MULTI-DETECTOR ROW CT OF THE HEART: METHODOLOGICAL EVALUATION AND APPLICATION IN HIGH-RISK PATIENTS

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MULTI-DETECTOR CT VAN HET HART: METHODOLOGISCHE EVALUATIE EN TOEPASSING BIJ PATIËNTEN MET EEN HOOG RISICO

(met een samenvatting in het Nederlands)

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Aan mijn moeder

CONTENTS

CHAPTER 1

GENERAL INTRODUCTION

Chapter 1

INTRODUCTION

Cardiovascular diseases are the most important cause of morbidity and mortality in the Netherlands as well as in other developed countries [1]. Coronary heart disease mortality comprises thirty percent of the cardiovascular deaths [1]. Although age-standardized death rates have shown a decrease recently, the absolute numbers of deaths from cardiovascular diseases continue to increase [2] and cardiovascular diseases are still projected to be the leading cause of death worldwide by 2020 [3].

Many deaths due to coronary heart disease occur suddenly and before symptoms of ischemic heart disease have arisen [4]. In the current guidelines for cardiovascular risk management, the use of risk scores like the Framingham risk score (in the USA) or the HeartScore (in Europe) is recommended [5,6]. These risk scores define ten-year risks for myocardial infarction and cardiac death based on several established cardiovascular risk factors such as hypertension, hypercholesterolemia, diabetes and smoking [6]. Based on the estimates of 10-year risk non-pharmacological or pharmacological therapy is initiated. Although these risk scores are regularly used in clinical practice, there is sufficient room for improvement since these functions are modest in adequately identifying subjects at risk. Subjects designated to the low risk group can still suffer from early cardiovascular events and not all subjects assigned to the high risk group die from a cardiovascular cause. About 40% of subjects in the general population have an intermediate risk (10-20% 10-year risk) according to the Framingham risk score [4]. These subjects do neither have such a low risk that preventive treatment is not indicated, nor do they have such a high risk that preventive treatment is necessary. The optimal treatment strategy in the intermediate-risk group is uncertain. Thereby, these risk scores have been specifically developed to be applied in subjects without symptoms of cardiovascular disease. Subjects with symptoms, e.g. patients with intermittent claudication, automatically enter the highest-risk group and are thus eligible for intensive preventive medical treatment. The use of risk estimators to further differentiate risk among patients in the highest-risk group and thereby to select those eligible for further diagnostic testing is uncommon in current clinical practice.

Non-invasive tests may on the one hand be applied in asymptomatic subjects to improve risk estimation by risk scores and on the other hand in patients with symptoms of cardiovascular disease to select those eligible for a further diagnostic workup with more invasive tests. Several non-invasive tests have been studied for their ability to improve risk estimation, such as ECG exercise testing, carotid intima-media thickness measurements by ultrasonography and coronary calcium scoring by computed tomography (CT) [7-9]. Echocardiography, myocardial perfusion SPECT, cardiac MRI and cardiac CT may be applied in symptomatic patient groups to select those who need a

further workup [10,11]. In this thesis the focus is on cardiac imaging with CT: both CT calcium scoring and coronary CT angiography.

CORONARY CALCIUM SCORING

CT calcium scoring has shown excellent results in large populations for the prediction of events [9,12-15]. It has been shown to improve risk estimation by the Framingham risk score, especially in the intermediate-risk group [16]. In a clinical expert consensus document on coronary artery calcium scoring by computed tomography published in 2007 [17] the use of calcium scoring for screening was allowed in certain patient groups, while in the previous guidelines from 2000 the use of coronary artery calcium scoring was discouraged [18].

The optimal CT technique for calcium scoring remains an issue. Originally, CT calcium scoring was performed with electron beam computed tomography (EBCT) [19]. Most follow-up data on calcium scores that have been published used EBCT calcium scores. Calcium scoring with single-detector row CT was not a realistic option due to the long rotation and scan times. The introduction of MDCT improved temporal resolution and allowed ECG-synchronization. This opened up the opportunity to also perform calcium scoring with MDCT. Studies comparing EBCT and MDCT calcium scores showed good inter-scanner correlations [20-23]. However, the high inter-scan variability of EBCT and MDCT calcium scoring with prospective ECG-triggering remained a problem and the underlying causes have not been entirely elucidated [24]. The reproducibility of retrospectively ECG-gated calcium scoring was found to be much better [25-27], but a main disadvantage of this approach is the high radiation dose [28]. This high radiation dose has even lead to the fact that the cardiovascular working group of the American Heart Association state in their guideline that prospectively ECG-triggered CT scanning for calcium scoring purposes is strongly recommended despite the poorer reproducibility [29].

In **chapters 3 to 5** of this thesis calcium scoring techniques are further evaluated. In **chapter 3** the effect of scan starting position on inter-scan reproducibility of calcium scoring is elucidated. In **chapter 4** is studied if the reproducibility of prospectively ECG-triggered calcium scoring scans can be improved by using overlapping sections instead of contiguous sections. In **chapter 5** is studied what the optimal application of ECG-based tube current modulation during retrospectively gated scanning is to maximally decrease patient radiation dose without inducing large calcium score errors.

CORONARY COMPUTED TOMOGRAPHY ANGIOGRAPHY

CT calcium scoring has been criticized for being nonspecific as compared with coronary angiography [17]. Invasive angiography is currently the standard test to verify the presence of coronary artery disease in symptomatic patients and it is the mainstay for decision

making processes. Invasive coronary angiography, however, is an examination with high costs and the complication rates are too high to be neglected when applying it in cardiac asymptomatic individuals, even if these individuals are at a high risk for cardiac morbidity and mortality [30-33].

With the advent of multi-detector row CT non-invasive coronary angiography has become a realistic option. 4-detector row CT did suffer from a large portion of non-evaluable segments due to the long scan time (40 s) and poor temporal and spatial resolution [34-37]. However, scan time drastically decreased with the arrival of 16-detector row CT (20-30s) and later 32-, 40- and 64-detector row CT (8-15s) [38]. This made scanning during a single breath-hold feasible in almost all patients. Shorter tube rotation times caused an increase in temporal resolution and thinner detectors improved spatial resolution. Still, the temporal resolution of invasive conventional angiography has not been met but the studies that compare CT coronary angiography and invasive coronary angiography generally have shown excellent results [39-42]. Only a few studies gave less optimistic results but these studies did appear to show a more realistic viewpoint on the value of CT coronary angiography [43-45]. As for many other emerging techniques, results outside the expert centers will probably even be worse.

As always with continuously improving technology newer is naturally considered to be better. Was 16-detector row CT 'state-of-the-art' at its arrival in 2002, it lost this title soon to 64-detector row CT, which became available in 2004 [38]. Improvements in scan protocols largely depend on scanner performance and thus on the efforts of manufacturers to improve scanner performance. Higher resolution, less motion-sensitivity and shorter scan durations have been the focus of attention. Ways to achieve this have been studied and tried out extensively.

Less attention has been given to the optimization of contrast medium injection protocols, despite changing demands on contrast injection protocols. With the improvements in CT scanners scan times decreased and contrast enhancement needed to be reached faster. Simply decreasing contrast injection duration would result in lower enhancement, therefore, higher concentration contrast media were considered necessary to accommodate the injection of a larger iodine dose in a shorter time frame [46].

In **chapters 6 and 7** of this thesis we study contrast injection parameters for 64-detector row CT of the heart. In **chapter 6** two contrast medium concentrations are compared under otherwise identical parameters to determine if higher is truly better. In **chapter 7** the application of a new contrast injection protocol is studied to find out if new features in contrast injector design allow optimization of the contrast injection with a decrease in contrast medium volume administered to the patient.

EXPANDING INDICATIONS FOR CARDIAC CT

Improvements in CT scanner technology not only allow the replacement of invasive procedures by non-invasive techniques, but also create a window of opportunity with regard to new indications. So far, the main focus of studies has been on replacing invasive coronary angiography by non-invasive coronary CT angiography for several clinical problems, such as confirmation or exclusion of coronary artery disease and follow-up of coronary artery bypass grafts and stents [38,47-51]. Since most studies comparing coronary CT angiography and invasive angiography find a high negative predictive value, the exclusion of significant coronary artery disease has been a main focus. Coronary CT angiography may be used as a selection tool in the work-up for diagnostic angiography and in patients presenting with chest pain in the emergency department [52-54]. If coronary CT angiography is negative, diagnostic angiography may not need to be considered. The role of cardiac CT could, however, be expanded outside the clinical applications of invasive coronary angiography. An interesting option for non-invasive cardiac CT is screening. If cardiac CT is applied for screening it is no longer used to exclude coronary artery disease but rather to diagnose significant coronary artery disease eligible for treatment. It is, so far, unknown if this option requires further consideration. In **chapter 8** the rationale and design of the GROUND study are described. In this study peripheral arterial disease patients who are cardiac asymptomatic undergo screening for cardiac disease with CT for a morphological evaluation and MRI for a functional evaluation of the heart. In **chapter 9** baseline results are analyzed with specific attention for the value of calcium scores in this cardiac high-risk patient group.

SUMMARY

In summary, the focus of this thesis is on the methodological evaluation of cardiac CT and the application of cardiac CT in a high-risk patient group. **Chapter 2** provides an introduction into the technical background of cardiac CT scanning as well as contrast injection parameters. Before exploring a potential new indication of cardiac CT in the third part of this thesis, current protocols are evaluated in the second part. In the first three chapters of the second part (**chapters 3-5**) the evaluation of CT calcium scoring techniques are dealt with: can CT calcium scoring technique be optimized? In **chapters 6 and 7** evaluation of contrast injection protocols for contrast-enhanced cardiac CT is performed: does contrast medium behave as we expect it to based on current models? In the third part (**chapters 8 and 9**) the application of cardiac CT is studied in a screening protocol for patients with a high risk for cardiac morbidity and mortality. Finally, all findings of this thesis are discussed in **chapter 10** and summarized in **chapter 11**.

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CHAPTER 2

MULTI-DETECTOR ROW COMPUTED TOMOGRAPHY OF THE HEART – TECHNICAL BACKGROUND

Chapter 2

INTRODUCTION

Imaging of the heart, including the coronary arteries, puts high demands on the modality used since a high temporal and spatial resolution are needed to deal with the rapid cardiac motion and the small dimensions of the coronary arteries. Conventional single-detector row CT scanners did not supply for this. The advent of 4-detector row computed tomography in 1998 substantially improved the temporal and spatial resolution of computed tomography scanners and this created a window of opportunity for non-invasive imaging of the heart [1,2]. Since then CT imaging of the heart has undergone a rapid development [3]. Currently 64-detector row systems are available as well as a dual source CT scanner with two rotating X-ray tubes in a single gantry [4-6]. In 2007 developments certainly have not stopped and CT scanners with detector rows up to 256, that allow imaging of the heart in a single heartbeat, are on their way [7].

Computed tomography is not the only non-invasive modality that can be used to image to heart. Echocardiography is the most used imaging modality in cardiology. Mostly functional studies are performed with this technique, it does not allow visualization of the coronary arteries. Magnetic resonance imaging is also increasingly used for cardiac imaging. Both cardiac morphology and function can be studied with this technique. Visualization of the coronary arteries with MRI appears feasible. While MRI has the advantage of no application of radiation dose and a high temporal resolution, MDCT can be performed faster, is less expensive, allows patients with intra-cardiac devices and has a higher spatial resolution. Short scan durations, a sub-millimeter spatial resolution, a relatively high temporal resolution, and reconstruction techniques including ECG synchronization turn MDCT the modality of choice for non-invasive imaging of the coronary arteries at this moment, the year 2007. These different aspects of MDCT are further explained in the following paragraphs, succeeded by a brief explanation of contrast injection parameters important for contrast-enhanced cardiac CT scans.

SCANNING PARAMETERS

Spatial resolution

Spatial resolution is a measure of the detail of an image. The higher the spatial resolution, the more details can be distinguished. Since the coronary arteries have small dimensions of only a few millimeters a high spatial resolution is needed to visualize and detect luminal narrowing and plaques. To increase spatial resolution along the z-axis with a certain type CT scanner, a longer scan duration is generally needed. With current 64-detector row CT scanners a section thickness between 0.5 and 1.0 mm is usually chosen. This is not nearly as good as the spatial resolution of 0.2 mm of conventional invasive angiography. It is unlikely that isotropic voxels of 0.2 mm in all three directions

will ever be used since the radiation dose needed to reach this will be too high. One possibility to increase the spatial resolution without drastically increasing the radiation dose is by using the best spatial resolution in-plane – any plane – combined with a through-plane resolution of several millimeters to improve the signal to noise ratio.

ECG synchronization

ECG synchronization is performed to obtain motion-free images of the heart despite a scan duration of several heartbeats (Figure 2-1). ECG synchronization is divided into prospective ECG-triggering and retrospective ECG-gating (Figure 2-2). With prospective ECG-triggering the scanner performs a single rotation or less at a defined time point after

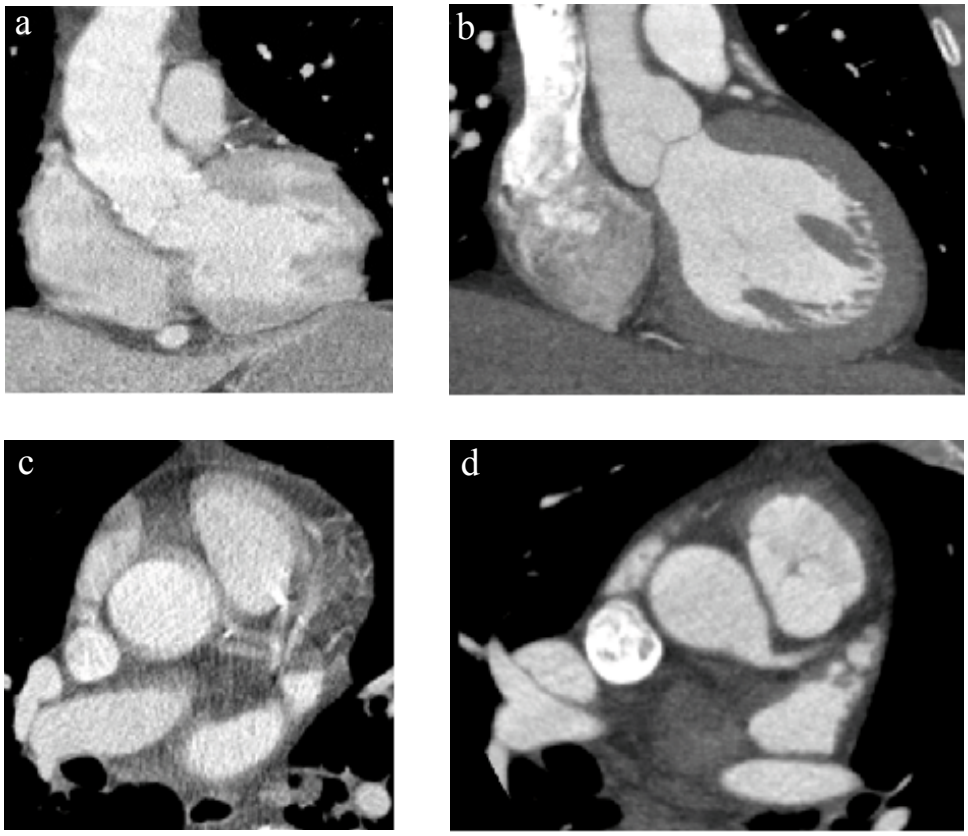

Figure 2-1. *Upper row: coronal images of the heart obtained without (a) and with (b) ECG synchronization. Bottom row: axial images at level of left main origin obtained without (c) and with (d) ECG synchronzation. Note the cardiac motion artifacts present in (a) and (c).*

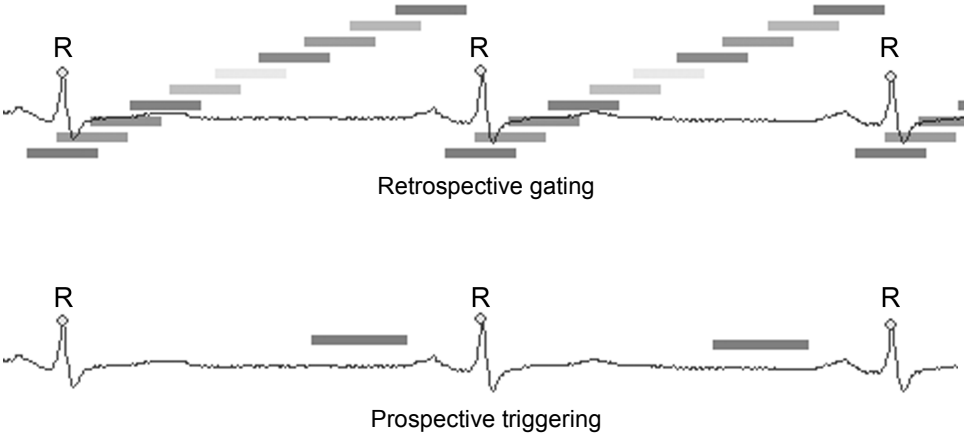

Figure 2-2. *Schematic views of retrospective ECG-gating and prospective ECG-triggering. With retrospective ECG-gating scanning is continuous and afterwards data reconstruction can be performed of the complete volume during different phases of the RR-interval (represented by the ten bars). With prospective ECG-triggering the scanner performs a single rotation or less at a defined time point after the R-peak to obtain images in a single phase of the RR-interval (bar represents a mid-diastolic phase).*

the R-peak to obtain images in one single phase of the RR-interval, usually mid-diastole. Between tube rotations the table moves the distance of the used scanner collimation (number of detector rows x detector width). This technique is very sensitive for motion artifacts due to heart rate variability and is not suited for imaging the coronary arteries. Imaging of the coronary arteries is generally performed with retrospective ECG-gating. A continuous scan throughout the RR-interval is performed with simultaneous ECG-recording. Afterwards data reconstruction can be performed of the complete volume during different phases of the RR-interval (defined by the percentage of the RR-interval with the R-peak at 0% or by the time before/after the R-peak in ms). The data set at the most optimal time point can be chosen after the scan has been performed. Since it allows reconstructions at any time point of the RR-interval, cardiac function can also be evaluated.

Temporal resolution

The temporal resolution is the time it takes to assemble the necessary data for reconstructing one image. A high temporal resolution is necessary when imaging the heart to minimize cardiac motion-induced artifacts. The temporal resolution of CT is dependent

on the time of one gantry rotation. Data acquired in projections of 180° plus the width of the fan beam is needed to reconstruct a cross-sectional image (i.e. partial scan reconstruction technique). This data can be acquired from a single rotation; temporal resolution then amounts to around half of the gantry rotation time. With prospective ECG-triggering this is always the case. If retrospective ECG-gating is performed one method to improve the temporal resolution is to use data from several consecutive heart beats and thereby to reduce the data assembly time window to for instance one-quarter rotation by assembling data from two consecutive heart beats. This technique is called multi-phase reconstruction. The dual-source CT scanners can also reach a temporal resolution of one-quarter rotation without applying multi-phase reconstruction techniques since the two X-ray tubes are arranged at an angle of 90°. With current 64-detector row CT scanners rotation times are ≤ 420 ms and a temporal resolution of 50 ms can be reached with the application of multi-phase reconstruction. Further improving temporal resolution by shortening scan rotation times is restricted by physical limitations due to the enormous forces acting on the rotating tube. Therefore, dual-source scanning and advances in reconstruction techniques are more likely to improve the temporal resolution.

With an increase in temporal resolution image quality will become less dependent of low heart rates. Cardiac CT is now preferably performed at heart rates below 65 beats per minute since the length of the quiet phase of the heart at mid-diastole is then long enough to obtain motionless images [8]. The length of this quiet phase at mid-diastole exponentially decreases with an increase in heart rate [9]. To obtain these low heart rates most institutions apply beta-blockers before scanning (either orally or intravenously).

Radiation dose

The radiation dose of cardiac CT is dependent on the ECG synchronization technique used. With prospective ECG-triggering the radiation dose that is applied to the patient is considerably lower than with retrospective ECG-gating: 1 to 4 mSv and 10 to 20 mSv, respectively [10,11]. With prospective ECG-triggering all radiation dose applied is used to reconstruct images; with retrospective ECG-gating highly overlapping data acquisition needs to be performed to obtain data at each position throughout the RR-interval and eventually much more dose is applied than is used for each image. CT calcium scoring is often performed with prospective ECG-triggering. Coronary CT angiography is performed with retrospective ECG-gating since this approach is less sensitive for motion artifacts than scanning with prospective ECG-triggering.

ECG-based tube current modulation has been developed to allow a reduction in radiation dose with retrospective ECG-gating. The maximum tube current is only applied during prospectively determined time intervals of the RR-cycle, e.g. mid-diastole. During the rest

of the RR-cycle the tube current is decreased to about 20% of the maximum. Dose savings of around 40% have been reported with this technique [12,13]. A drawback of this technique is that it requires a stable heart rate to function optimally since the modulation intervals are prospectively determined and cannot be altered afterwards. Most dose saving is achieved at low heart rates, which is another argument to administer beta-blockers right before the scan.

Scan duration

Without ECG-gating techniques a length of 30 cm (e.g. the length of a thorax-scan) can be encompassed in 10 s with a 16-detector row CT scanner and even in only 4 s with a 64-detector row CT if an effective section thickness of 1 mm is needed. Scanning the same length with a single-detector row spiral CT would have taken at least 30 s and section thickness would have been > 5 mm. To obtain motionless images of the heart ECG synchronization techniques are applied which demand strongly overlapping data acquisition, which lengthens the scan duration. At the same time it is important that scan duration remains within one breath-hold to prevent respiratory motion. With a 16-detector row CT a strongly overlapping ECG-gated data acquisition of the heart (i.e. 12 cm scan length) can be performed in less than 25 s, with 64-detector row CT within 12 s. A breath-hold of 12 s can be easily performed by the majority of patients. Therefore, scan duration is no longer a limiting factor for obtaining good quality images of the heart with 64-detector row CT scanners.

Contrast injection

Optimal visualization of the heart and especially the coronary arteries demands sufficient contrast enhancement. With the current short scan times a high contrast enhancement is preferably achieved fast and maintained during the scan acquisition. An injection protocol commonly used in coronary CT angiography is a monophasic contrast medium injection of about 20 seconds (scan duration + delay) at a high flow rate directly followed by a saline flush, which leads to washout of the right ventricle [14]. This right ventricle washout is advocated to allow optimal visualization of the right coronary artery. However, if cardiac CT is not only used for coronary artery stenosis detection but also for functional evaluation of the ventricles or if ECG-gated CT of the heart and large vessels is used for a triple workup (coronary artery disease, aortic dissection and pulmonary embolism), enhancement of the right ventricle and pulmonary arteries is also required. A biphasic contrast injection protocol with a first contrast medium injection phase to reach optimal enhancement of the coronary arteries, aorta and left ventricle and a directly following second contrast medium injection phase to maintain contrast enhancement in the right

ventricle and pulmonary arteries can be performed. This does not necessarily impede evaluation of the right coronary artery [15].

A contrast injection protocol is based upon the following parameters: contrast volume (ml), contrast agent concentration (mg Iodine/ml), injection rate (ml/s) and scan delay (s) (i.e. the delay between the start of the contrast injection and the start of the scan acquisition). These parameters can be varied to obtain an optimal contrast regimen for each application. Combined they determine magnitude of arterial enhancement. The duration of the scan delay largely determines the phase of contrast enhancement during the scan acquisition.

According to a relatively simple linear model the arterial enhancement grows proportionally with the injected iodine dose (= contrast volume × concentration) and with the iodine flux (= iodine administration rate = injection rate × concentration), which can be controlled by changing contrast concentration and/or injection rate. The expected effects of varying contrast concentration, flow rate and contrast volume on peak arterial enhancement and time to peak are provided in Table 2-1.

Studies on contrast dynamics have shown that a uniphasic contrast injection (constant rate) will not lead to a plateau of contrast enhancement in the aorta but rather to a hump-shaped enhancement curve [16]. A plateau-like enhancement can be achieved through a biphasic or multiphasic injection that starts with a high flow rate, which is decreased after several seconds to reach a plateau [17,18].

Table 2-1. Influence of variation of injection parameters on peak arterial enhancement and on time to peak arterial enhancement: (A) increase in iodine dose and flux, (B) increase only in iodine flux, (C) increase only in iodine dose, and (D) unchanged iodine dose and flux

	Contrast concentration (mg I/ml)	Injection rate (ml/s)	Total injected volume (ml)	Peak arterial enhancement (ΔHU)	Time to peak enhancement (s)
A	↑	=	=	↑	≈
B	=	↑	=	↑	↓
C	=	=	↑	↑	↑
D	↑	↓	↓	≈	≈

Since the spontaneous flow in the injection veins is usually slower than the injection rate, the inflow of contrast material slows as the injection is completed. This ends the aortic plateau before all contrast has even arrived. A saline flush, injected immediately after contrast administration at the contrast injection flow rate, pushes the contrast material forward and prolongs the aortic plateau phase [19,20].

Contrast enhancement also depends on many patient-related factors such as cardiac output, body mass, and blood volume [21-23]. A reduction in the cardiac output results in an increase in peak arterial enhancement because less dilution of the contrast agent occurs in the blood vessels. However, the upslope of contrast enhancement during the first pass is lower and the peak arterial enhancement is reached later. The use of a test bolus or of bolus tracking instead of a fixed delay can partially take the effect of cardiac output into account [24-26]. For a given contrast dose, arterial and organ enhancement are inversely proportional to body mass, so the ratio of contrast dose to body mass is a key determinant of enhancement. An increase in blood volume will result in more dilution of contrast and less enhancement. Increasing iodine dose and flux with an increase in patient size can adjust for this effect.

Summary

In summary, in this chapter we have introduced the aspects of current MDCT scanners that allow non-invasive imaging of the heart as well as the most important contrast injection parameters. Careful consideration of these various aspects is essential for improvement of scan and injection protocols. At the same time advances in scanner technology are likely to influence these aspects and to necessitate constant changes in protocols.

