients who may benefit from coronary revascularization. Chow et al showed that with the implementation of a CCTA program, the frequency of normal ICA decreased significantly from 31.5% to 26.8%, which was significantly different from centres without dedicated CCTA during the same time period (117). On the other hand, CCTA has a low degree of invasiveness, and this could lower the natural threshold to not examine a low-risk patient. With this in mind, and the high over estimation of non-significant stenoses in calcified plaque gives us the challenge to avoid that implementing CCTA results in an increasing number of referrals to ICA due to false-positive results.

The national guidelines for cardiac care (2008) from the National Board of Health and Welfare (Socialstyrelsen) in Sweden, recommends that CCTA should be used only within the context of scientific studies. This due to lack of scientific evidence for the result from CCTA to be equivalent with those from ICA, high radiation dose to the patient, heart rate dependent image quality, high number of non-diagnostic segments due to calcifications and complicated interpretation procedure. In an updated report, "2010 appropriate use criteria for cardiac CT" from the American College of Cardiology Foundation (ACCF) (118), ninety-three clinical indications were developed and classified into three sub-groups: appropriate use (n=35), inappropriate use (n=29) and uncertain use (n=29), based on current evidence. In general, the writing group found that CCTA is usually appropriate for diagnosis or risk assessment in patients with low or intermediate risk of coronary artery disease. However, testing is usually inappropriate for patients at high risk. Also, the criteria are generally unfavourable toward routine repeat testing and general screening with CCTA. Example of top-ranked appropriate use indications:

- Assessment of anomalies of coronary arteries
- Detection of CAD in symptomatic patient (non acute) when ECG is un-interpretable or patient unable to exercise and with intermediate pre-test probability of CAD
- Evaluation of graft patency after coronary artery by-pass graft (CABG)

The *radiation* aspects must, as always, be considered with great responsibility and knowledge. Of particular concern is the female breast that may receive a dose (from retrospectively ECG-gated CCTA) up to 10-30 times higher than received dose in mammography screening. The use of bismuth shielding to protect the breast should be considered if the image artefacts could be minimized. American guidelines from both radiological and cardiological societies regarding clinical competence levels for performing CCTA emphasises not only knowledge of the ALARA principle but also adequate *training* for this demanding examination including both usage of proper indications, performance of the scanning and reading and reporting of findings including incidental pathological findings outside the heart. All these aspects are important to pay attention to, especially for novices and newly started centre. To get the most successful heart evaluation team, a multimodality approach with close collaboration between radiologists, cardiologists, clinical physiologists and physicists are desirable.

Finally, despite acceptable image quality and diagnostic accuracy in 64-detector row CCTA the technique is still not fully developed. Promising technical improvements are already on the market and additional solutions just around the corner. In this decade we will probably also se the application of functional imaging of CAD by CCTA.

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