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CHAPTER 3

CORONARY CALCIFICATION: EFFECT OF A SMALL VARIATION OF SCAN STARTING POSITION ON AGATSTON, VOLUME AND MASS SCORES

Chapter 3

ABSTRACT

Purpose

To retrospectively evaluate the effect of a small variation of scan starting position on coronary artery calcium scores from non-overlapping 3-mm multi-detector computed tomography (MDCT) data sets.

Materials and Methods

A retrospective study was performed by using unenhanced prospectively ECG-triggered cardiac MDCT scans in 228 women (mean age, 67 yrs ± 5 [standard deviation]). From the original 1.5-mm data set, two sets of adjacent images with a section thickness of 3 mm and a variation in starting point of 1.5 mm were obtained. Calcium scoring was performed to acquire Agatston, volume and mass scores. Subjects were assigned to one of five risk categories (I-V) according to the Agatston score of each 3-mm data set and their average. Kappa value was calculated to assess agreement in risk category assignment. Differences and relative differences between scores obtained for both 3-mm data sets were calculated overall and per risk category. The effect of scoring algorithm on the relative differences between scores was analyzed with the Wilcoxon signed rank test.

Results

Categories I to V contained 102, 35, 48, 31 and 12 subjects, respectively. For all scoring algorithms, median relative differences decreased from more than 130% in category II to less than 10% in category V. In the three highest categories, relative differences were significantly smaller for volume and mass scores than for Agatston scores ($P<.05$). Twenty-one subjects were assigned to different risk categories between the two data sets (kappa 0.87). Eleven patients were assigned a nonzero score in one and a zero score in the other data set.

Conclusion

A small variation in scan starting position can substantially influence calcium measurements and poses an inherent limit to calcium scoring with contiguous 3-mm sections. Mass and volume scores are slightly less affected than Agatston scores.

INTRODUCTION

Calcium score appears to be a predictor of risk for future cardiac morbidity and mortality [1-5]. On the basis of calcium score, patients can be assigned to a risk category or percentile that defines which treatment is needed [6-10]. Calcium scores have also been suggested as a non-invasive tool for the follow-up of lipid-lowering treatment of coronary artery disease [11-13]. However, the use of calcium scoring for follow-up is controversial [14,15]. To use calcium scores for follow-up, a low inter-scan variability is necessary to detect small rates of change in the individual patient. Most data on calcium scoring and its predictive value have been obtained with non-overlapping 3-mm electron-beam computed tomographic (EBCT) data sets and the Agatston scoring algorithm [16]. Despite the high temporal resolution of EBCT, it has a relatively high mean inter-scan variability of 15-49% [17-22] . New scoring algorithms with continuous measures, such as calcium volume and mineral mass, were developed to replace the stepwise approach of the Agatston score [23-25]. Mineral mass quantification, or mass score, has been shown to be most reproducible [26,27].

With the increasing use of multi-detector computed tomography (MDCT) for cardiac examinations, calcium scoring is nowadays frequently performed with MDCT instead of EBCT. MDCT not only enables EBCT-like acquisitions with prospective electrocardiographic (ECG) triggering, but also enables helical retrospectively ECG-gated acquisitions with reconstruction of partially overlapping sections. This improves reproducibility, but radiation dose substantially increases compared with standard prospectively ECG-triggered acquisitions [28-31]. An international consortium was formed to standardize acquisition and evaluation of coronary calcium scoring scans [32]. While considerable consensus was reached with respect to scan acquisition parameters, the use of both transverse and helical acquisition modes was allowed because both have advantages: lower dose for transverse scanning and overlapping reconstructions for helical scanning. A recent scientific statement by the American Heart Association recommends prospectively ECG-triggered acquisitions because of the lower dose [33].

We hypothesized that scanning sequential 3-mm sections presents an inherent problem with regard to reproducibility because of the occurrence of partial volume effects regardless of scoring algorithm. Small variations in starting position of the scan can have a major influence on partial volume effects (Figure 3-1). These inherent effects could render the acquisition technique with contiguous 3-mm sections less suitable for risk categorization and treatment follow-up than an acquisition with reconstruction of overlapping sections. Thus, the purpose of our study was to retrospectively evaluate the effect of a small variation of scan starting position on coronary artery calcium scores from non-overlapping 3-mm MDCT data sets.

Chapter 3

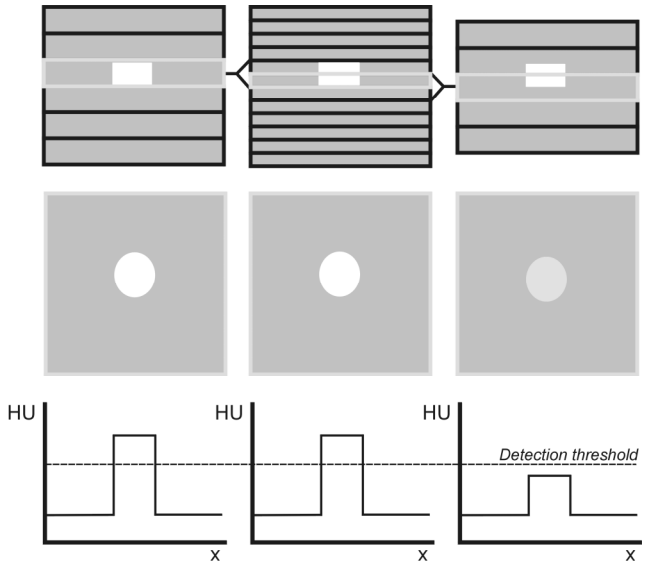


Figure 3-1. *Schematic drawing demonstrates effect of partial volume on calcium scoring. Middle column: 1.5-mm images. Left and right column: 3-mm images with 1.5-mm offset. Upper row: coronal view of CT data set. White square = calcification in two adjacent 1.5-mm sections. Middle row: transverse sections at level of calcification (corresponding to highlighted sections in upper row). Note that attenuation of calcification on left 3-mm image is unchanged (white) while attenuation of calcification is halved (light gray) on 3-mm transverse image with 1.5-mm offset because of partial volume effects. As attenuation falls below the detection threshold, calcium scores vary between two contiguous 3-mm data sets in the same subject.*

MATERIALS AND METHODS

Patients

Two hundred twenty-eight women (mean age, 67 years ± 5 [standard deviation]) underwent sequential unenhanced cardiac MDCT between December 2003 and May 2004 as part of a study on the association between age at menopause and cardiovascular risk. Local institutional review board approval was obtained. At inclusion all women provided informed consent. The women had an average weight of 71 kg ± 12 and an average heart rate during the scan of 69 beats per minute (bpm) ± 10.

Data acquisition

All examinations were performed with a 16-detector CT scanner (16-IDT, Philips Medical Systems, Cleveland, OH, USA). An unenhanced MDCT scan of the whole heart was obtained, starting approximately at the level of the tracheal bifurcation and ending below

the apex of the heart. The scanning parameters were a 16x1.5mm collimation, 120kVp, 40-70mAs (depending on patient weight), a 420-msec rotation time, and prospective ECG-triggering at a time point to obtain data within the diastolic phase.

A non-overlapping set of 1.5-mm-thick sections and a non-overlapping set of 3-mm-thick sections, both beginning at the original scan starting point, were reconstructed from the raw data. The scanner software did not allow reconstruction from the raw data of a 3-mm data set with a starting point 1.5 mm below the original scanning starting point. Therefore, two image sets with non-overlapping 3-mm sections were approximated by averaging sections from the 1.5-mm data set. The first set contained contiguous 3-mm sections beginning at the start of the 1.5-mm data set and therefore could be directly compared with the 3-mm data set reconstructed from the raw data. The second set also contained contiguous 3-mm sections, but this set had a starting point 1.5 mm lower than the first set. This way, two similar data sets of non-overlapping 3-mm-thick sections were created with an offset of 1.5 mm. The starting point of the second 3-mm data set was still above the highest coronary artery; therefore, no calcifications were discarded in the second data set.

Coronary artery calcium measurement

Image sets of all 228 patients were analyzed on a standard personal computer by a single investigator with experience of reading more than 500 cardiac scans. This was done to guarantee continuity and consistency of scoring. To avoid observer variability in calcium scoring, we used the following approach. First, the observer manually identified coronary calcifications in the 1.5-mm data sets, in which all regions with CT attenuation higher than the threshold of 130 Hounsfield units (HU) were marked. The identified calcifications in the 1.5-mm data sets were used as an overlay to determine the presence of calcifications in all 3-mm data sets, namely the data set reconstructed from the raw data and the two averaged data sets. All voxels in the 3-mm data sets at the location of calcifications in the corresponding 1.5-mm data set were automatically analyzed for their attenuation. Only voxels for which the CT attenuation in the 3-mm data set was higher than 130 HU were considered calcifications.

The Agatston, volume and mass scores for the 3-mm image sets were calculated using software written in C^{++}. Scores were implemented as outlined by Ulzheimer and Kalender [34].

Data evaluation

To determine if our method of obtaining two 3-mm data sets with a 1.5-mm offset by averaging sections from a 1.5-mm data set induced major errors, we first compared the calcium scores from the 3-mm data set reconstructed from raw data with scores from the

averaged 3-mm data set with the same starting position. Absolute differences (highest_score – lowest_score) and percentage differences,

$$\frac{2 \cdot (highest\_score - lowest\_score)}{highest\_score + lowest\_score} \cdot 100\%,$$

were calculated to assess variability between the scores from these two data sets.

Absolute differences and percentage differences were also calculated to assess variability between the two averaged 3-mm image sets. Calcium scores have a nonnormal distribution. Therefore, differences were summarized for the overall group and per risk category with medians and complete ranges (minimum to maximum difference) or interquartile ranges (IQR) (25th-75th percentile). Log transformation was attempted to normalize the data, but this did not result in a normal distribution.

Each subject was assigned to a risk category defined by Rumberger et al. based on only the Agatston score [7]. Each subject was assigned to a risk category on the basis of the Agatston score for each of the two averaged data sets and on the basis of the average Agatston score for the two data sets. The risk categories were as follows: category I, indicated an Agatston score of 0 (very low risk); category II, indicated Agatston score > 0-10 (low risk); category III, indicated Agatston score > 10-100 (moderate risk); category IV, indicated Agatston score >100-400 (moderately high risk); and category V, indicated Agatston score >400 (high risk).

Bland-Altman plots were constructed for each scoring algorithm to assess agreement between scores of the two averaged data sets. Differences between the scores of the two image sets were plotted against the average score of the two image sets.

Shifts in risk category assignment between the two 3-mm image sets with 1.5-mm offset were determined for each subject. The conversion rate was calculated as the number of subjects with a changed risk category between these two 3-mm data sets divided by the total number of subjects, multiplied by 100.

Statistical analysis

To determine if the scoring algorithms (i.e., Agatston, volume, and mass) that were applied have an effect on the relative differences found between the two averaged data sets, Wilcoxon signed rank tests were used. Because calcium scores have a nonnormal distribution, testing was performed after patients were assigned to risk categories on the basis of their average Agatston score. A two-sided P-value of less than 0.05 was considered to indicate a significant difference.

To assess agreement in risk category assignment between the two averaged 3-mm data sets kappa value was calculated. All statistical analyses were performed with software (SPSS for Windows, version 12.0.1, 2004; SPSS, Chicago, Ill).

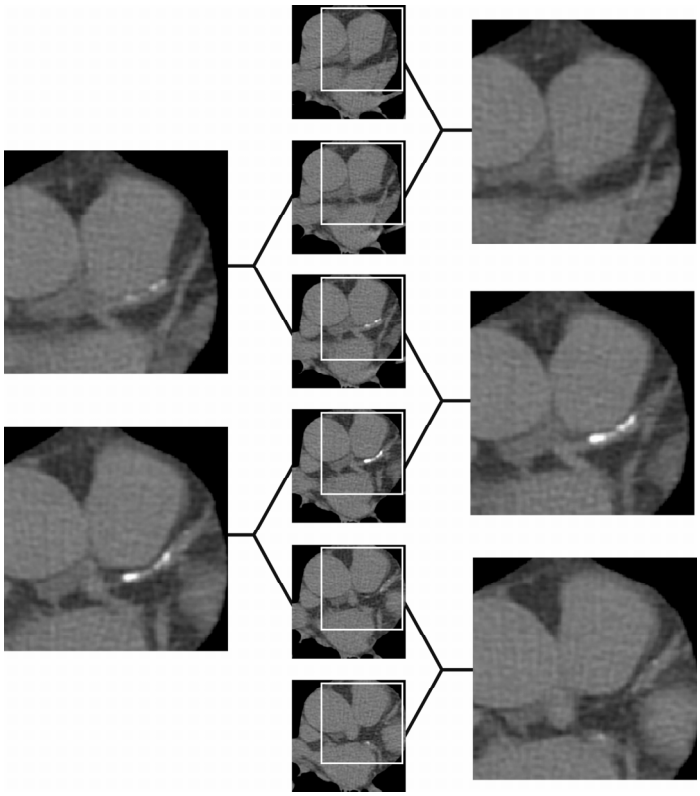


Figure 3-2. *Images show changes occurring in appearance of calcifications on 3-mm CT images, obtained by averaging 1.5-mm sections. Middle column: 1.5-mm images. Left and right columns: corresponding 3-mm images with 1.5-mm offset. Note that both images in left column show calcifications in left anterior descending coronary artery, while on images in right column, calcifications are seen only on middle image. This, invariably, leads to variation in calcium scores.*

RESULTS

Scores

Median average Agatston score was 1 (range 0-2207). Median average volume score and calcium mass were 3 mm^3 (0-1824 mm^3) and 0.3 mg (0-386 mg), respectively. 102 of 228 had a zero score, which means no calcium was detected in either data set. 35 subjects had a score > 0-10, 48 subjects > 10-100, 31 subjects > 100-400 and 12 subjects > 400.

Raw data reconstruction versus averaging

All raw data reconstructions with a zero score also showed a zero score on the averaged data set for all scoring algorithms. Median differences, after exclusion of all zero scores, were 0.3 (IQR 0-0.8) for Agatston score, 0.5 mm^3 (0-1.0 mm^3) for volume score and 0.06 mg (0.01-0.11 mg) for calcium mass. Corresponding median percentage differences were 0% (IQR 0-1%), 0% (IQR 0-2%) and 0% (IQR 0-1%), respectively, after exclusion of all zero scores. All (percentage) differences between the raw data reconstruction and the corresponding averaged 3-mm data set were smaller than those between the two averaged data sets.

Table 3-1. Absolute percentage differences between calcium scores of two contiguous 3-mm data sets with 1.5 mm offset in starting point

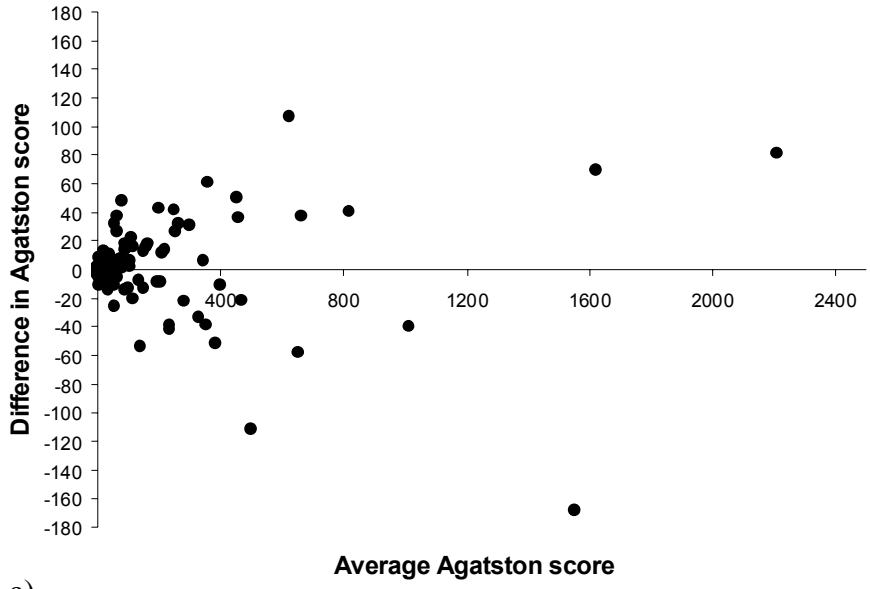
	Calcium scoring algorithm		
Risk category	***Agatston***	***Volume***	***Mass***
II (>0-10)	147% (0-200%)	138% (0-200%)	140% (0-200%)
III (>10-100)	17% (2-64%)	12% (0-60%)*	11% (1-57%)*
IV (>100-400)	10% (2-38%)	6% (0-25%)*	5% (0-36%)*
V (>400)	7% (4-22%)	4% (1-19%)*	5% (0-12%)*

Note.- Data are median percentage differences, with ranges in parentheses.

** Percentage differences with volume and mass score are significantly smaller (P < 0.05) than percentage differences with the Agatston score.*

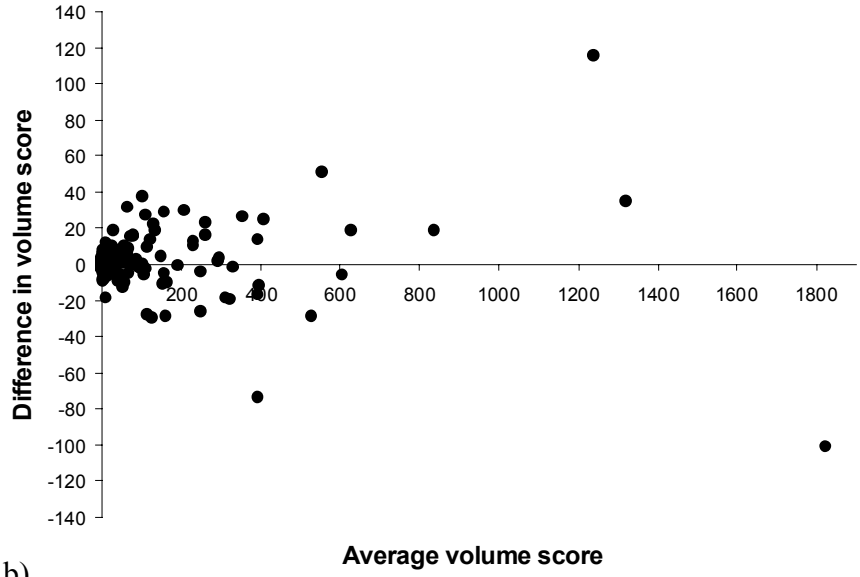
Reproducibility

Differences between the two reconstructions ranged from 0 to 168 for Agatston scores, from 0 to 115 mm^3 for volume scores and from 0 to 14 mg for calcium mass (Figure 3-2). Bland-Altman plots showed that there was an increase of differences with higher scores (Figure 3-3). Percentage differences ranged from 0% to 200% for all scores, with interquartile ranges of 0-18%, 0-12% and 0-13% for Agatston, volume, and mass scores, respectively. Percentage differences decreased with higher scores. Wilcoxon signed rank test results showed that the percentage differences for volume and mass scores were significantly smaller than for Agatston scores in risk categories III and higher ($P < 0.05$) (Table 3-1). There was no significant difference between percentage differences of volume scores and that of mass scores in these categories ($P > 0.05$).

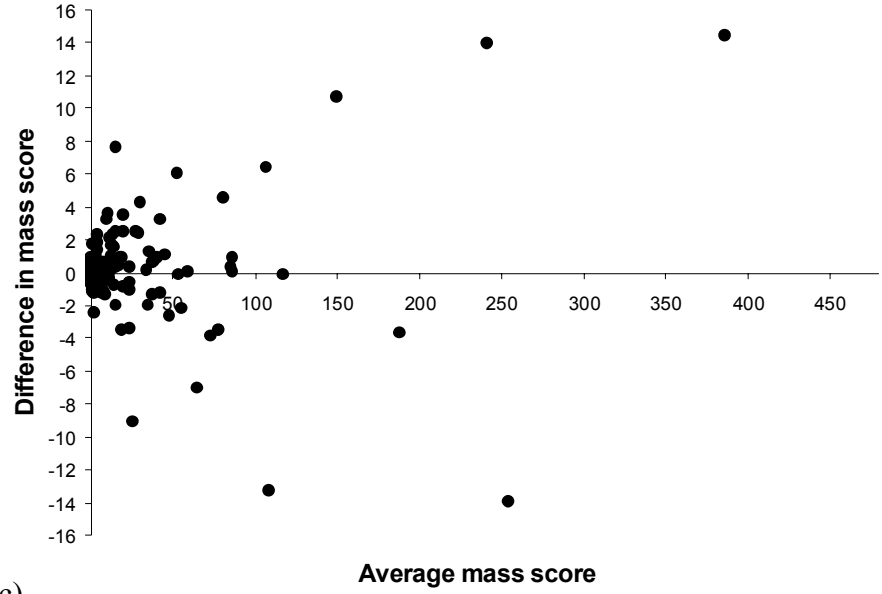


a)

Figure 3-3. *(a) Bland–Altman plot of Agatston scores. Average score from two averaged 3-mm data sets is plotted against difference between scores from two averaged data sets. Figure continues on next page.*



b)



c)

Figure 3-3 (continued). *Bland–Altman plots of (b) volume, and (c) mass scores. Average score from two averaged 3-mm data sets is plotted against difference between scores from two averaged data sets. All plots show an increasing difference with a higher average score.*

Risk stratification

Conversion rate between the Agatston scores of the two 3-mm data sets amounted to 21 (9%) out of 228 subjects (Table 3-2). Eleven (10%) out of 113 subjects with a zero score in at least one data set had a nonzero score in the other data set, regardless of scoring algorithm. If only one 3-mm data set is obtained, about 5% of the zero scores are false negative findings. In our study, it was either three (3%) out of 105 or 8 (7%) out of 110 (Table 3-2). The kappa statistic was 0.87 (i.e., excellent agreement). Although there were shifts in 9% of subjects it never involved a change of more than one category.

Table 3-2. Risk category shift between two 3-mm data sets with 1.5 mm offset in starting point

		Data set A					
	Category	**I**	**II**	**III**	**IV**	**V**	***Total***
Data set B	**I**	102	8	0	0	0	*110*
	II	3	21	3	0	0	*27*
	III	0	1	44	2	0	*47*
	IV	0	0	2	28	2	*32*
	V	0	0	0	0	12	*12*
	Total	*105*	*30*	*49*	*30*	*14*	***228***

Note. – Data are number of subjects.

No shifts of more than one category occurred. Most shifts occurred between zero and nonzero scores.

DISCUSSION

In our study, we identified minor variation in scan starting position as another important contributor to calcium score variability on sequential calcium scoring scans with 3-mm sections. The variability found in our study cannot explain all variability found in earlier reproducibility studies with non-overlapping data sets, but it does appear to explain a large part.

To our knowledge, our study is the first study that involves solely the effect of minor variation in scan starting position on score variability. An earlier study by Mohlenkamp et al. describes the effect of a table shift of 1.5 mm on the reproducibility of the Agatston score and of the calcium area quantification, but in this study two scan runs were performed [35]. The use of two subsequent scan runs introduces variations in patient-related factors, such as heart rate and heart rate variability, which also can influence reproducibility. In light of this, it is not surprising that median percentage differences in the three highest risk categories were almost twice as high as those found in our study. The reproducibility found in our study was truly based on the change in scan starting position; all other factors were constant.

Variability of calcium scoring depends on a large number of factors (e.g. observer, pulsation, breathing, and partial volume effects) [17,18,20-23]. As seen in our study as well, percentage differences decrease with higher scores while absolute differences between measurements increase with higher scores [20-23]. Inter- and intraobserver variability are factors that are mainly influenced by the decision whether to call a high-attenuation object a coronary calcification or not. We have explicitly excluded observer variability between the 3-mm data sets by manually identifying coronary calcifications on a 1.5-mm data set, and automatically calculating the resulting calcium scores for the various 3-mm data sets.

In recent years several studies have been done on the possibilities to improve reproducibility. Thinner sections, thicker sections, early diastolic triggering, resting heart rate adjusted triggering, lower minimum attenuation threshold, variation of minimum threshold dependent on noise level, increase in minimum area, volume score or mass score instead of Agatston score have all been suggested to decrease the inter-scan variability of non-overlapping data sets [17,18,20,21,23,24,26,36-43]. Our study results, however, show that minimal variation of scan starting position highly influences calcium measurements in contiguous data sets. How much of the variability is explained by variation in scan starting position is not entirely clear. As mentioned previously, the variability we found in our study was about half the variability found in a study by Mohlenkamp et al. [35]. However, the inter-scan variability reported by Lu et al. was very similar to the median variabilities found in our study [44]. A change in scan starting position therefore can explain a large part of the inter-scan variability that occurs with the use of contiguous 3-mm sections for calcium scoring.

Partial volume effects and the threshold used for identifying calcifications are the reasons starting position affects calcium scores. Partial volume effects reduce the CT number of a voxel that is only partially filled by a calcification. If the CT number falls below the threshold, this voxel will no longer contribute to the calcium score. This will affect the

volume of a calcification but indirectly also Agatston score and calcium mass. One way to overcome this cause of decreased reproducibility is to use retrospective ECG-gating, which allows reconstructing overlapping sections and thus reduces the influence of partial volume effects. However, use of retrospectively ECG-gated scanning does substantially increase radiation dose [45-47], which should be avoided, especially in a screening population. Another option for reducing the influence of partial volume effects is to use thinner sections. However, thinner sections raise noise levels, especially at the diaphragmatic surface of the heart. Higher noise results in an increase in false-positive findings, which can negatively influence reproducibility. This is in accordance with the fact that a better reproducibility has been found with even thicker sections [21]. However, with sections thicker than 3 mm, small calcifications are missed because of partial volume effects, and small non-zero scores are mistaken for zero scores, regardless of scoring algorithm. Because MDCT has an improved signal-to-noise ratio compared with that of EBCT, lowering of the detection threshold from 130 HU to 90 HU when using an MDCT scan for calcium scoring could also be an option to reduce the influence of partial volume effects [48]. The chance that a voxel containing calcium reaches the 90-HU threshold is more likely, and partial volume effects may have less influence. However, the differentiation of noise from small calcifications is more difficult, and this will induce more score variability. Lowering the detection threshold is not an option with EBCT because of the high noise level.

In the past, several investigators have suggested to improve inter-scan variability by obtaining two consecutive scans and averaging the calcium scores [19,35,49,50]. Major disadvantages of obtaining two consecutive scans are that subjects receive twice the radiation dose and the total examination time is longer. An optimal solution would be the possibility to reconstruct overlapping data sets from raw data acquired with prospective ECG-triggering. This would combine a low radiation dose with the advantage of overlapping sections. However, this option is currently not available in the majority of scanners. The current rapid development of CT technology has substantially improved results of coronary CT angiography [51]. However, the advances in scanner technology will probably have a much smaller effect on coronary calcium scoring. Thinner sections or lower thresholds for calcium scoring will induce substantially more image noise and therefore may be less advantageous if a low-dose scanning technique is used.

In our study, 113 subjects had either one scan with a zero score or had a zero score on both scans. Eleven (10%) of these 113 subjects had a nonzero score on the other scan, regardless of scoring algorithm used. Results of recent studies suggested using calcium scoring as a first screening test in, for instance, emergency department settings. Individuals with a zero Agatston score would be sent home, whereas anyone with a

nonzero Agatston score would undergo further testing. In our study, a slight variation in scan starting position would have led to different patient management in around 10% of patients. In case of a zero score in a 3-mm data set, there is a 5% chance that this is a false-negative zero score. A slightly higher percentage of 11% was found for conversions between two consecutive scans in an earlier study by Devries et al. [22]. Therefore, use of calcium scoring as a screening test in the emergency setting should first undergo careful consideration.

Our results demonstrated that, in case of an Agatston score higher than 10, mass and volume scores showed better reproducibility than Agatston scores, which is in accordance to previous studies [20,23,26,27]. This improved reproducibility for volume and mass scores could not be shown in the category of subjects with an Agatston score between 0 and 10. This is probably because 11 out of the 35 subjects in this category had a conversion from a zero to a nonzero score. This conversion occurs regardless of scoring algorithm and always gives a variability of 200%. We found no significant differences between the variabilities of volume and mass quantification.

Our study had limitations. First, we could not perform two 3-mm reconstructions with an offset of 1.5 mm from the raw data. To work around this, we chose to obtain the two 3-mm data sets by averaging. We tested the validity of our averaging approach by comparing calcium scores obtained from the 3-mm raw data reconstruction with scores obtained from the corresponding averaged 3-mm data set. We did not find identical scores, but differences were extremely small. Therefore, we expect our results to be representative of results obtained for two 3-mm data sets with 1.5-mm offset reconstructed directly from the raw data. Another limitation of our study was that it included a low-risk population of post-menopausal women. Almost 50% of the subjects had a zero score. To be able to determine the conversion rate from zero to nonzero scores, we did not exclude these subjects. Relatively few subjects had a high score. Although we found lower percentage variabilities in the higher calcium-score categories compared with the lower calcium-score categories, which is consistent with previous studies on inter-scan reproducibility [20-23], changes in scan starting position seem to explain a large part of the variability in all categories.

In conclusion, minimal variation in scan starting position has a substantial effect on the variability of calcium scores. Agatston, volume, and mass scores are all vulnerable to slight changes in scan starting position. This poses an inherent limitation to the reproducibility of calcium scoring by using contiguous 3-mm sections and prospective ECG-triggering techniques.

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Chapter 3

CHAPTER 4

CALCIUM SCORING WITH PROSPECTIVELY ECG-TRIGGERED CT: OVERLAPPING RECONSTRUCTION DECREASES INTER-SCAN VARIABILITY

Chapter 4

ABSTRACT

Purpose

To compare the inter-scan variability of prospectively ECG-triggered calcium-scoring scans using overlapping 3-mm reconstructions to non-overlapping 1.5-mm and 3-mm sections.

Materials and Methods

75 women (59-79 years old) underwent two sequential prospectively ECG-triggered calcium-scoring scans with 16×1.5-mm collimation in the same session. Between the two scans the patients got off and on the table. From each of the two 1.5-mm data sets a non-overlapping 3-mm data set and an overlapping 3-mm data set with an increment of 1.5 mm were created. Agatston and mass scores were measured for all data sets. Inter-scan variability was calculated between comparable data sets. Effective radiation dose was estimated.

Results

Calcium scores for 1.5-mm sections ranged from 0-1786 (Agatston) and 0-310 mg (mass). Median inter-scan variability between non-overlapping 3-mm data sets was 13% (Agatston) and 11% (mass). Median variability was reduced to 10% with non-overlapping 1.5-mm data sets for both Agatston and mass scores. With overlapping 3-mm sections median variability was reduced to 8% (Agatston) and 7% (mass). Total effective radiation dose varied from 0.4 to 1.0 mSv depending on subject size.

Conclusion

Overlapping reconstructions of prospectively ECG-triggered calcium scoring scans show an improvement of inter-scan variability compared to standard 3-mm reconstructions without increasing patient radiation dose.

INTRODUCTION

The amount of calcification is related to the extent of coronary atherosclerosis [1]. It is also a risk indicator for future cardiac morbidity and mortality [2-6]. Non contrast-enhanced computed tomography (CT) scanning with quantification of the amount of coronary calcification is increasingly applied for risk stratification [7-11]. The use of calcium scores for follow-up is currently controversial [12,13]. To apply calcium scoring in risk stratification and follow-up calcium scores require a high reproducibility. The highest reproducibility of calcium scoring is obtained with retrospectively electrocardiographically (ECG)-gated scanning performed on multi-detector row CT (MDCT) scanners [14-16]. This scan method allows retrospective selection of the most motion-free phase to reduce motion artifacts and reconstruction of overlapping sections to reduce the influence of partial volume effects. While retrospectively ECG-gated scanning is very reproducible, its main drawback is the high radiation dose to the patients. With dose-lowering techniques such as ECG-based dose modulation a reduction of radiation dose to the patients by a maximum of 37-48% has been described but dose remains higher than the dose applied with prospectively ECG-triggered scanning [17-20].

Prospectively ECG-triggered sequential scans have been advocated by the American Heart Association for reasons of radiation dose [21] but neither retrospective phase selection is possible using this technique nor does the standard technique for prospectively ECG-triggered EBCT or MDCT rely on overlapping data reconstruction. The increased speed of MDCT scanners with 16 or more detector rows now makes it possible to image the whole heart with prospective ECG-triggering within one breath-hold, even when using a thin collimation of, for instance, 16×1.5mm. This makes it feasible not only to reconstruct non-overlapping sections from the raw data but rather to reconstruct overlapping 3-mm sections with 1.5-mm increment from the same data set. This implies that the advantage of overlapping sections can be combined with the advantage of a low radiation dose. In this study we compared the inter-scan variability of prospectively ECG-triggered calcium scoring scans using non-overlapping 1.5-mm or 3-mm sections with overlapping 3-mm sections.

MATERIALS AND METHODS

Subjects

In our study 75 women with a mean age of 67 ± 5 years (standard deviation, SD) underwent two prospectively ECG-triggered MDCT scans in the same setting. Scanning was performed between November 2004 and January 2005 as part of a study on the association between age at menopause and cardiovascular risk [22]. The local institutional review board approved the study. All subjects provided written informed consent after

being informed of the procedure. Consent included approval of future use of assembled data. Mean heart rate during the scan was 72 beats per minute (±11 [SD]) and average weight of the women was 71 kg (±13 [SD]).

Data acquisition

In one session two consecutive non contrast-enhanced sequential scans of each subject were obtained on a 16-detector row CT scanner (Mx8000 IDT, Philips Medical Systems, Cleveland, OH, USA). Between the two scans the patients got off and on the table. The scan volume ranged from the level of the tracheal bifurcation to below the apex of the heart. The scan parameters were a 16×1.5-mm collimation, 420 ms rotation time, and prospective ECG-triggering at a time point to obtain images in the mid-diastolic phase. Exposure parameters were 120 kVp and a tube current that depended on weight: <70 kg 40 mAs, 70-85 kg 55 mAs, and >85 kg 70 mAs.

A contiguous 1.5-mm and a contiguous 3-mm data set were reconstructed from each raw data set, yielding two 1.5-mm and two 3-mm data sets for each patient. The scanner software did not allow the reconstruction of an overlapping 3-mm data set with 1.5-mm increment. Therefore, from each of the two non-overlapping 1.5-mm data sets a non-overlapping 3-mm data set and an overlapping 3-mm data set with an increment of 1.5 mm were approximated by averaging slices from the 1.5-mm data set. The averaged non-overlapping 3-mm data sets were created to verify the validity of this approach; calcium scoring results from these data sets could be compared to the calcium scoring results from the 3-mm data sets reconstructed directly from the raw data.

The CT dose index ($CTDI_{vol}$), calculated by the scanner after the scan, was recorded for each scan. An estimate of the effective radiation dose in milliSievert (mSv) was obtained by multiplying the CTDI by a weighting factor k of 0.017 $mSv \cdot mGy^{-1} \cdot cm^{-1}$ for the thorax and by the scan length [18].

Coronary artery calcium measurement

All 150 (75x2) 1.5-mm image sets were analyzed on a standard PC by a single investigator who had previously evaluated over 500 cardiac scans. This was done to guarantee continuity and consistency of scoring. To avoid observer variability in calcium scoring we used the following approach. In the 1.5-mm data sets all regions with attenuation above the threshold of 130 HU were automatically marked as potential calcifications. Among these candidate regions, the observer identified those representing coronary artery calcifications. The identified calcifications in the 1.5-mm data set were used as an overlay to determine the presence of calcifications in the non-overlapping and the overlapping 3-mm data sets. All voxels in the 3-mm data sets at the location of

calcifications in the corresponding 1.5-mm data set were automatically analyzed for their attenuation. Only voxels for which the CT density in the 3-mm data set remained above 130 HU were considered calcifications. The observer randomly checked thirty 3-mm data sets for calcium scoring errors due to this approach. The Agatston score and calcium hydroxyapatite mass ('mass score') for the 1.5-mm and 3-mm image sets were calculated using software written in C^{++}. The scores were implemented as outlined by Ulzheimer and Kalender [23].

Data analysis

Absolute differences, $|score\_1 - score\_2|$, and percentage differences,

$$\left| \frac{2 \cdot (score\_1 - score\_2)}{score\_1 + score\_2} \right| \cdot 100\%,$$

(i.e. inter-scan variability) were calculated for Agatston and mass scores.

We first compared non-overlapping 3-mm data sets obtained by averaging and non-overlapping 3-mm data sets obtained by reconstruction from the raw data. To determine the validity of our averaging approach we calculated absolute and percentage differences between scores derived from these two image data sets.

We then determined inter-scan variability by calculating absolute and percentage differences between the two consecutive scans in the same patient. We evaluated scores from 1.5-mm data sets, non-overlapping 3-mm data sets (obtained by raw data reconstruction), and overlapping 3-mm data sets. Median and inter-quartile range (IQR; 25^{th} to 75^{th} percentile) or complete range (lowest to highest) were used as summary measures because calcium scores have a non-normal distribution. Bland-Altman plots were constructed to assess agreement between scores of the two overlapping 3-mm data sets. Differences between the scores of the two overlapping 3-mm image sets were plotted against the average score of these two image sets.

Based on Agatston score every data set was assigned to a risk category defined by Rumberger et al [8]. The risk categories are as follows: (I) score 0, very low risk; (II) score >0-10, low risk; (III) score >10-100, moderate risk; (IV) score >100-400, moderately high risk; and (V) score >400, high risk. For successively obtained data sets (1.5-mm non-overlapping data sets, 3-mm non-overlapping data sets and 3-mm overlapping data sets) agreement matrices were made. Risk category shifts were recorded and linearly weighted kappa values were calculated. The conversion rate was calculated as the number of subjects that changed risk category between two corresponding data sets divided by the total number of subjects, multiplied by 100%.

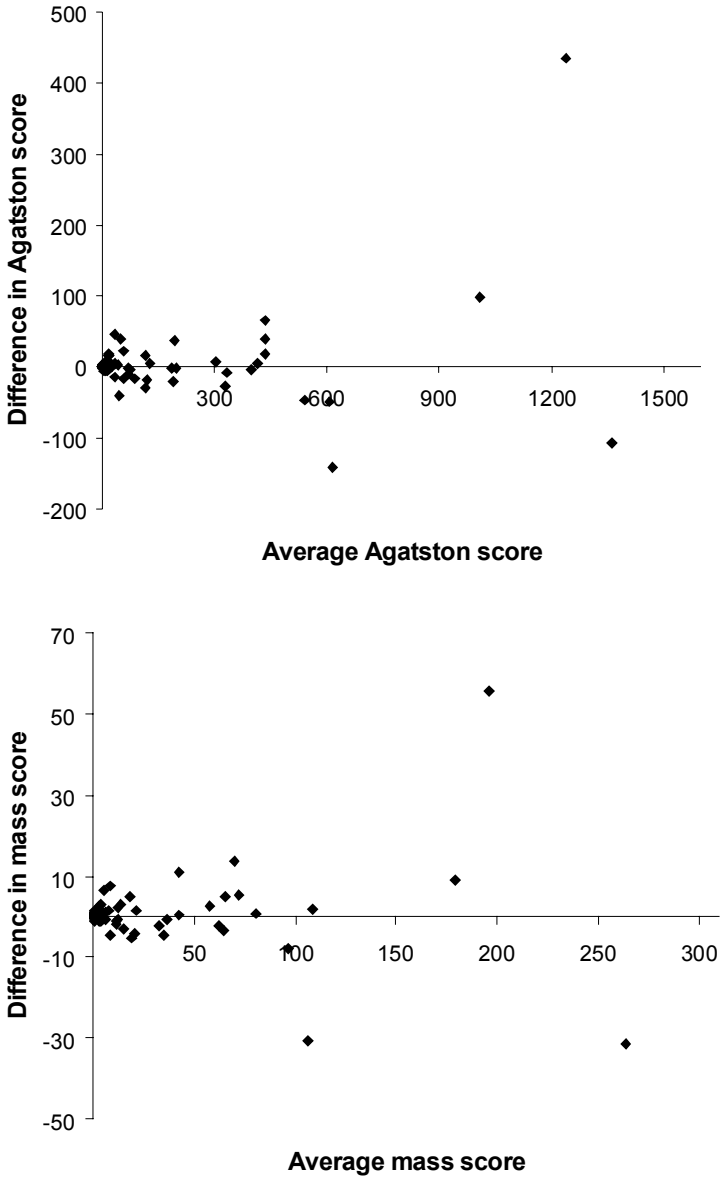

Figure 4-1. *Bland-Altman plots for assessing the agreement between Agatston scores (top) and between mass scores (bottom) of the two overlapping 3-mm data sets. Differences in scores increase with increasing average score.*

RESULTS

Radiation dose

$CTDI_{vol}$ ranged from 2.7 to 5.0 mGy depending on the applied tube current. Scan length ranged from 12 cm to 16.8 cm. Total effective radiation dose varied between 0.5 and 1.4 mSv (mean 0.9 mSv) depending on both the applied tube current and the scan length.

Calcium scores

Scores ranged from 0-1786 for Agatston and 0-310 mg for mass in the 1.5-mm data sets. No calcifications were missed in the thirty random 3-mm data sets due to our approach of performing the scoring in the 1.5-mm data sets. Scores from 3-mm data sets were always lower than the scores from the 1.5-mm data set of the same patient, except in case of zero scores. Overlapping 3-mm scores could turn out higher or lower than non-overlapping 3-mm scores.

Validation of averaging approach

A zero score on non-overlapping 3-mm data sets obtained by raw data reconstruction always corresponded to a zero score on averaged non-overlapping 3-mm data sets. Median differences, after exclusion of all zero scores, were 0.3 (IQR 0-0.8) for Agatston score and 0.06 mg (0.01-0.11) for calcium mass. Corresponding median percentage differences were 0% (IQR 0-1%) and 0% (0-1%), respectively, after exclusion of all zero scores.

Inter-scan variability

Differences in Agatston scores between successively obtained overlapping 3-mm data sets, non-overlapping 3-mm data sets and non-overlapping 1.5-mm data sets ranged from 0 to 436, from 0 to 455 and from 0 to 465, respectively; in mass scores these differences ranged from 0 to 56 mg, from 0 to 58 mg and from 0 to 53 mg, respectively. Differences in scores increased with increasing average score while relative differences and height of the score showed an inverse relationship (Figure 4-1). Median inter-scan variability between non-overlapping 1.5-mm data sets was 10% for both Agatston and mass score. For 3-mm non-overlapping data sets this slightly increased to 13% for Agatston scores and 11% for mass scores. Median variability was lowest with overlapping 3-mm sections: 8% for Agatston scores and 7% for mass scores (Table 4-1 and Figure 4-2).

Risk category shift

A shift in risk category between consecutive scans occurred in 12 pairs out of 75 pairs of scans (16%) with non-overlapping 1.5-mm data sets (Table 4-2). This number increased to 18 pairs (24%) with non-overlapping 3-mm data sets (Table 4-3). Risk category shift

decreased to 11 pairs (15%) with overlapping 3-mm data sets (Table 4-4). Risk category shift was never more than one category. The weighted kappa value decreased from 0.90 for 1.5-mm non-overlapping data sets to 0.85 with 3-mm non-overlapping data sets and was highest (0.91) with 3-mm overlapping data sets.

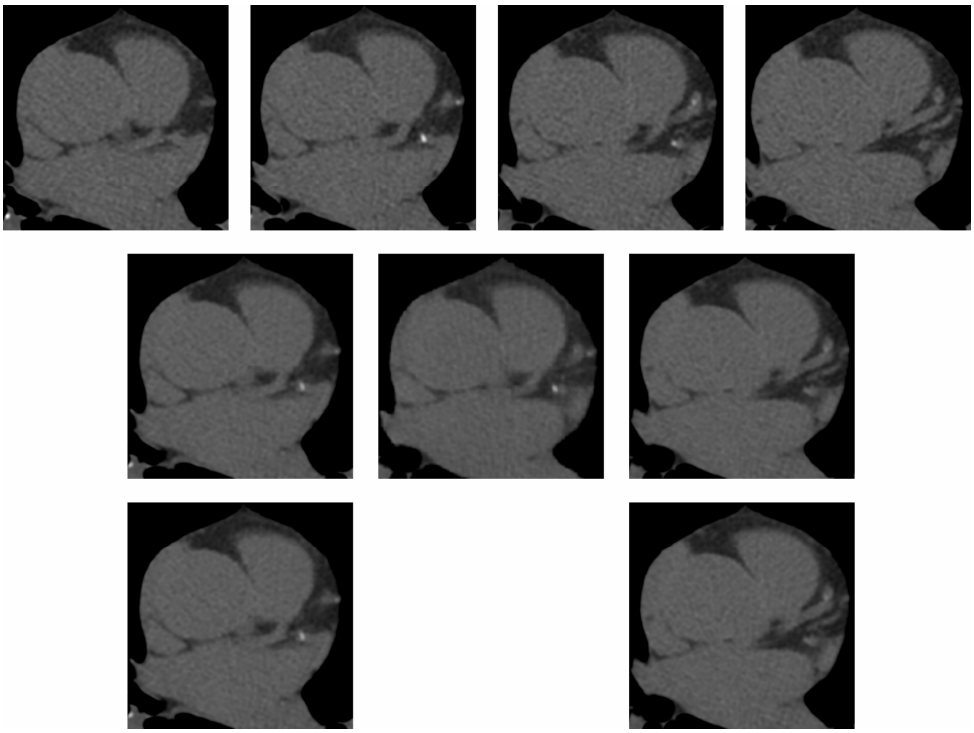

Figure 4-2. *Axial CT images of 1.5-mm thickness without overlap (upper row), 3-mm thickness with 1.5-mm overlap (middle row) and 3-mm thickness without overlap (lower row) at the same table position. The images of the 3-mm sections are each positioned underneath the two images of the 1.5-mm sections that are combined to yield the 3-mm section. Note that the calcification in the left circumflex artery on the 3rd 1.5-mm thick section from the left is 'lost' on the non-overlapping 3-mm sections (lower right image) due to partial volume effects, while it does contribute to the calcification in the middle image of the overlapping 3-mm sections.*

Table 4-1. Inter-scan variability between two non-overlapping 1.5-mm, two non-overlapping 3-mm slices and overlapping 3-mm slices: given are medians with inter-quartile ranges between parentheses

Data sets	Agatston	Mass
1.5 mm, no overlap	10% (0%-31%)	10% (1%-36%)
3.0 mm, no overlap	13% (0%-44%)	11% (0%-32%)
3.0 mm, 1.5-mm overlap	8% (0%-38%)	7% (0%-29%)

Table 4-2. Agreement matrix for risk categorization based on calcium scores from two 1.5-mm non-overlapping data sets

		Data set A					
	Category*	**I**	**II**	**III**	**IV**	**V**	***Total***
Data set B	**I**	18	3	0	0	0	*21*
	II	3	5	2	0	0	*10*
	III	0	0	17	3	0	*20*
	IV	0	0	1	11	0	*12*
	V	0	0	0	0	12	*12*
	Total	*21*	*8*	*20*	*14*	*12*	***75***

Table 4-3. Agreement matrix for risk categorization based on calcium scores from two 3-mm non-overlapping data sets

		Data set A					
	Category*	**I**	**II**	**III**	**IV**	**V**	***Total***
Data set B	**I**	25	2	0	0	0	*27*
	II	1	2	6	0	0	*9*
	III	0	4	12	2	0	*18*
	IV	0	0	2	10	1	*13*
	V	0	0	0	0	8	*8*
	Total	*26*	*8*	*20*	*12*	*9*	***75***

Table 4-4. Agreement matrix for risk categorization based on calcium scores from two 3-mm overlapping data sets with 1.5-mm overlap between slices

		Data set A					
	Category*	**I**	**II**	**III**	**IV**	**V**	***Total***
Data set B	**I**	24	3	0	0	0	*27*
	II	1	3	5	0	0	*9*
	III	0	2	15	0	0	*17*
	IV	0	0	0	12	0	*12*
	V	0	0	0	0	10	*10*
	Total	*25*	*8*	*20*	*12*	*10*	***75***

DISCUSSION

Our study shows that creating overlapping reconstructions from a prospectively ECG-triggered axial scan is feasible and that this approach reduces inter-scan variability compared to non-overlapping data sets. Our approach of reconstructing overlapping sections from a prospectively triggered scan combines the advantages of the low radiation dose of prospective triggering with the advantages of overlapping reconstruction.

The ability to reconstruct overlapping data sets used to be an advantage of retrospectively ECG-gated CT scanning. Previous studies demonstrated an improved reproducibility of calcium scores obtained with retrospectively ECG-gated scanning compared to prospectively ECG-triggered scanning [14-16]. This improvement of reproducibility is attributed to a decreased influence of partial volume effects due to the use of overlapping sections. Partial volume effects are thought to be a main cause for inter-scan variability in case of 3-mm-thick non-overlapping sections [24-27].

Retrospectively ECG-gated scanning, however, demands a substantially higher radiation dose to the patient. Radiation doses applied for retrospectively ECG-gated calcium scoring have been reported to vary between 2.5 and 4.5 mSv [17,18]. Even when dose-reducing techniques such as ECG-based tube current modulation are applied [19] radiation dose remains higher than with prospectively ECG-triggered scanning [17,18]. The maximum reported reduction in radiation dose with tube current modulation is 48%, which corresponds to a best case scenario of 1.3 to 2.3 mSv of radiation dose with retrospectively ECG-gated scanning, while the mean estimated radiation doses used in our study was 0.9 mSv, which corresponds to the reported radiation doses with prospectively ECG-triggered scanning techniques of 0.7 to 1.1 mSv [17,18].

We detected an improvement of inter-scan variability also with the use of thinner non-overlapping sections (1.5 mm) instead of non-overlapping 3-mm sections. This advantage of using thin sections was also found in a recent study by Horiguchi et al. [28]. In our study the decrease in inter-scan variability with thinner sections was smaller than with the application of overlapping 3-mm data sets. In both instances, the improvement in variability is likely a result of less influence of partial volume effects. The smaller improvement in variability with thinner sections compared with overlapping data sets may be due to the increase in image noise in thinner sections. The differentiation between small calcifications and noise can be problematic and cause inter-scan variability [29]. Both erroneously labeled noise pixels and less partial volume may have caused the on average higher scores with thin 1.5-mm sections. Most available outcome data with calcium scores is obtained with the use of data sets with 3-mm sections.

Our results are in concordance with the results of a phantom study which compared the reproducibility of calcium scoring data sets with non-overlapping 3-mm sections with data sets with overlapping 3-mm sections with a 2-mm increment [30]. However, in that phantom study CT scanning was performed with EBCT and overlapping sections were obtained by using a smaller table feed than the section thickness. This means that after obtaining a single section the table moves and then the next section is scanned. Consequently, scanning the whole heart with this scan method to obtain overlapping sections would take over one minute, far longer than a single breath-hold. Other studies have also shown improved reproducibility with overlapping sections but these scans were obtained with retrospective ECG-gating [14-16]. With retrospective ECG-gating a continuous spiral data acquisition is performed, while with prospective ECG-triggering several contiguous axial scans are obtained. For the creation of overlapping data sets from data acquired with sequential scans every thin axial slice is combined with the succeeding axial slice. While most combinations will be within the volume obtained during one rotation, some combinations occur at the interface between two subsequently obtained volumes and discontinuities may occur. This effect becomes smaller with wider detectors, as in 64-detector row scanners and will be non-existent if the whole heart is obtained in one rotation as with 256-detector row scanners. Our study with a 16-detector row scanner shows that an improvement of inter-scan variability with the use of overlapping sections from prospectively ECG-triggered scans occurs despite these 'interface problems' and shows that overlapping sections can even be obtained from prospectively ECG-triggered scans, which entails substantially less radiation dose to the patient.

Standard implementation of software on CT scanners - including EBCT scanners - that would allow the formation of an overlapping data set from raw data acquired with prospective ECG-triggering would improve reproducibility without increasing patient radiation dose. Improving inter-scan variability with the use of retrospectively ECG-gated scanning or by acquiring two prospectively ECG-triggered scans in one session, and thus doubling the radiation dose to the patient, to allow averaging of the two scores may not be needed [31-34]. Especially when calcium scoring is applied as a screening test radiation dose should be as low as reasonably achievable. Further improvements in calcium scoring reproducibility in prospectively ECG-triggered scans are likely to result from improvements in the temporal resolution of CT scanners which will decrease the occurrence of motion artifacts.

Our study has several limitations. Firstly, the overlapping data sets we used were not created directly from the raw data but were obtained by averaging of thin slice data sets. Due to software limitations direct reconstruction of overlapping data sets was not feasible. Since we found only minor differences in scores between the non-overlapping 3-mm data

sets obtained by raw data reconstruction and that obtained by averaging 1.5-mm slices, we estimated our approach did generate valid results. Secondly, all subjects in this study were low-risk post-menopausal women. Their risk for or presence of coronary artery disease was not a selection criterion. Therefore, calcium scores were low, despite a relatively high average age. 18 out of 75 subjects even showed no calcifications on the 1.5-mm data set. To allow evaluation of shifts from non-zero to zero scores we did not exclude these patients from the analysis.

In conclusion we can state that overlapping reconstructions show an improvement in inter-scan reproducibility of prospectively ECG-triggered calcium scoring scans compared to standard 3-mm reconstructions. With this method less inter-scan variability can be reached without increasing radiation dose in contrast to retrospectively ECG-gated scanning or scanning twice in one session.

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Chapter 4

CHAPTER 5

VARIABILITY OF CORONARY CALCIUM SCORES THROUGHOUT THE CARDIAC CYCLE: IMPLICATIONS FOR THE APPROPRIATE USE OF ECG DOSE MODULATION WITH RETROSPECTIVELY GATED CT

Chapter 5

ABSTRACT

Purpose

To study how much the calcium scores at various phases throughout the cardiac cycle deviate from the score in the most motionless phase during retrospectively ECG-gated MDCT of the heart and to evaluate how to optimize ECG-based tube current modulation so that errors in calcium scoring can be minimized while dose savings can be maximized.

Materials and Methods

In 73 subjects with known or suspected coronary artery disease we performed retrospectively ECG-gated 64-detector row CT for calcium scoring. 4 subjects were excluded after scanning because of breathing artifacts or lack of coronary calcification. Heart rate during the scan was recorded. In each patient, calcium scoring (Agatston, AS, mass, MS, and volume score, VS) was performed on ten data sets reconstructed at 10%-intervals throughout the cardiac cycle. The most motionless phase was subjectively determined and used as the reference phase. For the score in each phase deviation from the score in the reference phase was determined. An ECG-simulator was used to determine the amount of dose saving with use of dose modulation during varying intervals.

Results

Mean heart rate was 63 (±13) beats per minute (bpm). In 51% of patients the reference phase was the 70% phase. Using the calcium score in the 70% phase (mid-diastole) instead of the reference at heart rates <70 bpm would have induced a median score deviation of 0% (inter-quartile range (IQR): 0-6% (AS, MS and VS)) and using the calcium score in the 40% phase (end-systole) at heart rates ≥70 bpm would also have induced a median score deviation of 0% (IQR: 0-7% (AS), 0-5% (MS), 0-3% (VS)). Dose savings increased with lower heart rates and shorter application of diagnostic dose.

Conclusions

The optimum phases for dose modulation are 70% (mid-diastole) at heart rates below 70 bpm and 40% (end-systole) at heart rates at or above 70 bpm. Under these conditions dose saving is maximum and a median error of 0% is found for the various calcium scoring algorithms.

INTRODUCTION

Coronary arterial calcifications are a known marker of coronary atherosclerotic disease [1,2]. CT coronary calcium scoring is a broadly applied method to quantify coronary calcifications [3]. Traditionally it has been performed using electron beam computed tomography (EBCT) [4-7] but in recent years, multi-detector row CT (MDCT) has evolved as a more readily available alternative. Inter-scan reproducibility with retrospectively ECG-gated MDCT was even shown to be superior to that with prospectively ECG-triggered EBCT [8-10].

The main reasons for the improved inter-scan reproducibility are firstly that retrospectively ECG-gated MDCT allows the reconstruction of overlapping sections, which reduces the influence of partial volume effects, and secondly that retrospectively ECG-gated MDCT allows for the retrospective selection of the most motionless phase, which reduces motion artifacts. The reproducibility of coronary calcium scoring is predominantly influenced by partial volume effects and cardiac motion artifacts [11-14]. However, a disadvantage of retrospectively ECG-gated calcium scoring is the substantially larger radiation dose that is delivered to the patient compared to when prospectively ECG-triggered calcium scoring is performed [15]. A scientific statement on cardiac imaging by the American Heart Association even strongly recommends prospectively ECG-triggered scanning for calcium scoring because of the lower radiation dose with this technique [16].

Thus, lowering radiation exposure for retrospectively ECG-gated MDCT is crucial if the improved inter-scan reproducibility of calcium scoring with this technique is to be profited from without having the disadvantage of a high radiation dose. One possible approach is the use of ECG-based tube current modulation [17,18]. However, this technique requires the prospective selection of one or more phases of the RR-cycle in which dose is kept at the predefined diagnostic level. During other phases, dose is reduced. As a consequence images reconstructed outside the selected phase no longer are of diagnostic quality. Errors due to cardiac motion may be induced if the prospectively selected phase is not the most motionless phase, while retrospective selection of the most motionless phase is no longer feasible.

Up to now, to our knowledge, it has not been studied if and how the optimum phase for ECG-based tube current modulation can be selected in such a way that the induced error in calcium scoring relative to the most motionless phase is kept to a minimum and radiation dose saving is maximum. In this study we examined how much the calcium scores at various phases throughout the cardiac cycle deviate from the score in the most motionless phase during retrospectively ECG-gated MDCT of the heart and we evaluated

how to optimize ECG-based tube current modulation so that errors in calcium scoring can be minimized while dose savings can be maximized.

MATERIALS AND METHODS

Study population

Seventy-three patients (mean age 62±6 yrs) underwent retrospectively ECG-gated CT between January 2005 and March 2006 for the purpose of coronary calcium scoring. The calcium-scoring scan was performed in combination with a coronary CT angiography as part of a research protocol approved by our Institutional Review Board. The main aim of the research protocol was to compare the performance of CT and conventional angiography (CAG) in patients referred for CAG. Written informed consent was obtained from each participant. All subjects had known or suspected coronary artery disease. Previous stent placement, cardiac surgery, arrhythmia, and contra-indications for contrast medium application, e.g. contrast medium allergy, were reasons for exclusion. In an approach similar to that taken by Schlosser et al. [19] we excluded all those subjects from the present evaluation in which no coronary calcifications could be detected on any of the reconstructed cardiac phases. Apart from their daily medication patients did not receive beta-blockers prior to the calcium-scoring scan.

Table 5-1. Fixed (percentage) delay after R-peak calculated for an end-systolic (40%) and a mid-diastolic (70%) physiologic phase defined with a delay algorithm (see ref 20)

	Physiologic phase of RR-interval			
	40%		70%	
Heart rate (bpm)	Absolute delay (ms)	Percentage delay (%)	Absolute delay (ms)	Percentage delay (%)
40	504	34	1003	67
50	427	36	814	68
60	376	38	688	69
70	339	40	598	70
80	312	42	531	71
90	291	44	478	72
100	274	46	436	73

Note.- Delay defines center of reconstructed phase.

MDCT protocol

A non-contrast-enhanced retrospectively ECG-gated CT scan of the heart was performed on a 64-detector row CT scanner (Brilliance 64, Philips Medical Systems, Cleveland, OH, USA). The scan was performed during a single breath-hold and started at the level of the tracheal bifurcation. We used a section collimation of 64×0.625 mm, a pitch of 0.2, a 205-mm field of view, a 512×512 reconstruction matrix and a medium smooth reconstruction filter (CB). Rotation time was 0.42 s. Dose settings were 120 kVp and 150 mAs, resulting in a $CTDI_{vol}$ of 11 mGy. Estimated effective dose (mSv) can be calculated by multiplying the $CTDI_{vol}$ by the scan length and the conversion factor for the chest 0.017 $mSv \cdot mGy^{-1} \cdot cm^{-1}$. No tube current modulation was used. Average, minimum and maximum heart rate during the acquisition were recorded. Data sets of 3-mm thick sections with an increment of 1.5 mm were reconstructed every 10% of the RR-interval using a multisegment reconstruction algorithm to increase temporal resolution [20]. The number of segments used for reconstruction is automatically optimized from beat to beat to ensure maximum temporal resolution. The phase reconstructions were performed with a delay algorithm that captures the same physiologic phase during the cardiac cycle (e.g. mid-diastole) instead of a fixed (percentage) delay after the R-peak [21]. The physiologic phase of the delay algorithm can be expressed as a fixed (percentage) delay after the R-peak that varies with heart rate to increase the generalizability of our study (Table 5-1). Scans were transferred to an offline workstation (Extended Brilliance Workspace, Philips, Cleveland, OH).

Dose saving estimations

We performed retrospectively ECG-gated calcium scoring scans with ECG-based tube current modulation on a perplex cylinder at various stable heart rates (60, 75 and 100 beats per minute (bpm)) using an ECG-simulator (Model 430B, Medi Cal Instruments Inc.). The scan parameters were identical to those previously mentioned for the patient scans. The scan range was 14 cm. Dose modulation was implemented so that maximum dose was given during one or more (non-)connected phases (e.g. connected, 70% and 80% phase; non-connected, 40% and 70% phase) of the heart cycle. During the rest of the RR-interval tube current was reduced by around 80%. The percentage dose saving,

$$\left(1 - \frac{dose\_with\_modulation}{dose\_without\_modulation}\right) \cdot 100\%,$$

was estimated by the scanner software.

Chapter 5

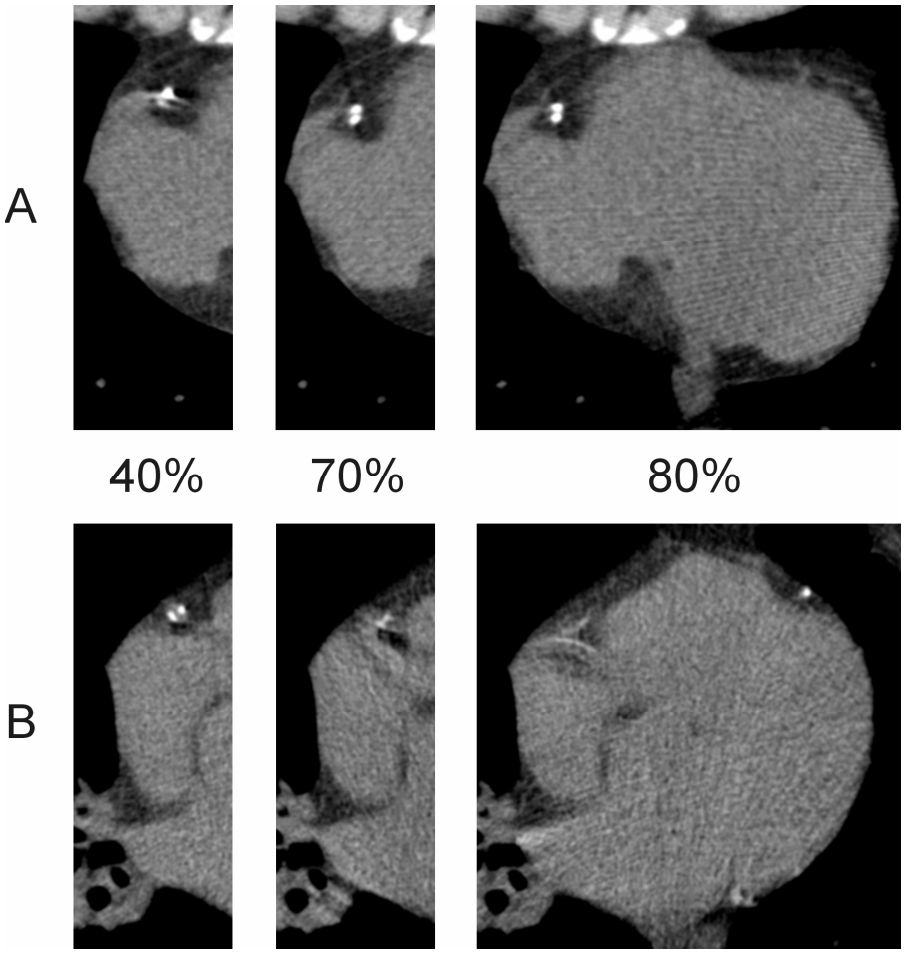

Figure 5-1. *CT calcium scoring images of two patients (A and B) with calcifications in the right coronary artery at 3 different phases and with differing motion scores: 40% (end-systole), 70%, and 80% (both mid-diastole). Patient A had an average heart rate of 65 bpm during the scan and patient B 89 bpm. At an average heart rate of 65 bpm the calcifications are sharply delineated (motion score 1) in mid-diastole (70% and 80%) and show severe motion (motion score 3) in end-systole (40%). However, at an average heart rate of 89 bpm the calcifications are sharply delineated in end-systole (motion score 1) and show severe motion in mid-diastole (motion score 2 in 70% phase and 3 in 80% phase).*

Measurements and data analysis

One observer with 3 years of experience in cardiac CT measured coronary calcium in all ten reconstructions of each patient using commercially available software (Heartbeat CS, Philips Medical Systems, Cleveland, OH). We used the Agatston score (AS) [22], calciumhydroxyapatite mass (mass score, MS) [23] and calcium volume (volume score, VS) [24] to quantify the amount of coronary calcium. Calcifications were identified per coronary artery with a threshold of 130 HU and a minimum plaque size of 0.5 mm^2 on axial sections.

All phases were subjectively scored for cardiac motion on a 3-point scale by two observers (one with an experience of over 1000 calcium scoring scans, one with an experience of around 400 calcium scoring scans) (Figure 5-1): 1, no or little motion artifacts, sharply delineated vessels and/or lesion(s); 2, moderate motion artifacts, blurred vessels or lesion margins, minor tail-shaped artifacts; 3, severe motion artifacts, non-distinguishable vessels, major tail-shaped artifacts, star-shaped artifacts, doubling or discontinuity of calcium.

The observers were blinded to the phase and the corresponding calcium score in that phase while assigning motion scores. The most motion-artifact-free phase ('reference phase') was identified in consensus and the resulting calcium scores (AS, MS and VS) were used as reference scores.

Since the calcium score has a non-normal distribution we applied median and (inter-quartile (IQR)) range for summary statistics instead of mean and standard deviation (SD). For each patient, differences and relative differences between scores and reference were determined for each phase of the cardiac cycle. The difference was calculated by subtracting the reference score from the score in each phase. The relative difference was calculated by dividing the difference by the reference. The outcome was multiplied by 100% to obtain a percentage. The results were displayed in box plots. Per motion category we also summarized relative differences between scores and reference in box plots.

We used the methods described above to determine the cardiac phase that had the least difference relative to the reference phase, in order to evaluate how large a difference would be found if only one pre-defined phase instead of the most motionless phase was used for calcium scoring. To study the effect of heart rate, we also subdivided patients into two groups with high and low average heart rates using the following cutoff values: 60 bpm, 65 bpm and 70 bpm.

To determine the influence of the score variability on risk stratification we assigned all subjects, for each phase of the cardiac cycle, to one of the risk groups defined by

Rumberger et al. [5]. The groups were as follows: very low risk (AS= 0), low risk (>0-10), moderate risk (>10-100), moderately high risk (>100-400), and high risk (>400). The percentage of subjects in each of the five risk categories was calculated per phase and for the reference phase.

RESULTS

Seventy-three scans were performed of which one scan showed severe breathing artifacts due to an insufficiently long breath-hold. This scan was excluded from further analysis as well as three scans which did not show any coronary calcifications in any of the reconstructed phases. Analyses are based on the resulting 69 scans. Scan duration was 10±1 s (mean±SD). Scan range was 14±1 cm (mean±SD), which yielded an estimated effective radiation dose of 2.6±0.2 mSv (mean±SD). Heart rate during the scan acquisition was 63±13 bpm (mean±SD). Mean difference between maximum and minimum heart rate during the scan acquisition was 6±9 bpm. Further patient characteristics are summarized in Table 5-2.

Table 5-2. Patient characteristics

Variable	All subjects *(n=69)**
Men : women	46 : 23
Age (mean ± SD)	62 ± 6 years
Weight (mean ± SD)	83 ± 14 kg
Length (mean ± SD)	173 ± 8 cm
BMI (mean ± SD)	28 ± 4 kg/m^2
Heart rate during scan (mean ± SD)	63 ± 13 bpm
Heart rate ≥ 70 bpm	19 of 69 subjects
Systolic BP (mean ± SD)	157 ± 23 mmHg
Diastolic BP (mean ± SD)	83 ± 15 mmHg
Daily beta-blocker use	42 of 69 subjects

SD = standard deviation, BMI = body mass index, BP = blood pressure

** After exclusion of 4 subjects*

Most motionless phase

The most motionless phase was found to be in the diastole (70%, 80% or 90% phase) in 75% of patients and in the 70% phase in 51% (Figure 5-2). In patients with a mean heart rate below 70 bpm (n=50; mean heart rate 57±8 (SD)) we found the most motionless phase to coincide with a diastolic phase in 45 out of 50 subjects (90%). With higher average heart rates (≥ 70bpm) (n=19; mean heart rate 78±9 (SD)) the 40% phase (end-systole) was the reference phase most often (12 of 19 subjects, 63%).

Dose saving estimations

The maximum dose saving of 38% was obtained with application of maximum radiation dose during only a single phase of the RR-interval and at a low heart rate of 60 bpm, i.e. a reduction from 2.6 mSv to 1.6 mSv in our study. The percentage dose saving decreased with increasing heart rate. Diagnostic dose during a longer interval yielded less dose saving. If diagnostic dose is applied during 4 or more connected phases (almost) no dose saving occurs (Figure 5-3).

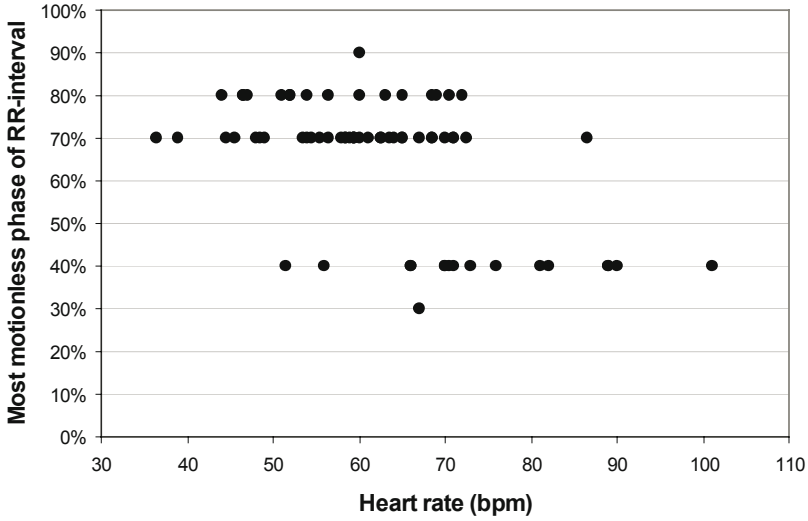

Figure 5-2. *The most motionless phase during the RR-interval varies with mean heart rate. For each patient, the phase with least motion artifacts is related to the mean heart rate of this patient. Note that at 40% of the RR-interval (end-systole) the heart rate is more likely to be above 70 bpm, while in mid-diastole (70% or 80% of the RR-interval) the heart rate is often lower than 70 bpm.*

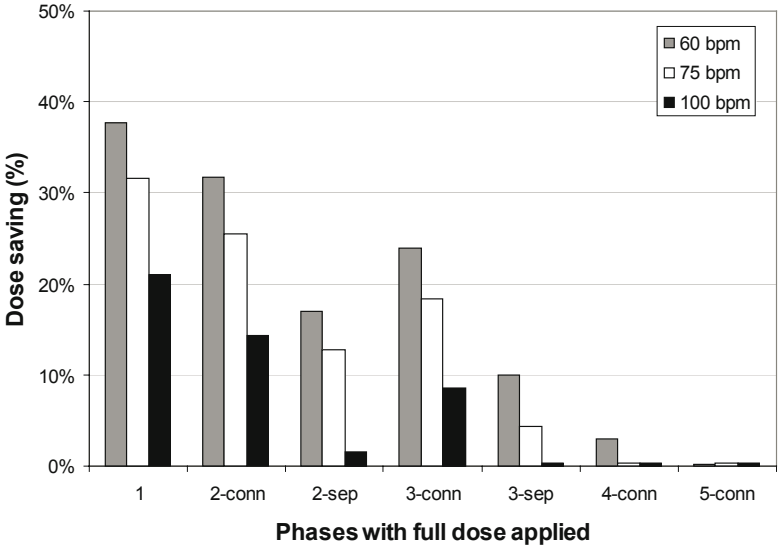

***Figure 5-3**. Bar graph that displays the dose saving as a percentage of the dose that would have been applied without ECG-based tube current modulation. Maximal dose is applied in one phase (1, e.g. 40% or 70%), 2 connected phases (2-conn, e.g. 70% and 80%), 2 non-connected phases (2-sep, e.g. 40% and 70%), 3 connected phases (3-conn, e.g. 70%, 80%, and 90%), 3 non-connected phases (3-sep, e.g. 40%, 70%, and 80%), 4-connected (e.g. 40% to 70%) or 5-connected phases (e.g. 40% to 80%). Grey bar shows the result at a heart rate of 60 bpm, white bar at 75 bpm, and black bar at 100 bpm. Note that the percentage dose saving progressively decreases with increasing heart rate and increasing number of phases during which maximal dose is applied. Also, selecting 2 non-connected phases yields less dose saving than selecting 3 connected phases for the application of maximal dose.*

Differences and relative differences

AS, MS and VS in the reference phase ranged from 0.5 to 3757, from 0.2 to 672.7 mg, and from 1.5 to 3781 mm^3, respectively. Differences obtained by subtracting the reference score from the other scores throughout the RR-interval ranged from –805 to 1060 for AS, from –141.3 to 71.2 mg for MS, and from -738 to 1197 mm^3 for VS. These differences were least with low calcium scores and increased with higher calcium scores. Over all phases the median relative difference was -14% (IQR, -35%-0%; range, -100%-139%) for AS, -13% (IQR, -30%-0%; range, -100%-267%) for MS, and -5% (IQR, -22%-2%; range, -100%-222%) for VS. The median relative differences for AS, MS and VS in the 70% phase (mid-diastole) were 0%; in all other phases the median relative differences were

below 0%, except for the 40% phase with the VS (Figure 5-4). The scores at 80% (mid-diastolic), and 30% or 40% (both end-systolic) were close to the reference scores. Other phases, especially 10%, 50% and 90%, showed large deviations from the reference scores. For patients with an average heart rate < 70 bpm the reconstruction at 70% showed the best results (Figure 5-5) with an absolute median difference relative to the reference of 0% (IQR, 0-6%) for both AS, MS, and VS. In patients with an average heart rate ≥70bpm during the scan the 40% phase showed an absolute median relative difference of 0% (IQR, 0-7% (AS), 0-5% (MS), 0-3% (VS)). In these patients the absolute median relative difference in the 70% phase increased to 6% (IQR, 0-24%) for AS, 7% (IQR, 2-20%) for MS, and 8% (IQR, 0-18%) for VS. A cutoff heart rate lower than 70 bpm, for instance 65 bpm, showed worse results for the 40% phase (Table 5-3). If the 70% phase is used at heart rates below 70 bpm and the 40% phase at heart rates at or above 70 bpm in around 10% of subjects the calcium score error is more than 10%.

Table 5-3. Absolute median relative differences between Agatston scores of each phase and the reference phase according to heart rate during the scan with cutoff at 60, 65 and 70 bpm.

Patient heart rate during scan	Number of patients	Absolute median relative difference (inter-quartile range)	
		40% phase	70% phase
All	69	8% (0-18%)	0% (0-9%)
<60 bpm	27	14% (4-33%)	0% (0-5%)
≥60 bpm	42	3% (0-11%)	0% (0-16%)
<65 bpm	39	12% (3-26%)	0% (0-6%)
≥65 bpm	30	3% (0-10%)	1% (0-17%)
<70 bpm	50	11% (3-22%)	0% (0-6%)
≥70 bpm	19	0% (0-7%)	6% (0-24%)

Note.- A cutoff of 70 bpm will lead to a median error of 0% and the smallest inter-quartile ranges if the 70% phase is used for heart rates < 70 bpm and if the 40% phase is used for heart rates ≥ 70 bpm.

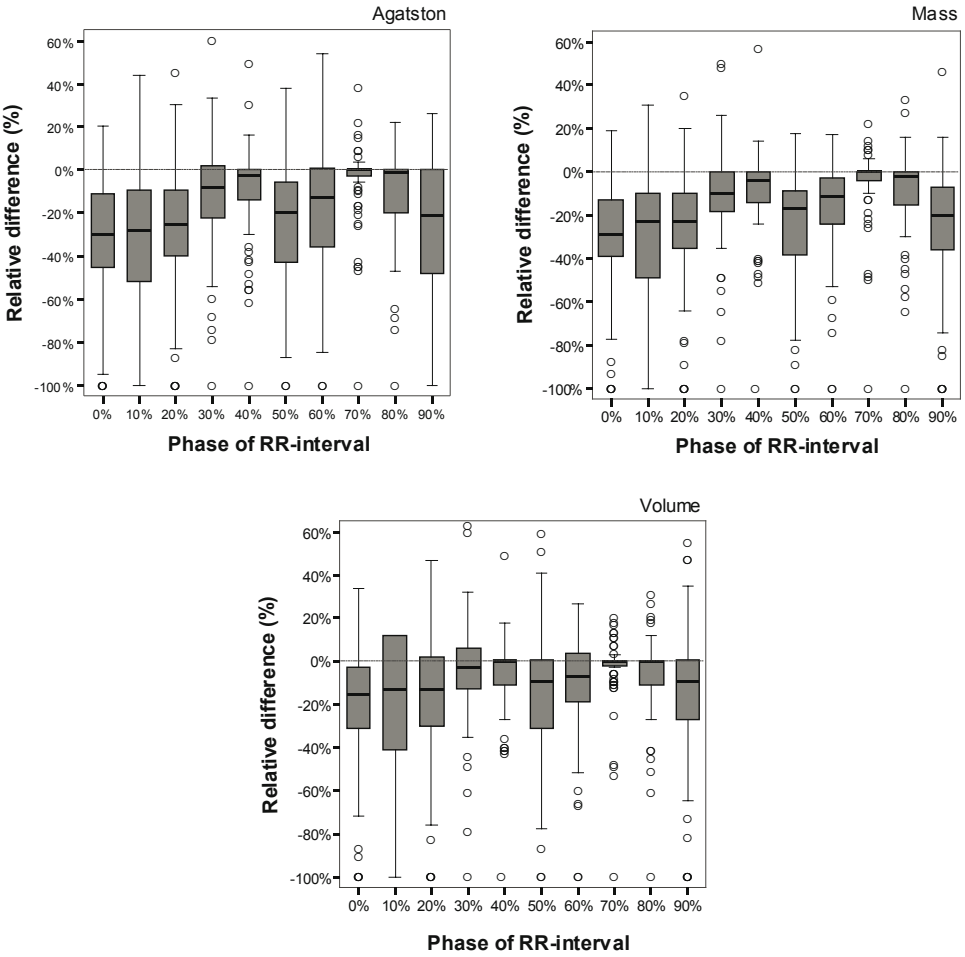

Figure 5-4. *Box plots that demonstrate the relative differences between Agatston scores (a), mass scores (b), or volume scores (c) of each phase and the reference phase for all subjects. Boxes are the inter-quartile range, the line within the box is the median, the lines projecting out of the box contain the adjacent values, which are not more than 1.5 times the height of the box. All remaining points are outliers. To accentuate the differences between phases, we limited the scale on the y-axis to between -105% and 65%. Consequently, not all outliers in the 80% phase are shown. Note that the 70% phase shows the best results and that all medians, except in the 70% phase, are below zero.*

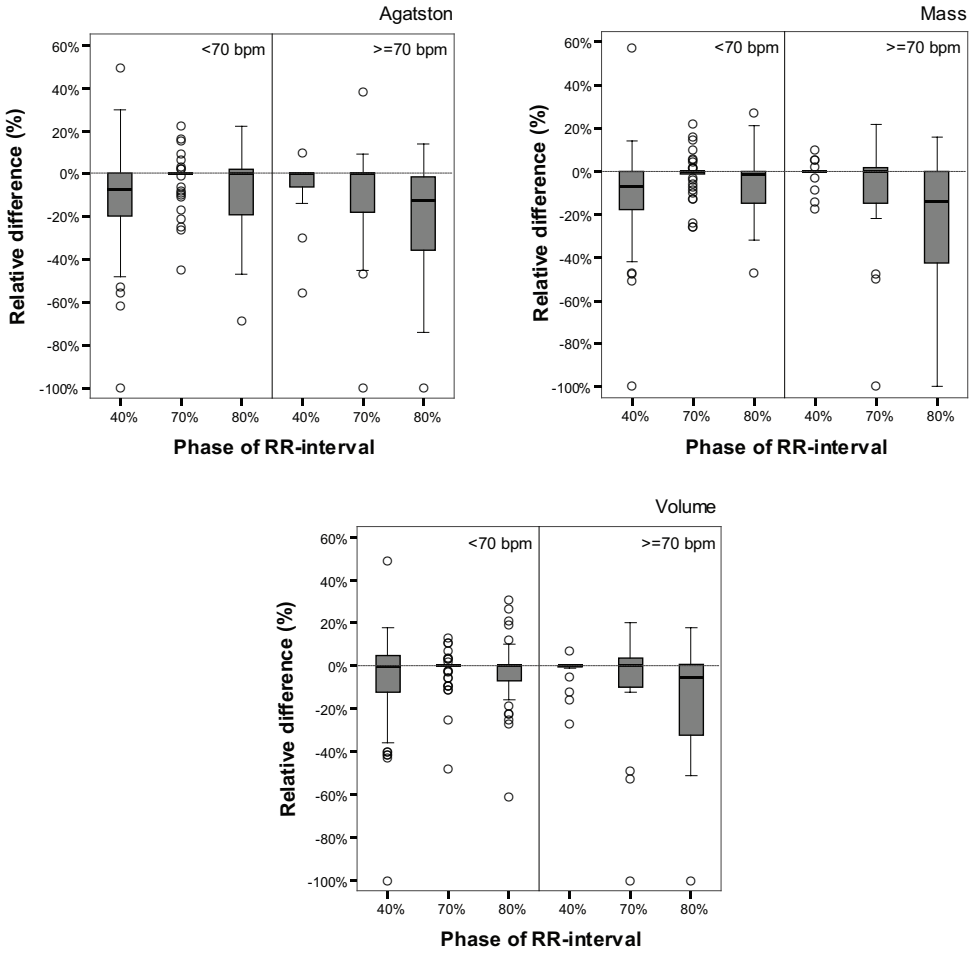

Figure 5-5. *Box plots that demonstrate the relative differences between Agatston scores (a), mass scores (b) or volume scores (c) of the 40%, 70%, and 80% phase and the reference phase for patients with a heart rate < 70 bpm and patients with a heart rate ≥ 70 bpm. To accentuate the differences between phases, we limited the scale on the y-axis to between -105% and 65%. Consequently, not all outliers in the 80% phase are shown. Note that the 70% phase shows the best results for the subset of patients with a heart rate < 70 bpm and the 40% shows the best results for the subset of patients with a heart rate ≥ 70 bpm.*

For patients with an average heart rate < 70 bpm the reconstruction at 70% showed the best results (Figure 5-5) with an absolute median difference relative to the reference of 0% (IQR, 0-6%) for both AS, MS, and VS. In patients with an average heart rate ≥ 70 bpm during the scan the 40% phase showed an absolute median relative difference of 0% (IQR, 0-7% (AS), 0-5% (MS), 0-3% (VS)). In these patients the absolute median relative difference in the 70% phase increased to 6% (IQR, 0-24%) for AS, 7% (IQR, 2-20%) for MS, and 8% (IQR, 0-18%) for VS. A cutoff heart rate lower than 70 bpm, for instance 65 bpm, showed worse results for the 40% phase (Table 5-3). If the 70% phase is used at heart rates below 70 bpm and the 40% phase at heart rates at or above 70 bpm in around 10% of subjects the error is more than 10%.

Motion categories

The relative differences became larger with increasing cardiac motion and ranged from a median relative difference of 0% with a motion score of 1 to -24% (AS), to -21% (MS) and to -11% (VS) with a motion artifact score of 3 (Fig 6). MS and VS seemed to show only slightly less variability than AS (Figure 5-6).

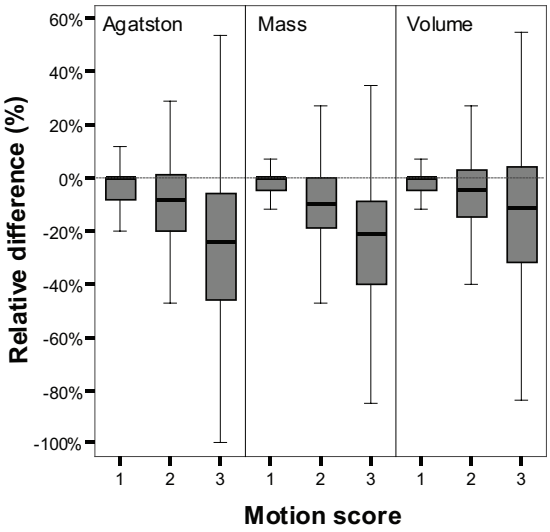

Figure 5-6. *Box plot that summarizes per motion category the relative differences between calcium scores and their reference (left: Agatston score, middle: mass score, right: volume score). Relative differences increase with higher motion scores. Using the mass score or volume score yields slightly smaller relative differences. Note that the median is zero for a motion score of 1.*

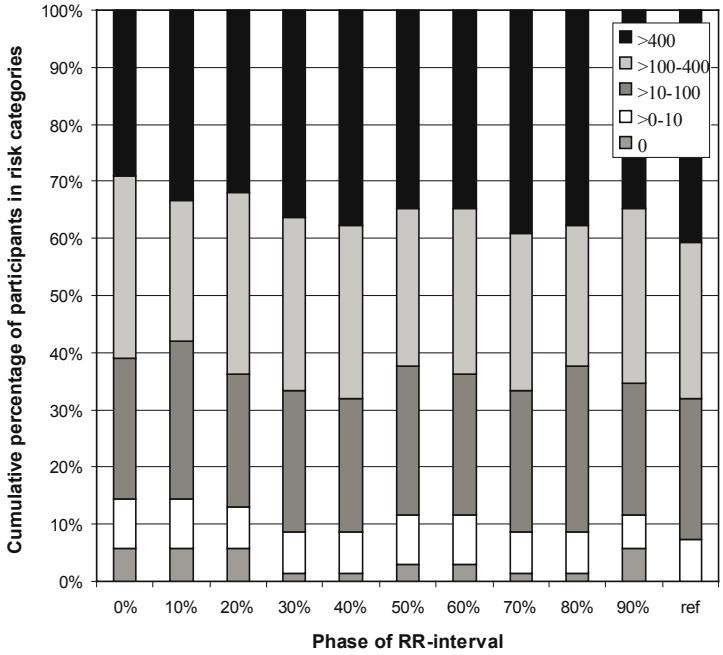

Figure 5-7. *Bar graph showing the distribution of scores over risk categories per phase and in the reference phase. The distributions in the phases which are most likely to be most motionless (40%, 70% and 80%) are most similar to the distribution in the reference phase.*

Risk stratification

The assignment of subjects to the risk groups demonstrates that in the phases that are most likely to be free of motion artifacts subjects are assigned to higher risk groups (Figure 5-7). The distribution in the 70% phase is most similar to the distribution in the most motionless phase.

DISCUSSION

The results of our study suggest that retrospectively ECG-gated CT with ECG-based tube current modulation can save a substantial amount of radiation dose to the patient without inducing major deviations in calcium scores. The best results are obtained if the maximum dose is applied during a mid-diastolic phase (70% phase) in patients with a heart rate < 70 bpm and during an end-systolic phase (40% phase) in patients with a heart rate ≥ 70 bpm. The ratio between the time window in which dose is kept at the diagnostic level and the total scan time determines the amount of dose saving. Maximum dose saving

can be achieved in combination with low heart rates and with application of diagnostic dose during only a single phase of the RR-interval. Application of diagnostic dose in all those phases that could be the most motionless phase (30%, 40%, 70%, 80%, 90%) regardless of heart rate will leave little time for down-regulating dose and will yield almost no dose saving.

Careful application of ECG-based tube current modulation during retrospectively ECG-gated calcium scoring is necessary since we found that the variability in calcium scores obtained in various phases throughout the cardiac cycle are substantial even with a 64-detector row scanner. The variations in scores throughout the RR-interval found in our study were similar to previously found variations throughout the cardiac cycle in a 4-detector row [25] and a 16-detector row study [19]. Variations reported in a previous 64-detector row scanner study were limited to mid-diastolic phases and only in patients with low heart rates (mean heart rate 57±4 (SD) bpm) [26]. In the most extreme cases we found a maximum difference over the cardiac cycle of over 1000 in AS and of over 100 mg in MS. Scores can increase or decrease relative to the most motionless score, as was found in a phantom study [27]. On average, however, scores tended to decrease. This is probably due to smearing of calcifications and a resulting decrease in CT number, which may reduce the total number of pixels that reach the detection threshold and lower weighting factors due to the decreased CT number.

We also observed in our study that the differences relative to the reference score in the most motionless phase increased with increasing cardiac motion artifacts. Unless temporal resolution of CT scans used for calcium scoring is so high that cardiac motion can always be “frozen”, even during phases of rapid cardiac motion such as ventricular contraction, variations in calcium scores over the cardiac cycle will continue to be present with future scanners.

Cardiac motion artifacts have been previously identified as a main limiting factor for the reproducibility of calcium scoring. Horiguchi et al. showed a negative impact of cardiac motion artifacts on inter-scan reproducibility. They found this by calculating the variability between scores obtained in the 70% phase of two consecutive 16-detector row scans and subjectively scoring motion artifacts in these two scans [14]. Their findings support the notion that the most motionless phase should be preferably used for calcium scoring. This is also implied by the results of a study by Sandstede et al. in which the detection of a zero calcium score was studied [28]. They concluded that several phases need to be evaluated before assigning a zero score. This conclusion might be further refined by adding that a zero score can only be reliably assigned in a single phase in the absence of motion artifacts.

The most motionless phase was most frequently found in diastole (75% of subjects overall, 90% of subjects with heart rate < 70 bpm). The mid-diastolic 70% phase showed excellent results as a predefined phase for a group of patients with a heart rate < 70 bpm. In case of heart rates ≥ 70 bpm the end-systolic 40% phase showed the best results. This finding corresponds with results of studies on the best reconstruction interval for coronary CT angiography [29-32] and on coronary arterial motion velocity [33]. With heart rates < 70 bpm the preferred phase is likely to be mid-diastolic, since this phase shows least cardiac motion at low heart rates. With increasing heart rate the length of diastole decreases rapidly and the relatively motionless period at end-systole takes up a larger percentage of the RR-interval. Important to realize is that the length of the mid-diastolic and end-systolic rest periods for a certain heart rate show large inter-individual variations and are generally shortest for the right coronary artery [34,35].

Since dose savings increase at lower heart rates, the use of heart-rate-lowering drugs, such as beta-blockers, may be considered. In addition, beta-blockers not only decrease average heart rate but also decrease heart rate variability. Less heart rate variability is likely to yield more optimal application of ECG-based dose modulation, because this technique is prospectively applied. Thereby, Leschka et al. showed a greater impact of heart rate variability than of average heart rate on image quality during CT angiography [36]. Improved image quality with fewer motion artifacts may result in less score deviations.

Our study has several limitations. First, the reduction in radiation dose with ECG-based tube current modulation was studied in vitro and not in vivo. We chose this study setup because it allowed us to study and compare various potential options for dose modulation (single phase, dual or multiple phase modulation) that could not have been studied in a clinical setup because of radiation dose constraints. We consider the results valid because the dose modulation program performs in a predictable manner depending on the RR-interval length and does the same in a clinical setting. The only difference in a clinical setting is found when the heart rate varies during the scan. However, the dose savings then should vary accordingly, depending on the corresponding heart rates. For this reason, our experiment gives an indication how much dose reduction can be expected under certain well-defined conditions. Secondly, we analyzed a limited number of scans with a large range of scores. However, we do not think the range of scores in this study affects the general conclusion. A greater influence on the results is the average heart rate in the population studied. The subjects we scanned had an average heart rate of 63 bpm. With a higher average heart rate we may have found larger differences and the mid-diastolic 70% phase would have been less likely to be a good alternative to the most motionless phase for the overall population. For this reason, we subdivided subjects into subsets with high and low heart rates.

Thereby, in our study we assumed that use of the most motionless phase would yield the best inter-scan reproducibility. We could not determine inter-scan reproducibility to verify this. However, a study by Horiguchi et al. has shown that the inter-scan reproducibility in retrospectively ECG-gated calcium-scoring is largely influenced by motion artifacts [14] and that the most motionless phase should be used for calcium scoring.

In conclusion, the optimum phases for dose modulation are 70% (mid-diastole) at heart rates below 70 bpm and 40% (end-systole) at heart rates at or above 70 bpm. Under these conditions dose saving is maximum and a median error of 0% is found for the various calcium scoring techniques with score errors of more than 10% in around 10% of subjects.

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Chapter 5

CHAPTER 6

INFLUENCE OF CONTRAST CONCENTRATION ON ENHANCEMENT IN CARDIAC CT: IS HIGHER BETTER?

Chapter 6

ABSTRACT

Purpose

Iodine flux and total iodine dose have been described as the major determinants for contrast enhancement in computed tomography angiography (CTA). We determined the additional influence of contrast material concentration on enhancement in cardiac CT using a dual phase injection protocol.

Materials and Methods

One hundred and fifty nine patients underwent cardiac CTA on a 64-detector row CT scanner. Patients were randomized on a per day basis to either a moderate (300 mg Iodine (I)/ml) or a high contrast concentration (370 mg I/ml). Contrast material injection included a second injection phase targeted at enhancement of the right ventricle to allow functional analyses. Independent of contrast concentration, injection duration (and thus, total iodine dose) was adapted to scan duration, and iodine flux was adjusted to patient weight (<70kg: 1.6g/s; 70-85kg: 1.8g/s; >85kg: 2.0g/s). Attenuation was measured at different levels in the heart and vessels. Attenuation was compared between the two concentrations overall and per weight group.

Results

84 patients received the moderate concentration contrast medium and 75 patients the high concentration contrast medium. Contrast attenuation in the aorta and left ventricle was significantly higher for the patients receiving the lower concentration contrast medium. This remained true for the two higher weight groups. No difference was found in the lowest weight group or in the right ventricle and pulmonary outflow tract.

Conclusion

Lower concentration contrast medium results in higher contrast attenuation in the aorta and left ventricle if total iodine dose and iodine flux are kept unchanged and a weight-adapted dual phase injection is used.

INTRODUCTION

The substantially decreased scan durations with the new generations of computed tomography (CT) scanners (32-, 40- and 64-detector row) have made it necessary to adjust contrast injection protocols for cardiac CT angiography (CTA) in such a way that a high arterial enhancement level is reached faster but is maintained over a shorter period of time. Arterial enhancement is determined by patient-related factors (e.g., blood volume, cardiac output) as well as by the contrast injection parameters (e.g., contrast material concentration and volume, flow rate, added saline chaser bolus) [1-3]. Recent publications suggest that a higher iodine concentration provides superior enhancement characteristics but this superior enhancement was achieved by an increase in iodine flow rate (iodine flux in grams iodine injected per second = flow rate × concentration) or an increase in the total amount of iodine (iodine dose in grams = volume × concentration) [4,5]. Iodine flux and iodine dose are considered to be the determining factors for enhancement [2,6].

We evaluated the effect of contrast medium concentration on cardiac and arterial enhancement in 64-detector row cardiac CT under otherwise identical iodine injection parameters (i.e. constant iodine flux and constant iodine dose). A dual phase contrast injection protocol with high initial contrast injection rates and with adjustments for patient weight and scan duration was applied to obtain optimal enhancement of the coronary arteries for assessment of coronary artery disease and of both left and right ventricle for functional analyses. Two different contrast medium concentrations were used while iodine dose and iodine flux were kept unchanged. Our hypothesis was that no substantial differences in enhancement would be detected.

MATERIALS AND METHODS

We performed a prospectively randomized study financially supported by Bayer-Schering AG (Berlin, Germany). The nonemployee authors had full control of the data and information submitted for publication. The institutional review board granted permission to perform this study. All patients signed informed consent.

Based on the requirements of an inter-individual comparison to test non-inferiority for arterial enhancement by a two-group t-test (power of 80%, one-sided alpha of 2.5%, non-inferiority margin (Δ) of 10%) a minimum of 174 patients needed to be included in this study. Between May 2005 and March 2006 we included 182 consecutive patients scheduled for cardiac CT. They either received contrast medium with 300 mg iodine (I)/ml or 370 mgI/ml (Iopromide, Schering, Berlin, Germany) during the examination. The cardiac CT scans were performed on a 64-detector row scanner (Brilliance 64, Philips Medical Systems, Cleveland, OH, USA). Scan parameters are summarized in Table 6-1.

Table 6-1. CT scan parameters

Collimation (mm)	64 × 0.625
Direction	↓ (cranial to caudal)
Scan range	15 mm above coronaries to 15 mm below apex
Location bolus tracker ROI	At start planned scan range
Bolus tracker threshold (HU)	100
Start delay post-threshold (s)	8
Scan length (cm)	10 – 16 (average 12)
Scan duration (s)	8 – 11 (average 10)
Pitch	0.2
Tube current (mAs)	500 – 1000 (depending on patient size)
Peak tube potential (kVp)	120
FOV (mm)	205
Matrix	512 × 512
Recon section thickness (mm)	0.9
Recon section increment (mm)	0.45

Patients were excluded if a needle smaller than 18 gauge (G) was used for intravenous injection due to small vessel size, since an 18G needle was needed to accommodate the applied flow rates, or if the scan range was extended beyond the region of the heart. Of the 182 consecutive patients undergoing cardiac CT 23 were excluded. 6 patients received a 20G needle due to small vessel size, 8 patients had to undergo a cardiac CT with an extended scan range, e.g. bypass graft evaluation, and 9 patients were excluded because of deviations from scan protocol, such as change of post-threshold delay, which could influence contrast enhancement.

Contrast medium injection protocol

Randomization to one of the two contrast medium concentrations was performed on a per day basis for logistic reasons. We applied a dual phase contrast injection protocol with two connected phases of contrast medium injection immediately followed by a saline flush of 30 ml modified from Garcia et al. [7] injected with a dual syringe injector (Stellant D, Medrad, Indiana, PA, USA). This protocol was used to achieve similar enhancement in the left and right ventricle to allow functional analyses beside the coronary artery analysis. A similar contrast injection protocol is needed in triple rule out studies to achieve adequate enhancement of aorta, coronary arteries and the pulmonary artery [8].

Table 6-2. Contrast medium injection protocol

Injection phase[#]	Weight group	Iodine flux I (g/s)	Flow rate F (ml/s)		Volume V (ml)[##]		Injection duration T (s)
			Contrast concentration				
			300 mg/ml	370 mg/ml	300 mg/ml	370 mg/ml	
I	<70 kg	1.6	5.3	4.3	85-101	69-82	Scan duration + 8*
	70-85 kg	1.8	6.0	4.9	96-114	78-93	
	>85 kg	2.0	6.7	5.4	107-127	86-103	
II	<70 kg	0.8	2.7	2.2	27	22	10
	70-85 kg	0.9	3.0	2.4	30	24	
	>85 kg	1.0	3.3	2.7	33	27	

** Start delay for bolus tracking was set to 8s after reaching a threshold level of 100 HU in a ROI in the descending aorta at the start of the planned scan range*

[#] Phase II immediately followed phase I and a saline flush of 30 ml with the same flow rate as phase II was always performed immediately after phase II

Volume is given as range. For an individual patient exact contrast material volume in each phase can be calculated from injection duration T and flow rate F as follows: V = T x F

Note. - The injected amount of iodine M (total iodine dose) per phase can be calculated from T and iodine flux I: M = T x I. Iodine flux I and total iodine dose M are independent of contrast material concentration and even the same for both contrast material concentrations.

The first contrast medium injection phase is similar to the single contrast medium injection phase commonly used for cardiac CTA and yields sufficient enhancement of the coronary arteries [3,9,10]. The second, directly consecutive, contrast medium injection phase was applied to prevent washout of the right ventricle, a portion of the circulation proximal to the coronary arteries. This allowed analysis of left and right ventricular function, including left ventricular wall thickness and thickening, which is not possible with complete washout of the right ventricle. Every patient was assigned to one of three weight categories, each with its own iodine flux (g/s) for the first injection phase (<70kg: 1.6g/s; 70-85kg: 1.8g/s; >85kg: 2.0g/s) (Table 6-2). Iodine flux for each weight category was based on previous data to obtain an attenuation of 300 Hounsfield Units (HU) in the

coronary arteries. Iodine flux was independent of the contrast medium concentration used. The duration of the first injection phase was the scan duration plus 8s. Iodine flux in the second contrast medium phase, that lasted 10s, was 50% of the flux in the first phase. Between the two contrast medium injection phases and between contrast medium injection and saline flush no time delay occurred. The flow rate (ml/s) during each phase of the contrast medium injection and the volume of contrast medium (ml) to be injected during each phase was calculated in a spreadsheet program (Excel, Microsoft Office 2003, Redmond, WA) (flow rate (ml/s) = iodine flux (g/s) / contrast medium concentration (g/ml) and volume (ml) = flow rate (ml/s) × injection duration (s)) (Table 6-2).

The total iodine dose (g) injected could be calculated by multiplying iodine flux and scan duration and was also independent of contrast medium concentration. The 370 mgI/ml contrast material was heated to 37°C before use to decrease the viscosity. Time to threshold and the maximum injection rate reached were recorded.

Data evaluation

Vascular enhancement was measured by placing regions of interest (ROI) of 1 cm^2 in the left and right ventricle, and the descending aorta at three levels (cranial, mid and caudal) and in the ascending aorta and pulmonary artery, right above the aortic and pulmonary valve, respectively.

In a subsample of 20 patients in the weight category between 70 and 85 kg (10 for each contrast medium concentration; matched for patient characteristics in Table 6-3) the pattern of vascular enhancement throughout the scan was measured by placing a ROI of 1 cm^2 in the descending aorta every tenth slice (i.e. every 4.5 mm) from cranial to caudal (i.e. scan direction). The measurements at each level were averaged for all ten patients in each contrast medium concentration group to compare the enhancement pattern between both groups.

Contrast opacification in the coronaries was subjectively scored on a 5-point scale (1 = poor to 5 = excellent) by a single observer with 3 years of experience in cardiac CT. Patients were interviewed after the examination to determine patient (dis)comfort on a scale from 1 to 10 (1 = severe discomfort, 10 = no discomfort at all). Any allergoid reactions and contrast extravasations were recorded.

Statistical analysis

Continuous variables were summarized using mean and standard deviation and categorical variables using median and range. An independent t-test was used to compare the two groups in case of continuous measures such as vascular enhancement for each measurement location. In case of categorical variables, such as subjective scores for

opacification, a Wilcoxon rank sum test was used to compare the two groups. A P-value < 0.05 was considered significant. Data analysis was performed with software for statistical analysis (SPSS for Windows, 2004, version 12.0.1, Chicago, IL).

RESULTS

Patient characteristics of the included patients are summarized in Table 6-3. Patient comfort scores were a median of 7 in both groups (P>0.05). No contrast extravasations occurred. Four patients developed a mild allergoid reaction (nausea or urticaria); three patients in the high concentration group and one patient in the moderate concentration group. Intended contrast injection rates were always reached. Mean time to threshold was 19 s (range 16-25 s) for the 300 mgI/ml group and 20s (range 15-25 s) for the 370 mgI/ml group (P>0.05).

Table 6-3. Patient characteristics overall and per weight category

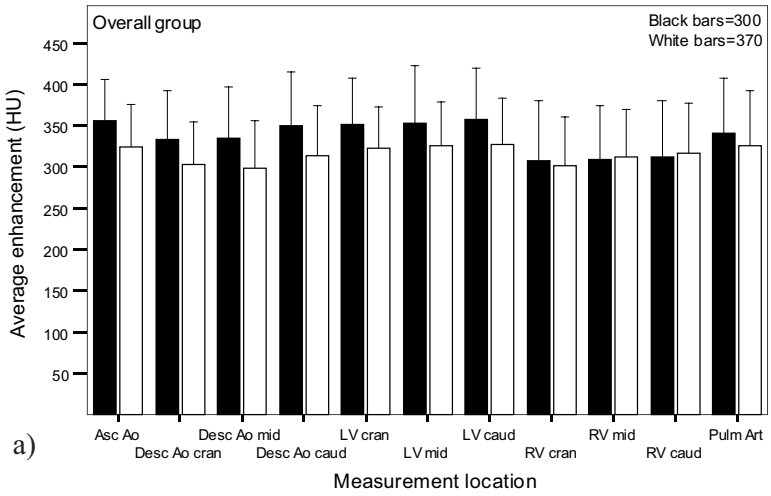
	Overall *(n=159)*		<70 kg *(n=22)*		70-85 kg *(n=77)*		>85 kg *(n=60)*	
	300	370	300	370	300	370	300	370
Total # (men)	84 (61)	75 (60)	15 (7)	7 (5)	40 (31)	37 (27)	29 (23)	31 (31)
Age (years)	58.2 (9.4)	57.0 (9.5)	61.8 (5.6)	61.3 (11.9)	57.5 (7.4)	57.3 (9.6)	57.4 (12.7)	55.7 (8.9)
Heart rate (bpm)	57.6 (8.4)	57.5 (7.6)	59.7 (10.6)	62.9 (4.3)	56.6 (7.6)	58.1 (8.0)	57.9 (8.3)	55.6 (7.2)
Weight (kg)	81.5 (12.6) [60-115]	83.0 (11.4) [59-118]	65.4 (3.4) [60-69]	62.9 (3.7) [59-68]	77.6 (5.0) [70-85]	78.2 (4.5) [70-85]	95.2 (8.6) [86-115]	93.3 (7.9) [86-118]
BMI (kg/m^2)	26.9 (3.5)	26.9 (3.2)	23.5 (2.2)	23.3 (3.0)	26.1 (2.6)	25.9 (2.2)	29.6 (3.2)	28.9 (2.9)

Note.- Numbers are means with standard deviation between parentheses (and for weight the range between brackets). Only in first row total numbers are given with number of men between parentheses.

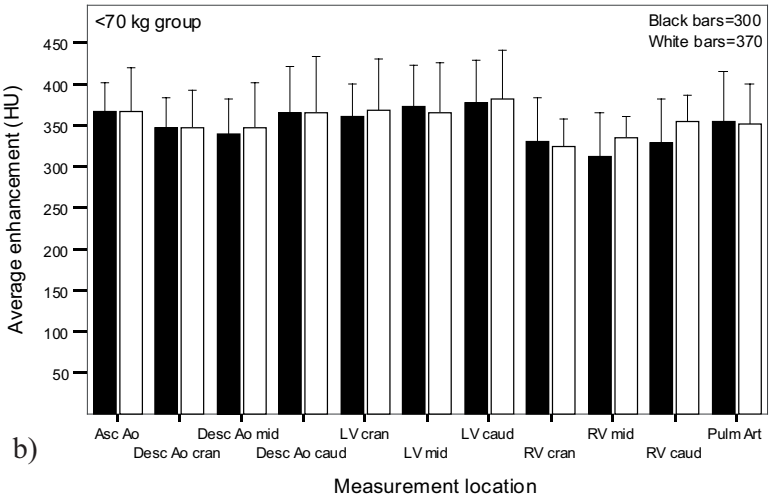
No significant differences were found between the 300 mg I/ml group and the 370 mg I/ml group for these characteristics. (BMI = body mass index)

Vascular enhancement

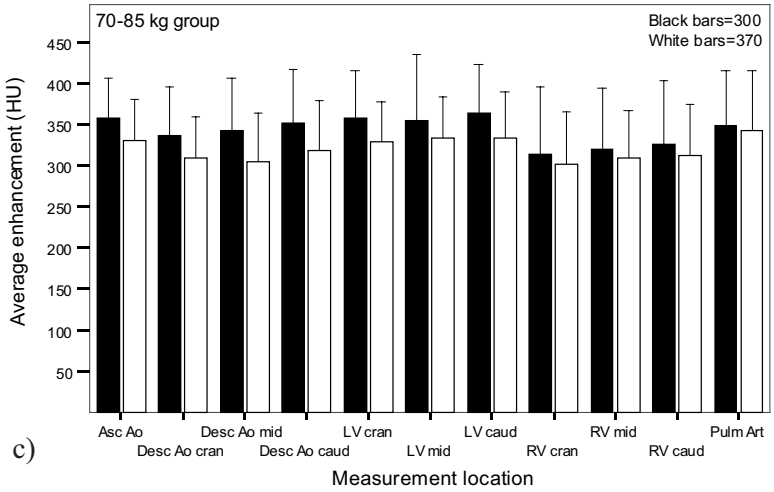
Mean attenuation in the aorta and left ventricle was significantly higher in the subjects in the moderate concentration group ($P<0.05$) (Figure 6-1). This was seen in the overall study population and in the two higher weight groups (≥70 kg). This difference was not found in the lowest weight group (<70 kg). The mean attenuation at the various levels in the right ventricle and in the pulmonary artery were never shown to be significantly different ($P>0.05$).



a)



b)



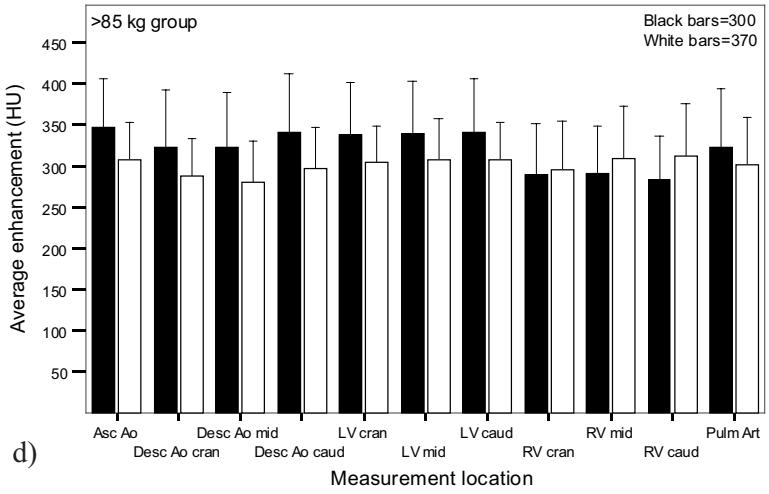


Figure 6-1. *Continued from previous page. Bars display average enhancement at each measurement location per contrast medium concentration group for all subjects (a), and the three weight categories (b-d); error bars display one standard deviation. Significantly higher enhancement was found in the lower concentration contrast medium group (black bars) at the measurement locations in the aorta and left ventricle for the overall group and the two higher weight categories but not in the lowest weight category. (Asc Ao=ascending aorta, Desc Ao =descending aorta, LV=left ventricle, RV=right ventricle, Pulm Art=pulmonary artery, cran=cranial, m=mid, caud=caudal).*

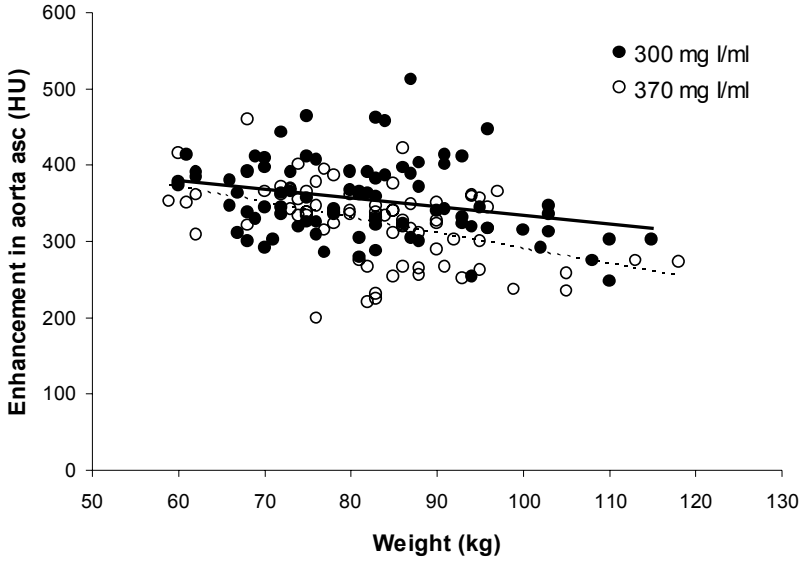


Figure 6-2. *Enhancement in the ascending aorta versus weight. Note that enhancement decreases with increasing weight in both contrast medium concentration groups (continuous line: 300 mg I/ml group; dashed line: 370 mg I/ml group) despite the use of three weight categories in the injection protocol.*

Despite the use of a weight-adapted contrast injection protocol the attenuation decreased with increasing weight (Figure 6-2). Figure 6-3 provides examples of CT images from both groups.

Enhancement pattern

At the beginning of the scan, more cranial in the descending aorta, the average attenuation in the 300 mgI/ml group is higher than in the 370 mgI/ml group (Figure 6-4). At the end of the scan, more caudal in the descending aorta, the curves coincide due to a gradual increase of average enhancement in the 370 mgI/ml group.

Subjective scores

In both groups scores of 3 or more were given for the contrast opacification in the coronary arteries. The subjective scores of the coronary arteries were on average slightly, but not significantly, higher in the lower contrast concentration group (4.1 vs. 3.7) ($P>0.05$).

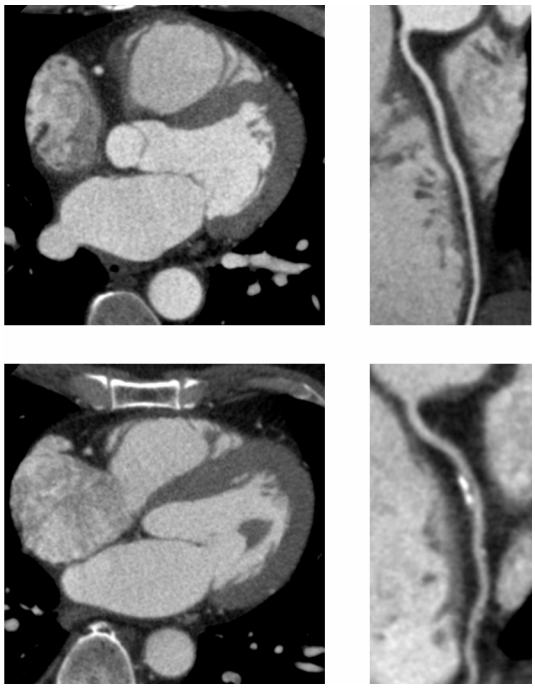


Figure 6-3. *Examples of axial CT images (left) and curved planar reformations of the right coronary artery (right) with both 300 mg I/ml contrast medium (top) and 370 mg I/ml contrast medium (bottom). Note that with both concentrations of contrast medium sufficient contrast enhancement of the heart is reached. The right coronary artery is little affected by the presence of contrast medium in the right atrium and ventricle*

DISCUSSION

In this study we found a difference in arterial enhancement between high and moderate contrast medium concentrations in favor of the moderate concentration. This was seen despite injection protocols based on identical iodine flux and iodine dose. Our finding seems to contradict the conclusion of previous studies comparing different contrast medium concentrations for cardiac CT in which better enhancement with higher concentration contrast medium was found [4,5]. However, these studies kept contrast injection rate or injection duration constant, therefore varying the iodine flux and/or iodine dose.

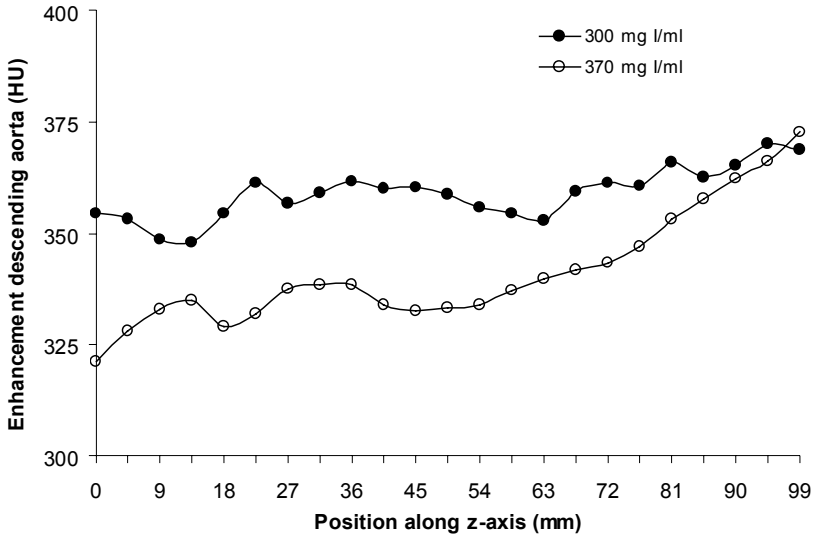


Figure 6-4. *Curves of enhancement throughout the descending aorta for both contrast medium concentration groups in subjects between 70 and 85 kg. Attenuation was measured in the first (most cranial) slice and then every tenth slice (i.e. every 4.5 mm). The average enhancement in the lower concentration contrast medium group is higher at the start, but the average enhancement in the higher concentration contrast medium group starts to increase in the second half of the scan. The curves even coincide at the end of the scan range.*

Increasing contrast medium concentration is not the only method for achieving higher iodine flux and higher arterial enhancement. An increase in contrast injection rate while keeping contrast medium concentration constant will also result in a higher iodine flux. Theoretically, neither method should be favored over the other [1,2,6,11]. Therefore we powered this study to determine equivalence between both concentration groups, which resulted in large group sizes to confidently exclude small differences between groups. Our study, however, demonstrated that higher flow rates should be preferred over higher concentration to achieve a desired iodine flux.

In practice, use of high concentration contrast medium requires smaller contrast medium volumes and lower flow rates, while the same total iodine dose is administered. However, high concentration contrast medium needs to be pre-heated because of its high viscosity at room temperature. Costs are comparable between the two concentrations: high concentration contrast medium is more expensive per volume unit but a smaller volume is

applied per patient. Lower concentration contrast media are currently used for most types of CT examinations, which results in a logistic advantage if the contrast medium (concentration) need not be changed for cardiac CTA.

Previous studies on arterial contrast enhancement in cardiac and abdominal CT with varying concentrations of iodinated contrast medium but equal iodine flux and equal iodine dose have shown conflicting results. Two studies with a iodine flux of 1 g/s in cardiac CT did not show an advantage for a moderate or high concentration contrast medium [12,13]. One study in abdominal CT also did not find a difference in arterial enhancement [14]. However, a study by Awai et al., with a very similar set-up as the aforementioned study in abdominal CT, did find a benefit for rapid administration of lower concentration contrast medium [15]. It is unclear why they did detect a difference in arterial enhancement while the other studies did not. This study did have the largest patient number in each group (more than 90 vs. less than 35 subjects per group in the other three studies).

Current knowledge does not provide an explanation for the difference in enhancement found in our study and in the study by Awai et al. Ideally, time-density curves are created for each injection protocol in a large group of patients by scanning at one reference level. Such a dynamic scan would entail a substantial additional radiation dose and extra contrast load for each patient and would have to be performed before the actual cardiac CT. For this reason, we can only suggest a number of potential explanations for our results: the difference in contrast material volumes, the difference in viscosity, differences in venous pooling or the dead venous space phenomenon [15].

At identical iodine flux and iodine dose, the injected contrast material volume is higher, both in total as well as per unit time. At a constant cardiac output, a higher volume of contrast entering the heart per unit time will lead to less blood mixing with the contrast material and therefore will cause a higher contrast concentration in the central blood compartment. This “volume effect” has been suggested by Bae [16] as an explanation of the effect seen by Awai et al. [15]. Cardiac output, however, does not necessarily have to stay constant during contrast injection: in young healthy individuals, a sudden volume load may induce an increase in heart rate and cardiac output while the same sudden volume load may induce a drop in cardiac output in older patients with a failing heart. Since cardiac output and enhancement are linked [17], the effect could go either way: increasing or decreasing enhancement.

The higher viscosity of higher concentration contrast media could hamper rapid administration and lengthen transit time of contrast medium [11,18]. The maximum flow rate in a vein phantom was found to decrease at higher contrast concentration: at 370 mgI/ml

the highest iodine flux was 2.2 g/s or 6 ml/s; at 300 mgI/ml a iodine flux of 2.4 g/s or 8 ml/s was reached [18]. However, these maximum injection rates are above the injection rates used in our study for both the high and moderate concentration group and data produced by the contrast injection pump confirms that the required injection rates were always reached. In addition, we pre-heated the 370 mg/ml contrast medium to 37°C to obtain a viscosity similar to that of 300 mg/ml contrast medium at room temperature. The fact that we found no significant difference in time to threshold between the two groups supports the notion of identical arrival times and discourages the idea that the higher viscosity contrast material traveled slower.

Venous pooling occurs when contrast material is "trapped" in small veins where it travels slower and therefore contributes less to downstream enhancement. This effect could lead to lower enhancement for more viscous contrast material or for higher flow rates: more viscous high concentration contrast medium on its way to the heart could be trapped in small veins or could stick to the vessel wall. With an increase in flow rate one could argue that a higher pressure is built up in the injection vein during the infusion of contrast medium and contrast medium may be pushed into smaller veins. The contrast medium may remain trapped in these small veins until the pressure in the injection vein drops.

The dead venous space phenomenon refers to the contrast material that remains in the dead venous space at the end of a contrast injection. This contrast material no longer travels with the original flow rate but, at most, with the speed of the venous blood towards the heart and therefore contributes less to enhancement than the earlier contrast material that was injected quickly [14]. This effect increases with higher flow rates. In a dual phase injection, the second phase is also subject to such a dead space phenomenon if injection rate is decreased: contrast material in the injection veins travels not faster than the flow of the second phase of the injection. Because the volume of the dead space is identical for the two contrast injection protocols, the amount of iodine contained in the dead space is larger for higher concentration contrast material. In the high concentration group less iodine is therefore traveling with the high flux of the first phase. The iodine in the venous dead space reaches the heart later, which may explain why right ventricular and pulmonary enhancement did not show a difference.

This study has several limitations. First, instead of applying a continuous increase in injection rates with increasing patient weight, we used three weight categories. Especially the highest weight category contained patients with a large range in weights. A slight decrease in attenuation was found with increasing weight throughout each category. The reason why we opted for three categories was mainly logistic; six pre-programmed injection protocols in the injector sufficed. Besides, a continuous increase in injection

rates with increasing weight would have resulted in too high injection rates in very heavy patients. Also, a large variability in enhancement exists between patients with similar weights, since weight is not the only determining patient-related factor.

Another limitation is the small size of the lowest weight group. Relatively few patients have a weight below 70 kg especially in this cardiac patient group. The results in this low weight group were not consistent with the results in the other two groups. However, this did not seem to be caused by the small size of the group, but rather by a true difference between the weight groups. Lower injection rates, less dead space and a relatively large iodine dose per kg patient weight might be underlying factors.

Finally, we did not perform attenuation measurements in the coronary arteries, despite the fact that these vessels are the most crucial for coronary CTA. We considered the coronary arteries too small to obtain reliable measurements, especially in the presence of coronary plaques. Instead we measured in the aorta and left ventricle at several levels. Contrast enhancement in these structures should be sufficiently representative of enhancement in the coronary arteries. In addition, measurements in the aorta and ventricles are probably more comparable due to larger ROI size and standardized measurement locations.

In conclusion, lower concentration contrast medium results in higher contrast attenuation in the aorta and left ventricle when using a weight-adapted dual phase injection protocol with high injection rates while keeping total iodine dose and flux constant between contrast concentrations. Higher flow rate should be preferred over higher contrast material concentration to achieve a desired iodine flux. Current models for the prediction of contrast enhancement may need to be expanded.

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Chapter 6

CHAPTER 7

OPTIMIZING CONTRAST INJECTION PROTOCOLS FOR CARDIAC CT BY SIMULTANEOUSLY INJECTING CONTRAST MEDIUM AND SALINE DURING THE SECOND INJECTION PHASE

Chapter 7

ABSTRACT

Purpose

To compare magnitude and homogeneity of contrast enhancement between a standard biphasic contrast injection protocol for cardiac CT and for two protocols that use simultaneous injection of contrast material (CM) and saline during the second injection phase.

Materials and Methods

Patients undergoing coronary CT angiography on a 64-detector CT scanner (n=165) were prospectively included in three sequential groups with different second phases of a biphasic CM injection protocol. To remove sources of bias groups were retrospectively matched regarding age, weight, length and heart rate by removing patients from the first two groups. The first injection phase was identical for all three groups. Second injection phase of 10 seconds consisted of non-diluted CM injected at half the first phase flow rate in group A (n=43), in group B (n=43) and C (n=33) CM was diluted to respectively 50% and 30% of the original concentration in the second phase and injected at first phase flow rate, which results in 12-13 ml CM reduction in group C. Attenuation was measured at various levels in heart and vessels. Coronary opacification and assessability, and contrast homogeneity in right ventricle were evaluated. Unpaired t-test and Wilcoxon rank-sum test were used to assess differences between groups.

Results

Aortic and left ventricular attenuation and coronary opacification and assessability did not differ significantly between groups. Right ventricular attenuation was significantly higher in group B ($P<0.05$). Subjective scores for right ventricular homogeneity were significantly better in group C compared to group A and B ($P<0.05$).

Conclusion

Biphasic CM injection with CM diluted to 30% in second phase yields similar levels of enhancement and better homogeneity of right ventricular enhancement than a standard biphasic protocol while less contrast medium is applied.

INTRODUCTION

Contrast-enhanced cardiac computed tomography (CT) is mainly used for coronary artery stenosis evaluation but can be extended to a comprehensive cardiac examination that includes functional measurements [1,2]. The simultaneous evaluation of coronary arteries and left and right ventricular function (including wall mass and wall thickening) demands good contrast enhancement of the coronaries as well as the ventricular cavities. Nowadays, a uniphasic contrast medium injection immediately followed by a saline flush is most commonly applied in contrast-enhanced cardiac CT [3-5]. This yields proper contrast enhancement of the coronary arteries and left ventricle and a washout of the right ventricle. To prevent washout of the right ventricle a biphasic contrast medium injection protocol can be applied [6].

The latest generation of dual syringe injectors not only allows consecutive injection of contrast medium and saline but also simultaneous injection of contrast medium and saline in various proportions. Such simultaneous injection techniques could be useful in biphasic contrast medium injection protocols because they allow constant injection rates between injection phases while contrast medium concentration and thus the amount of injected iodine can be reduced in the second injection phase. This combines a better contrast medium throughput with a reduction in contrast medium volume, similar to the effect of applying a saline flush [7-9]. Simultaneous injection of contrast medium and saline may also lead to a further reduction of streak artifacts in the injection veins and right atrium because simultaneous injection leads to dilution of contrast material already in the injection veins [8,9].

To our knowledge, the effect of diluting contrast medium with saline in the second contrast medium injection phase of a biphasic contrast medium injection protocol for cardiac CT has not been studied. We performed our study to compare artifact behavior as well as magnitude and homogeneity of contrast enhancement for a standard biphasic contrast injection protocol for cardiac CT and for two protocols that use simultaneous injection of contrast material and saline during the second injection phase.

MATERIALS AND METHODS

Subjects

We performed a prospective study between May 2005 and October 2007 in patients that underwent coronary CT angiography (cCTA) on a 64-detector row CT scanner (Brilliance 64, Philips Medical Systems, Cleveland, OH, USA) for clinical suspicion of coronary artery disease (scan parameters are summarized in Table 7-1). Three subsequent groups were included: group A (n=84) between May 2005 and March 2006, group B (n=48)

between May 2006 and January 2007 and group C (n=33) between March and October 2007. After inclusion these three groups were matched for age, gender, heart rate, weight and length by removing patients from group A and B. This was done to avoid bias in the comparison between groups.

Inclusion criteria for our study were a scan range covering the heart from just above the highest coronary artery to just below the apex, an intra-venous needle size of 18 gauge (G), a tube voltage setting of 120 kVp, a contrast material concentration of 300 mg iodine per ml and a post-threshold delay of 8 s, since variations in these factors can severely influence measured contrast attenuation at the predefined levels. The institutional review board waived the need to obtain permission for performing this HIPAA compliant study.

Table 7-1. Scan parameters

Collimation (mm)	64 × 0.625
Direction	↓
Scan range	15 mm above highest coronary to 15 mm below heart
Location bolus tracker ROI	At start planned scan range in descending aorta
Bolus tracker threshold (HU)	100 HU
Post-threshold start delay (s)	8
Scan length (cm)	11 – 14 (average 12)
Scan duration (s)	9 – 10 (average 10)
Pitch	0.2
Tube current (mAs)	500 – 1000
Peak voltage (kVp)	120
FOV (mm)	205
Matrix	512 × 512
Recon section thickness (mm)	0.9
Recon section increment (mm)	0.45

Table 7-2. Parameters for biphasic contrast medium injection protocol including two immediately consecutive injection phases followed by a saline chaser of 30 ml

<85 kg		Flow rate (ml/s)	CM volume # (ml)	NS volume (ml)	Injection duration (s)
Injection phase I		6.0	102-108	0	17-18*
Injection phase II	Group A	3.0	30	0	
	Group B	6.0	30	30	10
	Group C	6.0	18	42	
>85 kg		Flow rate (ml/s)	CM volume # (ml)	NS volume (ml)	Injection duration (s)
Injection phase I		6.7	114-121	0	17-18*
Injection phase II	Group A	3.3	33	0	
	Group B	6.7	33.5	33.5	10
	Group C	6.7	20	47	

** Injection duration was scan time plus 8s since start delay for bolus tracking was set to 8s after reaching a threshold level of 100 HU in a ROI in the descending aorta at the start of the planned scan range (i.e. 15 mm above highest coronary).*

 # Volume is given as range. For an individual patient exact contrast material volume in each phase can be calculated from injection duration T and flow rate F as follows: V = T x F.

Contrast medium injection

We used a dual syringe injector (Stellant, Medrad, Indiana, PA, USA) to perform biphasic contrast material injection protocols with two immediately subsequent phases of contrast medium injection directly followed by a saline flush of 30 ml (Table 7-2). These injection protocols were modified from Garcia et al. [10]. Every patient was assigned to one of two

weight categories, each with its own iodine flux (g/s) and thus contrast medium flow rate for the first injection phase (<85 kg: 1.8 g/s, 6 ml/s; >85 kg: 2.0 g/s, 6.7 ml/s). Iodine flux for each weight category was based on previous unpublished data to obtain an attenuation of approximately 300 HU in the coronary arteries.

The first phase of the contrast material injection protocols was identical in all groups and was used to ensure coronary enhancement. The second contrast material injection phase was different in each of the three groups and was used for obtaining a suitable level of right ventricular enhancement with low streak artifacts. The duration of the first contrast medium injection phase was chosen identical to the scan time + start delay (i.e. 17 or 18s). We chose 10s as the duration of the second contrast medium injection phase, independent of the contrast injection protocol. This duration was chosen because it is longer than the average transit time through the pulmonary circulation, thus enhancement of the right heart was dominated by the second phase of the injection.

Compared to iodine flux in the first phase, iodine flux during the second phase was reduced to 50% in groups A and B, and to 30% in group C. For group A, this reduction was achieved by reducing CM flow. In groups B and C, the reduction of iodine flux was achieved by diluting the contrast concentration by simultaneously injecting CM and saline while keeping the same flow rate as in the first phase (Table 7-2). The volume of diluted contrast medium injected in the second phase in groups B and C was twice the volume of the non-diluted contrast medium in group A. The amount of iodine injected in the second phase was identical for group A and B but 40% lower in group C.

The time from the beginning of the injection to reaching the threshold of 100 HU in the descending aorta was recorded. We also noted the maximum injection rate reached by the injector and any allergoid reactions and contrast extravasations.

Data evaluation

Vascular enhancement was measured by placing regions of interest (ROIs) of 1 cm^2 in the left and right ventricle, and the descending aorta at three levels (cranial, mid and caudal) and in the ascending aorta and pulmonary artery, right above the aortic and pulmonary valve, respectively.

In each group ten patients were selected to measure the pattern of vascular enhancement throughout the scan by placing a ROI of 1 cm^2 in the descending aorta every tenth slice (i.e. every 4.5 mm or 0.24 s of scan time) from cranial to caudal (i.e. start scan to end scan). The ten patients from each group were matched for age, gender, weight and heart rate to allow comparison of the enhancement pattern in the descending aorta between groups.

Homogeneity of contrast enhancement in the cranial, mid and caudal right ventricle was subjectively scored on a 5-point scale (1 = inhomogeneous to 5 = homogeneous). Contrast opacification in the proximal, mid and distal coronary arteries was subjectively scored on a 5-point scale (1 = poor to 5 = excellent). The assessability of the right coronary artery (RCA) was subjectively scored on a 5-point scale (1 = non-assessable to 5 = excellent assessability), since high contrast enhancement in the right atrium and ventricle can have a negative influence on the assessability of the RCA because of streaking artifacts extending outside the right atrium and ventricle through the RCA. Also, the extent of streaking artifacts from high density contrast in the superior vena cava was scored on a 5-point scale (1 = major streaking artifacts to 5 = no streaking artifacts). A single observer with 4 years of experience in coronary CTA performed all subjective scoring without knowledge of the contrast injection protocol applied. Transverse and coronal images as well as curved planar reformations of the coronary arteries were used.

Statistical analysis

Continuous variables were summarized using mean and standard deviation. Categorical variables were summarized with median and interquartile range, while mean is also used in the results section to allow better comparison between groups. An unpaired t-test was used to compare the two groups in case of continuous measures such as vascular enhancement for each measurement location. In case of categorical variables, such as subjective scores for opacification, a Wilcoxon rank sum test was used to compare the two groups. A P-value below 0.05 was considered significant. Data analysis was performed using software for statistical analysis (SPSS for Windows, Chicago, Il, USA).

Table 7-3. Patient characteristics for each injection protocol group

	Group A	Group B	Group C
Total no (men)	43 (39)	43 (39)	33 (30)
Age (years)	48 (16)	47 (12)	47 (17)
Heart rate (bpm)	56 (8)	56 (7)	55 (7)
Weight (kg)	86 (11)	87 (12)	86 (10)
BMI (kg/m^2)	27 (3)	27 (3)	26 (3)

Note.- Numbers are means with standard deviation between parentheses. Only in first row total numbers are given with number of men between parentheses.
(BMI = body mass index)

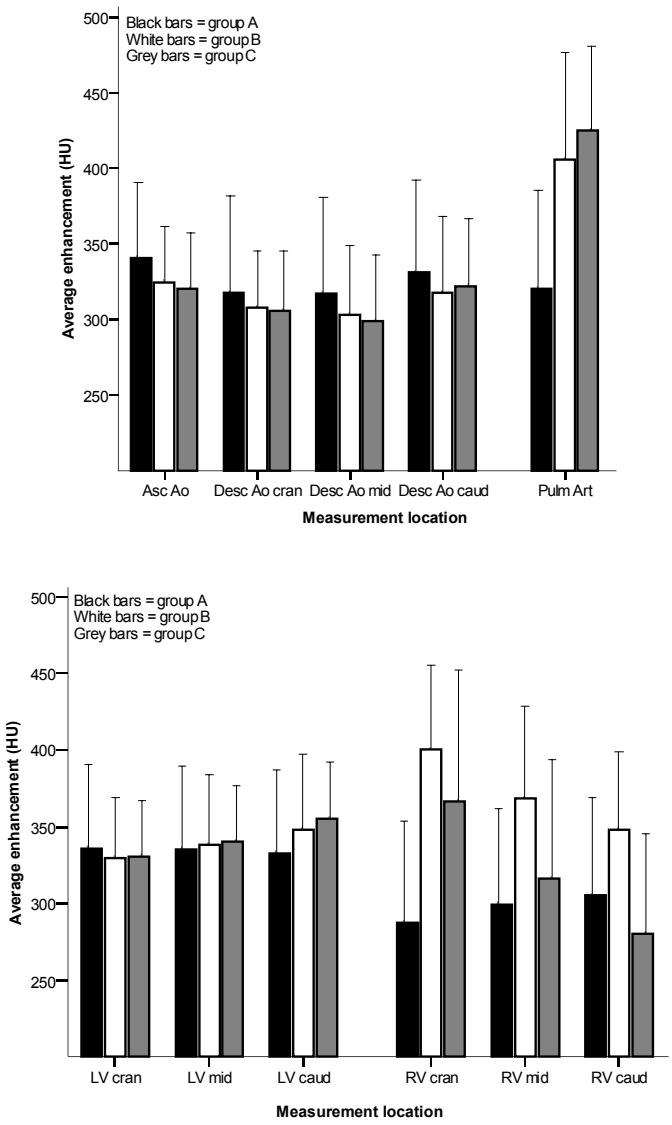

Figure 7-1. *Bars display average enhancement at each measurement location per injection protocol group; error bars display one standard deviation. Significantly higher enhancement was found: in the right ventricle at all levels for injection protocol group B versus group A and C, in the pulmonary artery for group B versus group A, and in the caudal left ventricle, the pulmonary artery and the cranial right ventricle for group C versus group A. (Asc Ao = ascending aorta, Desc Ao = descending aorta, LV = left ventricle, RV = right ventricle, Pulm Art = pulmonary artery, cran = cranial, caud = caudal)*

RESULTS

Patient characteristics of the included patients are summarized in Table 7-3. No contrast extravasations occurred. Three patients developed a mild allergoid reaction (nausea or urticaria); one in each group. Intended contrast injection rates were always reached. Mean time to threshold was 18 s for all groups (P>0.05).

Vascular enhancement

Mean attenuation in the aorta and left ventricle at all levels was not significantly different between the three groups (P>0.05) (Figure 7-1). The mean attenuation at the various levels in the right ventricle were significantly higher in group B compared to group A and group C (P<0.05) (Figure 7-1). The mean attenuation in the pulmonary artery was significantly higher in group B and C compared to group A (P<0.05). The attenuation caudal in the left ventricle and cranial in the right ventricle was significantly higher in group C compared to group A (P<0.05).

Enhancement pattern

Earlier in the scan range, more cranial in the descending aorta, the average attenuation is similar in all groups (Figure 7-2). The enhancement pattern throughout the descending aorta is very similar for group B and C. In the middle of the scan the enhancement in the descending aorta starts to increase in group B and C compared to group A.

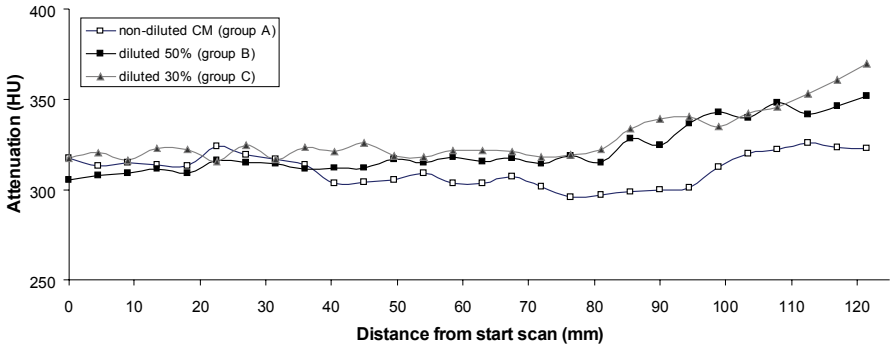

Figure 7-2. *Curves of enhancement throughout the descending aorta for all injection protocol groups in ten matched subjects for age, sex, weight and heart rate. Attenuation was measured in the first (most cranial) slice and then every tenth slice (i.e. every 4.5 mm). While the attenuation curves begin similarly, attenuation increases more caudal in the descending aorta in group B and C compared to group A. This difference is most likely due to the improved contrast medium throughput in the second contrast injection phase of group B and C.*

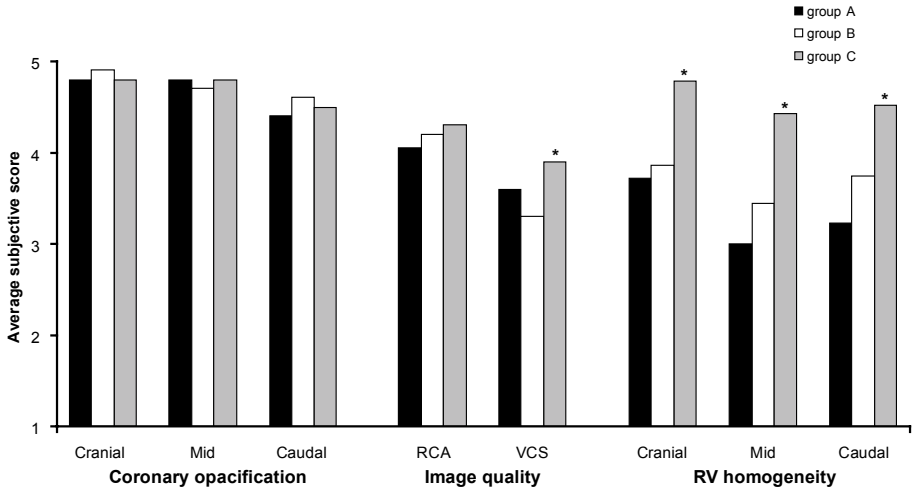

Figure 7-3. *Average subjective scores for opacification in coronary arteries (cranial, mid and caudal), assessability of the right coronary artery (RCA), streaking artifacts in the superior caval vein (VCS), and homogeneity of contrast enhancement in the right ventricle (cranial, mid and caudal). Subjective scores were significantly better at all levels in the right ventricle for group C versus group A and B, and in the superior caval vein in group C versus group B (*P<0.05). Subjective scores for coronary opacification and RCA assessability were not significantly different.*

Subjective scores

In all groups scores of 3 or more were given for the contrast opacification in the coronary arteries. The subjective scores for the opacification of the coronary arteries were not significantly different between groups (P>0.05) (Figure 7-3). The subjective scores for the homogeneity of the contrast enhancement in the right ventricle were significantly better in group C compared to groups A and B (P<0.05) (Figure 7-3). In all three groups the assessability of the RCA was little affected by the presence of contrast in right atrium and ventricle (all median score 4 (i.e. good assessability); P>0.05) (Figure 7-3). Subjective scores for streaking artifacts in the superior vena cava were significantly worse in group B compared to group C (P<0.05) but not in group A compared to group C (P=0.15) (group A: average 3.6; group B: average 3.3; group C: average 3.9).

DISCUSSION

In our study we found that application of saline-diluted contrast medium (dilution to 30% concentration) in a biphasic injection for cardiac CT yields good enhancement of the

coronary arteries and left and right ventricle, which allows a comprehensive cardiac evaluation. Total contrast medium volume can be reduced without decreasing enhancement.

The biphasic injection protocol we applied was aimed at good opacification of the coronary arteries as well as contrast enhancement in the right ventricle to allow functional analyses of left and right ventricle, including left ventricular wall mass and thickening. The first phase is similar to the first phase of uniphasic injection protocols more commonly applied in cardiac CTA [3-5]. The second contrast medium injection phase is not aimed at creating an enhancement plateau for the coronary arteries since this is not useful with the current short scan times (around 10s) but rather aimed at preventing a complete contrast medium washout of the right ventricle. The second contrast injection phase directly influences contrast enhancement in regions more proximal to the coronary arteries, such as the right side of the heart. Therefore, it is not surprising that our results show a difference in contrast enhancement in the right ventricle and pulmonary artery but no difference in the left ventricle and aorta, since we only changed the second contrast injection phase. The enhancement curves in the descending aorta for group B and C were similar despite a different iodine flux in the second phase of the injection protocol.

The effect of maintaining injection rate instead of lowering injection rate in the second contrast medium injection phase is similar to the effect of applying a saline flush [7-9]. In case a single contrast injection phase is used without a saline flush a certain volume of contrast medium lags behind in the injection veins after the injection has stopped. This contrast material is no longer subject to the high flow rate it was injected with. A saline flush at the same injection rate as the contrast medium injection serves to push the contrast medium in the injection veins into the central blood stream at a constantly high flow rate. This results in a higher peak of contrast attenuation [8]. Similarly, if injection rate is lowered between the first and second phase of a dual phase contrast injection the contrast medium present in the injection veins will be pushed further only at the speed of the second injection and not at the initial high injection rate. In both instances a certain volume of contrast medium reaches the right heart with a delay and will contribute less to contrast enhancement. This phenomenon is called the dead venous space effect [11]. Since in group B and C a decrease in contrast attenuation is found from cranial to caudal in the right ventricle, which is not found in group A, our results indirectly confirm the improved throughput of contrast medium.

Surprisingly, we found that more streaking due to high contrast attenuation occurred in the superior vena cava in the 50%-diluted contrast medium group (group B) than in the lower second injection rate group (group A). The most likely explanation for this

phenomenon is that less contrast medium enters the heart in the second contrast medium injection phase if it is injected at a lower rate. By decreasing the percentage of contrast medium in saline-diluted contrast medium from 50% to 30% these streaking artifacts decreased.

Our study had limitations. We did not perform randomization but included the groups consecutively. We did match the three contrast injection protocol groups for age, gender, weight, length and heart rate, but other differences, that could affect the results, may have been present.

As discussed above a uniphasic contrast medium injection with an immediate saline flush is usually applied during cardiac CT to reach washout of the right atrium and ventricle. The underlying reason is that the assessability of the right coronary artery could be affected by the presence of contrast medium in the right atrium and ventricle. In our study we found a good assessability of the right coronary artery in all groups. However, we did not perform a comparison between CT and invasive angiography for stenosis quantification. We also did not compare our results to the results of a uniphasic injection protocol with complete washout in the right ventricle.

Conclusion

A contrast injection protocol that uses a second phase with contrast material diluted to 30% yields similar enhancement throughout the heart and better homogeneity of right ventricular enhancement than a standard biphasic protocol while less contrast medium is applied.

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Chapter 7

CHAPTER 8

NON-INVASIVE CARDIAC ASSESSMENT IN HIGH-RISK PATIENTS (THE GROUND STUDY): RATIONALE, OBJECTIVES AND DESIGN OF A MULTI-CENTER RANDOMIZED CONTROLLED CLINICAL TRIAL

Chapter 8

ABSTRACT

Background

Peripheral arterial disease (PAD) is a common disease associated with a considerably increased risk of future cardiovascular events and most of these patients will die from coronary artery disease (CAD). Screening for silent CAD has become an option with recent non-invasive developments in CT-angiography and MR stress testing. Screening in combination with more aggressive treatment may improve prognosis. We propose to study whether a cardiac imaging algorithm, using non-invasive imaging tests followed by treatment will reduce the risk of cardiovascular disease in PAD patients free from cardiac symptoms.

Design

The GROUND study is designed as a prospective, multi-center, randomized clinical trial. Patients with PAD, but without symptomatic CAD will be asked to participate. All patients receive a proper risk factor management before randomization. Half of the recruited patients will only undergo CT calcium scoring (control group). The other half (index group) will undergo the non-invasive cardiac imaging algorithm followed by evidence-based treatment. First, patients are submitted to CT calcium scoring and CT angiography. Patients with a left main (or equivalent) coronary artery stenosis of >50% on CT will be referred to a cardiologist without further imaging. All other patients in this group will undergo dobutamine stress magnetic resonance (DSMR) testing. Patients with a DSMR positive for ischemia will also be referred to a cardiologist. These patients are candidates for conventional coronary angiography and cardiac interventions (coronary artery bypass grafting (CABG) or percutaneous cardiac interventions (PCI)), if indicated. All participants of the trial will enter a 5-year follow up period for the occurrence of cardiovascular events. Sequential interim analysis will take place. Based on sample size calculations about 1200 patients are needed to detect a 24% reduction in primary outcome.

Implications

The GROUND study will provide insight into the question whether non-invasive cardiac imaging reduces the risk of cardiovascular events in patients with peripheral arterial disease but without symptoms of coronary artery disease.

BACKGROUND

Peripheral arterial disease and coronary artery disease

Peripheral arterial disease (PAD) is the term used to refer to lower-extremity arterial disease. It is a sign of systemic atherosclerosis affecting millions of people, in particular the elderly. Reports from the Framingham Heart Study suggest that the prevalence of PAD has increased over the past 30 years [1,2]. Estimates are that approximately 10% of individuals >55 years have asymptomatic PAD (defined as an ankle-brachial index (ABI) <0.90) [3]. The prevalence of so called intermittent claudication (IC) in patients aged 55 to 74 is approximately 4.6% [3] and the prevalence of pain at rest and necrotic lesions (Fontaine stage IV) is approximately 1% [4]. Despite the relatively benign prognosis for the affected limb, symptoms of IC should be regarded as a sign of systemic atherosclerosis and a high risk of cardiovascular events. In a review on IC, Coffman et al. [5] described survival rates among IC patients of approximately 70% to 80% after 5 years, 40% after 10 years, and only 26% after 15 years. More recent studies showed an overall 5-year-mortality rate of 19.2% vs. 10% in controls [6] and 10-year-mortality rates of 61.7% among male and 33.3% among female patients with IC, compared to 16.9% of men and 11.6% of women without evidence of PAD [7]. The mean age of participants in these studies was 67 and 66 years, respectively. Mortality due to coronary artery disease (CAD) after 5 years in a study by Leng et al. was 5.5% vs. 2.6% in controls [6] and after 10 years cardiac death occurred in 35.3% of men and 9.1% of women with IC, compared to 5.5% of men and 2.2 % of women without IC [7]. So not only do PAD patients have a 2- to 3-fold increase in overall mortality, the risk of cardiac death is even 4-6 times higher [7].

This increase in cardiovascular mortality is not surprising since several studies showed a 2- to 3-fold increase in cardiovascular morbidity in PAD patients [6,8,9]. In 2003 Sonecha et al. published a study in which they found CAD in 46% of IC patients, compared to 6% in controls; 31% of claudicants even had 2-vessel or 3-vessel disease [10]. Aronow et al. found a prevalence of CAD in PAD patients of 58% [11]. Hertzer et al. described the results of coronary angiography (CAG) in 1000 patients scheduled for vascular surgery. In this group, 381 had complaints of lower extremity ischemia, of whom 166 (44%) had no cardiac complaints. CAG revealed the presence of CAD in 86% of these cardiac asymptomatic PAD patients [12]. Therefore, assessment of cardiac atherosclerotic abnormalities using non-invasive techniques followed by appropriate treatment may help to improve survival in patients with PAD but yet without cardiac symptoms.

Cardiac imaging with multi-detector CT and MRI

Since the discovery of selective coronary angiography (CAG) by Sones in 1958, it has been the method of choice for detection and follow-up of CAD. Several studies have

shown that diagnostic CAG has an average morbidity of 2% and a mortality of approximately 0.1% [13-15]. For screening purposes non-invasive imaging would be much more suitable. The rapid development of multi-detector computed tomography (MDCT) has made it possible to image the heart and its coronary arteries in a non-invasive way. It is much faster than older scanners and images are obtained with sub-millimeter spatial resolution and high temporal resolution. As a result of simultaneous recording of an electrocardiogram (ECG) signal, several image reconstructions are possible in different phases of the heart cycle [16].

Several studies showed the high accuracy of MDCT to detect significant coronary stenoses [17-19]. Not only the costs and risk of complications are lower with MDCT than with CAG, this technique also has the advantage of vessel wall visualization. Both the composition of the plaque and its impact on the vessel lumen can be detected. A distinction can be made between lipid, fibrous and calcified coronary plaques [13,20]. In recent years it has become clear that plaque composition may be a better risk-predictor for acute coronary events than stenosis grade. Rupture of so-called vulnerable plaques accounts for approximately 70% of sudden coronary deaths. Although the average absolute risk of severely stenotic plaques may be higher than the average absolute risk of mildly stenotic plaques, the number of plaques with mild stenoses overwhelmingly exceeds the number of plaques with severe stenoses [21].

Dobutamine stress cardiovascular magnetic resonance imaging (DSMR) is used to identify wall motion abnormalities of the left ventricle indicative of myocardial ischemia [22-26]. It has been shown to be an accurate and safe diagnostic modality to assess myocardial ischemia and viability in patients with proven or suspected CAD [23-28]. A study by Nagel et al. showed that the presence of myocardial ischemia can be detected more accurately with DSMR than with dobutamine stress echocardiography (DSE). Image quality of DSMR is higher and with MRI sensitivity increased from 74.3% to 86.2% ($P<0.05$) and specificity increased from 69.8% to 85.7% ($P<0.05$) compared to echocardiography [23]. With the use of myocardial tagging sensitivity can be increased up to 96% [26]. In this study by Kuijpers et al. the cardiovascular occurence-free survival rate was 98.2% after a negative DSMR during a mean follow-up of 17.3 months. Furthermore, MRI allows optimal detection of dysfunctional, but viable myocardium. This is of clinical importance since revascularization of dysfunctional, but viable myocardium may improve left ventricular function and thus prognosis [29].

In patients with non-specific symptoms of coronary artery disease DSMR can be used to assess risk levels for coronary events with high accuracy. In a group of 100 patients suspected of coronary ischemia Van Dijkman et al. found a positive predictive value of

98% and also a negative predictive value (NPV) of 98% for ischemia with DSMR [30]. In another study by Hundley et al. a 97% cardiac event free survival rate in 103 patients suspected of ischemia with a negative DSMR was observed [24]. Patients with a negative DSMR without rest wall motion abnormalities (RWMA) and without a history of CAD have an excellent cardiac prognosis and can be excluded from further clinical follow-up [31]. Compared to other non-invasive techniques, DSMR may be a valuable adjunct for the assessment of patients with (suspected) ischemic heart disease [32].

Treatment of silent coronary artery disease

According to the guidelines CABG or PCI may be considered as first line therapy in case of severe abnormalities in the coronary artery tree, even in asymptomatic patients [33]. Absence of cardiac symptoms should not be regarded as a sign of a more benign process [34]. In addition, silent myocardial ischemia has been shown to increase coronary artery disease risk and evidence indicates that in certain groups of these patients CABG or PCI treatment may reduce the risk. The results of the Asymptomatic Cardiac Ischemia Pilot (ACIP) study indicate that higher-risk patients with asymptomatic ischemia and significant coronary artery abnormalities, who undergo revascularization with CABG or PCI may have a better outcome as compared to those only receiving medical therapy [35]. Studies on the treatment of silent ischemia are all conducted in small groups of patients with coronary abnormalities [36]. In patients with left main disease, the survival benefit of CABG compared to medical therapy is 19.3 months at 10-year follow-up. Therefore, the benefit of surgery over medical treatment for patients with significant left main stenosis (>50%) is little argued [37].

STUDY OBJECTIVE

This prospective, randomized, controlled, multicenter trial is designed to evaluate whether a cardiac imaging algorithm using non-invasive imaging techniques followed by evidence based treatment will reduce the risk of cardiovascular disease in cardiac asymptomatic patients with peripheral arterial disease. This imaging algorithm consists of coronary calcium scoring, MDCT angiography, and dobutamine stress MRI. Participants will be followed up for a period of five years (Figure 8-1).

METHODS

Study population

The study population will consist of approximately 1200 patients with peripheral arterial disease without a history of symptomatic cardiac disease. Patients are recruited from the vascular surgery departments of the participating centers (appendix 1). The study is in compliance with the Helsinki Declaration and local ethics committees gave their approval.

Patients willing to participate will be asked to sign the informed consent form. Patients are eligible if they are 50 years or older and have peripheral arterial disease, at least stage Fontaine II, as diagnosed by the vascular surgeon. Patients will be considered not eligible for the study if they meet one of the following exclusion criteria: physician diagnosed history of symptomatic cardiac disease; cardiac rhythm other than sinus; unable to sustain a breath-hold for 25 seconds; asthma; contra-indications to MRI examination, such as vessel clips in the brain, metal splinters in the eye, insulin pump or other electronical devices that cannot be removed easily, metal implants, port-a-cath catheter, claustrophobia, etc.; contra-indications to iodinated contrast agent; severe arterial hypertension (>220/120 mmHg); significant aortic stenosis; unable to remain in supine position for at least 60 minutes; extreme obesity (BMI > 40 kg/m²); renal insufficiency (serum creatinine level exceeding 140 μmol/l); severe physical deterioration due to concomitant disease; language barrier; and contra-indications to dobutamine.

Baseline risk factors

At baseline, eligible patients complete a questionnaire on current medication use, risk factors and quality of life. Height, weight, blood pressure and ankle pressure for calculation of the ankle-brachial index will be measured in the outpatient clinic. Total cholesterol, high density lipoproteins (HDL), triglycerides, creatinine, homocysteine, glucose and high sensitivity c-reactive protein will be measured at the local laboratory. To prevent further progression of their present cardiovascular disease all patients will be treated according to the Dutch guidelines for treatment of atherosclerotic peripheral arterial disease [38]. These guidelines state that these patients should receive aspirin and a statin and, if indicated, antihypertensive medication. Patients also receive proper advice regarding exercise, healthy diet and cessation of smoking.

MDCT imaging

All centers participating in the GROUND study are experienced in making cardiac MDCT angiography scans and use at least a 16-slice CT scanner. The patient preparation will start with proper instruction of the patient. The ECG monitor is connected and sinus rhythm is monitored for 1 minute. Then the patient practices a 25 second breath-hold. The MDCT calcium scoring examination will follow a scout view. It will be done either prospectively ECG-triggered or retrospectively gated according to the local hospital protocol. For the patients randomized to the imaging arm of the study, calcium scoring will be followed by the contrast-enhanced retrospectively ECG-gated CT angiography. An 18 G intravenous line is started. Patients who have a heart rate over 60 bpm will be administered i.v. beta-blockers (minimum of 5 mg metoprolol). Patients will continue to receive beta-blockers until their heart rates are below 60 bpm, or 20 mg has been

administered. Blood pressure will be monitored. The contrast volume and infusion rate will be calculated individually depending on patient weight and scan duration and contrast concentration. Ten axial image datasets will be reconstructed every 10% of the RR-interval.

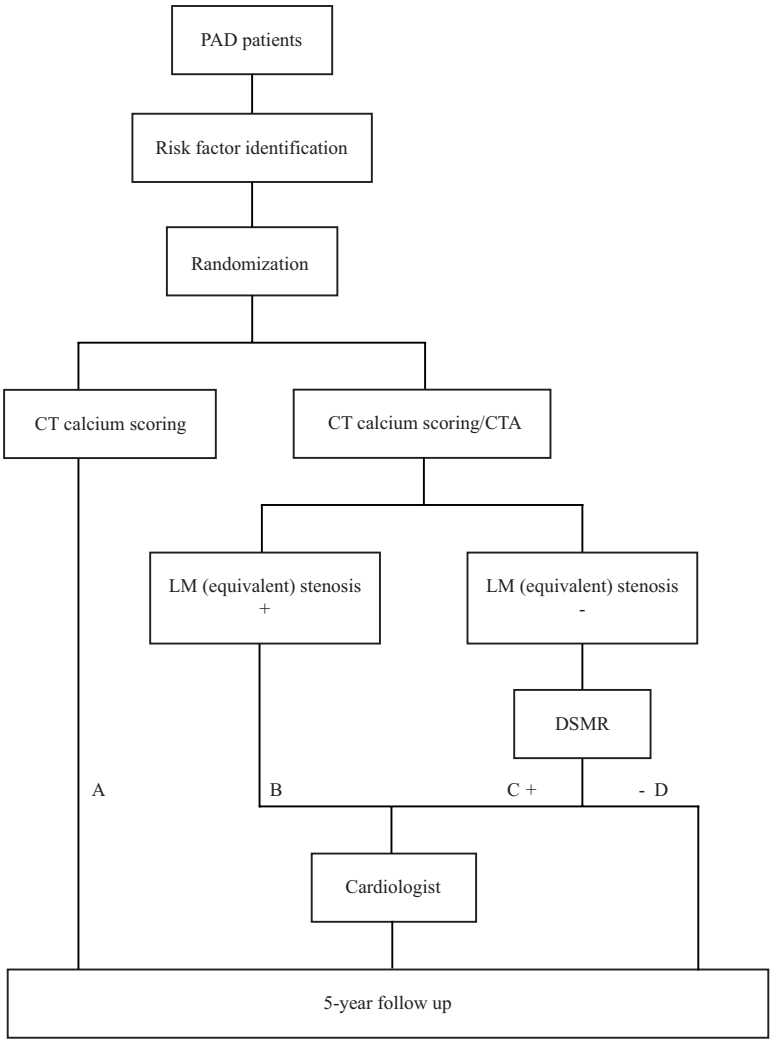

Figure 8-1. *Flow diagram of the GROUND study*

Total examination time for CT calcium scoring will be approximately 10 minutes and the total examination time for CT calcium scoring and CT angiography, including preparation of the patient, will be approximately 30 minutes.

MDCT Analysis

The cardiac MDCT data will be analyzed by the site investigator at the site. The reader will use the appropriate workstation for all data analysis. The site investigator is responsible for incidental abnormal findings in the dataset.

The calcium scoring study will be evaluated using an established analysis program. Agatston, mass and volume scores will be determined and recorded on case report forms. For the MDCT angiography the site investigator will identify the phase with the least amount of cardiac motion. This phase is then loaded into the appropriate application. Depending on the coronary morphology and quality of the scan several post processing techniques will be applied to assess the coronary arteries. The dataset will be evaluated in terms of contrast opacification, assessability, stenoses and plaques. The proximal, medial and distal coronary arteries and cranial, medial and caudal right ventricle are evaluated for contrast opacification and image noise using a 5-point scale (1=non-diagnostic, 2=limited diagnostic, 3=acceptable, 4=good, 5=excellent).

The 15-segment tree from the AHA literature will be used for segment definition. Each segment will be evaluated for assessability using a 5-point scale (1=non-diagnostic, 2=limited diagnostic, 3=acceptable, 4=good, 5=excellent). For the segments that are not assessable (score 1 or 2) the reader will indicate why the segment cannot be evaluated according to the following choices: (0) anatomical reason, (1) respiratory motion, (2) cardiac motion, (3) arrhythmia, (4) calcium, (5) vessel size (small caliber), (6) poor opacification, (7) streak artifacts, (8) scan range, (9) noise, (10) technical failure. Any luminal narrowing greater than 30% will be visualized from the curved MPR and will be quantified according to a 4-point scale: (1) 30-50%, (2) 50-70%, (3) 70-99% and (4) 100%. The type of visualized plaque will be indicated as soft, calcified or mixed.

DSMR imaging

Patients randomized to the imaging group will undergo dobutamine stress MRI within three weeks of the MDCT angiography. All beta-blocking medication will be stopped 4 days prior to the examination [27]. After instructions by the technician, the patient is positioned on the scanning table and an intravenous access will be established through an antecubital vein. ECG leads, a phased-array surface coil covering the heart, and a brachial blood pressure cuff are applied. During the procedure, a single-lead ECG will be

continuously monitored. Systolic blood pressure, diastolic blood pressure and heart rate will be recorded at baseline and every three minutes throughout the procedure.

Baseline imaging will consist of acquiring three short-axis cine images (basal (1.5 cm below mitral valves), mid-ventricular and apical) and one vertical long-axis cine image. Cine tagged images are made in the three short axis planes.

During the DSMR dobutamine will be infused intravenously using a digital pump injector situated outside the scanner room. The dose will be increased to 10, 20, 30 and 40 µg/kg/min with a six minutes time interval. In case of rest wall motion abnormalities (RWMA), infusion will be started at 5 µg/kg/min. Image acquisition will start three minutes after each dose increment. Imaging will consist of acquiring three short-axis cine images (basal, mid-ventricular and apical) and one vertical long axis with and without myocardial tagging. Criteria for ending the examination are (1) development of new or worsening wall motion abnormalities (NWMA) in more than 1 myocardial segment, (2) fall of systolic blood-pressure of >40 mmHg, (3) marked hypertension > 240/120 mmHg, (4) severe chest pain, (5) complex cardiac arrhythmia's and (6) intolerable side effects of dobutamine.

Both a radiologist (or a trained radiology resident) and a cardiologist (or a trained cardiology resident) will be present in the MR suite to monitor the condition of the patient and to directly evaluate the images. All participating centers have experience in dobutamine stress testing. Although side effects are rare, a protocol to remove the patient from the scanner room in case of an emergency is practiced regularly. Total examination time for a DSMR study, including preparation of the patient, will be approximately 50 minutes.

DSMR Analysis

The DSMR data will be analyzed by the site investigator at the site. The reader will use the appropriate workstation for all data analysis. For image interpretation multiple cine loop display will be used displaying at least three different stress levels for each slice simultaneously. Per segment wall motion will be graded using a 4-point scale according to the guidelines of the American Society of Echocardiography (1= normal or hyperkinesia, 2= hypokinesia, 3= akinesia and 4= dyskinesia). The sum of points is divided by the number of analyzed segments and yields the wall motion score. Normal contraction results in a wall motion score of one, a higher score is indicative of wall motion abnormalities. During dobutamine stress with increasing doses, a lack of increase in either wall motion or systolic wall thickening, a reduction of both or significant changes in the rotational pattern of left ventricular myocardium ('tethering') are indicative of

pathological findings. Myocardial ischemia will be defined as an induced WMA in at least two segments at consecutive planes of the left ventricle. RWMA will be defined as WMA in one or more segments at baseline. If RWMA's are present, which improve during low-dose dobutamine stress, but worsen during peak-stress, this will be considered diagnostic of inducible myocardial ischemia. If RWMA's are present, which do not improve with low-dose dobutamine, this will not be considered diagnostic of inducible ischemia.

Randomization

Randomization will be performed per hospital to ensure an equal distribution of groups of patients within hospitals using a randomization module at the GROUND website. Half of the patients will be randomized for the imaging-with-treatment algorithm (groups B, C and D, Figure 8-1), the other half of the patients (group A) undergoes only CT calcium scoring and enters follow-up. Patients randomized for the treatment groups (groups B, C and D, Figure 8-1) will be scheduled for MDCT angiography. If a stenosis of the left main coronary artery (LM) (or equivalent) of more than 50% is observed on the CTA of a patient in the imaging-with-treatment group, he/she will be referred to a cardiologist for further diagnosis and treatment (group B, Figure 8-1). A stenosis in the proximal left anterior descending coronary artery (LAD) in combination with a stenosis in the proximal circumflex coronary artery (LCX) is considered equivalent to a LM stenosis. All other patients in this group will undergo DSMR testing (groups C and D). Patients with a DSMR positive for ischemia are referred to a cardiologist for further diagnosis and treatment (group C).

Data collection

Study data will be collected on case report forms (CRFs) and submitted on line to the data management center, where all forms are reviewed for completeness. CRFs are available on the GROUND website. Data will end up in a dedicated database.

End points and follow-up

All patients will be asked to fill out a short follow up form every half year for a total period of five years. The occurrences of events are recorded. The quality of life assessment is based on the SF36 questionnaire and repeated after 12, 30, 48, and 60 months. Endpoints of the GROUND study are in concordance with the SMART study endpoints [39].

The term 'end points' is used to describe death, cardiovascular complications, and interventions. Apart from death the occurrence of an endpoint does not imply that the follow-up will be ended. Endpoints in the GROUND study are summarized as MACE: Major Adverse Clinical Events. Primary outcome is a composite endpoint comprising

fatal and non-fatal myocardial infarction and stroke, and vascular death (death due to vascular disease). Secondary end points are: fatal and non-fatal myocardial infarction; fatal and non-fatal stroke; vascular interventions; amputation; aortic rupture; end stage renal failure; extra cranial hemorrhage; complications of CABG or PCI and all cause mortality.

Reported endpoints are classified by the Endpoint Committee, which is unaware of the randomization allocation. Clinical information (letter of discharge) is obtained from the treating specialist or general practitioner. All reported endpoints enter an endpoint verification procedure. Copies of discharge records are sent to the members of the Endpoint Committee. The members of the Endpoint Committee do not share the information between each other, but classify the events independently. Only if discharge records are inconclusive further medical information is obtained (results from laboratory findings, copy of the ECG, copies of imaging reports). The classifications are compared. If two members do not agree the endpoint will be discussed with the research physicians of the GROUND study group. They will decide or consult an extra physician, whose judgment is regarded as final.

Sample size considerations

The sample size is determined by the estimated risk in the group of patients randomized to usual care (control group, A, Figure 8-1) and the risk observed in the groups that undergo cardiac imaging followed by subsequent treatment by a cardiologist as outlined in the protocol (groups B to D). Based on earlier studies in the Netherlands the 5-year-risk in the control group A is assumed 24% [40]. The 5-year risk of cardiovascular morbidity and mortality in these subgroups is estimated to be 66% for those with stenosis of the left main coronary artery (group B) [33], 32.8% for those with cardiac ischemia during the stress test (group C) and 16.4% for those without cardiac ischemia (group D). The estimates for patients in categories C and D are based on the assumption that those with cardiac ischemia have a two-fold risk compared with those without cardiac ischemia and that the risk of all groups combined should add up to 24%.

The effects of interventions performed by the cardiologist/surgeon on the risk observed in PAD patients who undergo cardiac imaging are based on published international data from the ACC and AHA guidelines. These effects are for the two appropriate subgroups: 70% reduction in 5-year event rate using reperfusion therapy (PCI/CABG) for group B and 40% reduction in 5-year event rate using reperfusion therapy (PCI/CABG) for group C. Patients without cardiac ischemia (group D) will receive no treatment.

Based on these estimates, the 5-year risk of cardiovascular morbidity and mortality will be 17.4% in the intervention group (the combined risk for groups B and C; 70% event reduction in the group with a risk of 66% applying to 8% of the population; 40% event reduction in the group of patients with a risk of 32.8% applying to 22% of patients), reflecting an estimated relative reduction in cardiovascular morbidity and mortality of 24%.

The total number of patients randomized to achieve this goal, with a two-sided alpha of 0.05 and 80% power will be 1222. A study of this size has a statistical power of 80% at a two-sided alpha level of 0.05. The reason for using interim analysis [41] is that on average fewer patients are needed in the study when the expected difference in the primary outcome variable is real or when no difference can be expected anymore, therefore increasing efficiency. Sequential analyses are performed on survival outcome variables according to the double triangular test as described by Whitehead [42] and implemented in the computer program PEST version 4 [43]. The sequential (interim) analyses will be performed by an independent data safety monitoring board (DSMB).

CONCLUSIONS

Peripheral arterial disease is a common disease among elderly persons and is associated with a very high risk of cardiovascular events. In this study patients with peripheral arterial disease, but without cardiac symptoms, are randomized to an imaging arm consisting of multi-detector CT angiography of the coronary arteries and dobutamine stress MRI or to a control group in which case only a coronary calcium CT scan will be performed at baseline. In case of a positive finding, patients are referred to a cardiologist who will take appropriate action. All participating patients will enter a 5-year follow-up for the occurrence of cardiovascular events. To the best of our knowledge GROUND is the first large trial designed to assess the value of multi-detector CT and MRI stress testing in reducing the morbidity and mortality of patients with peripheral arterial disease but yet without cardiac symptoms. At the time of writing this manuscript all centers are actively enrolling patients. The number of included patients is currently 231.

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APPENDIX I

Participating Centers. The following hospitals in the Netherlands have agreed to participate in the GROUND-study: University Medical Center Groningen; University Medical Center Utrecht; St. Antonius Hospital Nieuwegein; Meander Medical Center, Amersfoort.

Executive Committee. The Executive Committee (Appendix) is responsible for the design of the GROUND study. It will coordinate and direct the study to ensure its overall success and decide on practical issues concerning the study. It will act upon recommendations of the Data Safety and Monitoring Board regarding continuation of the study.

Members of the executive committee are:

Prof. W.P.Th.M. Mali, MD, PhD, University Medical Center Utrecht, responsible for the trial coordination

Prof. M. Oudkerk, MD, PhD, University Medical Center Groningen, responsible for the radiological coordination

Prof. F. Zijlstra, MD, PhD, University Hospital Groningen, responsible for the cardiological coordination

Dr. M.L. Bots, MD, PhD, University Medical Center Utrecht (Julius Center) responsible for the epidemiological coordination (project management and general data base management)

Steering Committee. The steering committee consists of radiologists, cardiologists, epidemiologists, vascular surgeons and researchers of the participating centers. The Steering Committee will perform the actual imaging procedures of the study. Members will inform the Executive Committee on the progress of the study regularly. The steering committee and the executive committee will meet twice annually.

Members of the steering committee are: M. Prokop, MD, PhD; P.A. Doevendans, MD, PhD; A. Rutten, MD; A.M. de Vos, MD; F. Moll, MD, PhD; E. Vonken, MD, PhD; M.J.M. Cramer, MD, PhD; B.K. Velthuis, MD, PhD (University Medical Center Utrecht); H.J. van der Zaag, MD; R.A. Tio, MD, PhD; T.P. Willems, MD, PhD; P.M. van Ooijen, PhD; R. Vliegenthart, MD, PhD (University Medical Center Groningen); B.J. Rensing, MD, PhD; H. W. van Es, MD, PhD; H.D. van de Pavoordt, MD, PhD (St. Antonius Hospital Nieuwegein); A. Mosterd, MD, PhD; B.G. Heggelman, MD; R.A. Buiskool, MD; A.J. Mackaay, MD, PhD (Meander Medical Center Amersfoort)

Endpoint Committee. The Endpoint Committee will systematically evaluate suspected endpoints. Members are: F. Zijlstra, MD, PhD; B. Rensing, MD, PhD; A. Mosterd, MD, PhD; J. de Keyser, MD, PhD; W.J. Schonewille, MD; T.W.M. Raaijmakers, MD, PhD; M.L. Bots, MD, PhD; A. Rutten, MD; A.M. de Vos, MD

Data Safety and Monitoring Board. The data safety and monitoring board performs statistical analyses of un-blinded interim data and formulates recommendations for the Steering Committee on the continuation of the trial. The DSMB may also offer unsolicited recommendations on the continuation of the trial, for example after publication of results of similar trials. Every three months the chair of the DSMB will be provided an interim dataset to perform sequential analyses. When appropriate, given the results from the interim analysis, the chair will call for a meeting with the other DSMB members. Members of the Data Safety and Monitoring Board are: I. van der Tweel, PhD; M.J.M. Cramer, MD, PhD; H.J. van der Zaag, MD, PhD; D.E. Grobbee, MD, PhD

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Chapter 8

CHAPTER 9

CORONARY CALCIUM SCORING IN CARDIAC ASYMPTOMATIC PATIENTS WITH PERIPHERAL ARTERIAL DISEASE: IS IT USEFUL?

Chapter 9

ABSTRACT

Purpose

Patients with peripheral arterial disease (PAD) are known to have a high risk for cardiac morbidity and mortality. These patients are eligible for secondary prevention of cardiac disease. We determined whether on top of risk factors coronary calcification, a risk indicator for cardiac disease, can help predict the occurrence of significant left main (LM) stenosis or equivalent, eligible for surgery, in this high-risk group.

Materials and Methods

Cardiac asymptomatic patients (n=219) with peripheral arterial disease underwent risk factor assessment and non-contrast-enhanced computed tomography (CT) scanning of the heart for calcium scoring. 108 of these patients were randomized to also undergo contrast-enhanced coronary CT angiography (cCTA) to determine the presence of a LM (equivalent) stenosis. If positive, invasive coronary angiography was performed and if indicated, surgery followed. Relations between risk factors and Agatston calcium score were determined. We used logistic regression modeling to evaluate the role of risk factors and Agatston score for the prediction of the presence of a significant LM stenosis, eligible for surgery.

Results

Median Agatston score was 276 (range 0-5135). Only an increase in age was significantly related to Agatston score ($P<0.05$). Twenty-two of 108 patients had a significant LM (equivalent) stenosis on cCTA. Eight of these twenty-two patients were eligible for surgery. Diabetes and score >400 were independent predictors of significant LM stenosis, with a 6.1 and 12.4-fold increased risk, respectively. These two factors were included in a multivariable logistic regression model for the presence of a significant LM stenosis, eligible for surgery (ROC-area 0.82; 95%CI 0.65-0.98).

Conclusion

Calcium scores and diabetic status may help in predicting the occurrence of significant coronary artery disease, eligible for surgery, in cardiac asymptomatic PAD patients.

INTRODUCTION

Patients with peripheral arterial disease (PAD) are at a high risk to have or develop concomitant coronary artery disease since both peripheral arterial disease and coronary artery disease are caused by atherosclerosis [1-4]. Cardiac morbidity and mortality are increased in PAD patients compared to in the general population [1,5,6]. Their risk for future cardiac events may be considered equivalent to the risk of individuals with a previous cardiac event [7,8]. This PAD patient group may therefore be eligible for screening for significant cardiac disease, e.g. left main coronary artery stenosis, and treatment in a cardiac asymptomatic stage.

Studies in large asymptomatic populations show that quantification of the amount of coronary calcification can aid in determining the risk for future cardiac morbidity and mortality [9-13]. PAD patients, however, already are expected to be in the highest calcium scoring risk group due to the presence of atherosclerosis in their peripheral arteries. It is unknown if calcium scoring can be used in a high-risk cardiac asymptomatic peripheral arterial disease patient group to further differentiate risk.

We studied the occurrence of coronary calcification in a high-risk group of cardiac asymptomatic patients with PAD in relation to conventional cardiovascular risk factors and we determined whether the amount of coronary calcification on top of risk factors may be of help in predicting the occurrence of a significant left main or left main equivalent coronary artery stenosis, eligible for surgery in an asymptomatic stage [14], in this high-risk group.

MATERIALS AND METHODS

Subjects are part of an ongoing large randomized multi-center trial, the GROUND study, into the effects on vascular events of screening for and treatment of an asymptomatic stage of significant cardiac disease (registered at ClinicalTrials.gov as NCT00189111) (**Chapter 8**). The study was approved by the institutional review board and patients signed informed consent after obtaining written and oral information. Subsequently they were randomized to either the first group that would undergo an elaborate non-invasive cardiac imaging algorithm including CT calcium scoring, coronary CT angiography and dobutamine stress MRI (DSMR) with subsequent treatment depending on the imaging results (intervention group) or the group that would only undergo CT calcium scoring (control group). Regardless of the results of randomization, risk factor assessment was performed and patients received treatment advice (medical and lifestyle) according to the current Dutch standards for the treatment of patients with peripheral arterial disease [15]. All

patients entered a 5-year follow-up after inclusion. Only baseline risk factor data and CT data are included in the following analysis.

Patient selection

Subjects were recruited between January 2005 and February 2007. Patients, aged 50 years or over, diagnosed with intermittent claudication by a vascular surgeon were eligible for this trial. Exclusion criteria were a history of symptomatic cardiac disease, arrhythmia, inability to sustain breath-hold for 25 seconds, asthma, contra-indications to MRI examination or dobutamine, contrast medium allergy, renal insufficiency, severe arterial hypertension (>220/120 mmHg), extreme obesity (BMI>40 kg/m^2), severe co-morbidity and/or a language barrier.

Risk factor screening

At baseline all trial participants completed a comprehensive questionnaire on medical history, medication use and quality of life. Height, weight and blood pressure at each arm were measured. Body mass index (BMI) was calculated as weight divided by height squared. Blood samples were taken to measure levels of total cholesterol and of creatinine to determine presence of hypercholesterolemia and to obtain a measure of renal function, respectively. Smoking status was subdivided in never and ever (i.e. both quit and current). No difference was made between quit and current, since most patients quit smoking shortly before inclusion. Hypertension was defined as a systolic blood pressure equal or higher than 140 mmHg and/or a diastolic blood pressure equal or higher than 90 mmHg and/or use of antihypertensive medication. Diabetes mellitus was determined by self-reporting and/or use of glucose-lowering medication. Hypercholesterolemia was also determined by self-reporting and/or as a total cholesterol higher than 6.5 mmol/l. Cholesterol lowering medication use was not taken into account since these are prescribed preventively.

CT calcium scoring acquisition and evaluation

CT calcium scoring was performed on either a 16- or a 64-detector row CT scanner (Mx8000 IDT 16 or Brilliance 64, Philips Medical Systems, Cleveland, OH, USA; Somatom 16, Sensation 64 or Dual Source Definition, Siemens Medical Solutions, Forchheim, Germany) or an EBT scanner (only CT calcium scoring scans; e-Speed, Imatron, San Francisco, USA) depending on the center of inclusion. Each center used its own optimal imaging protocol for the scan acquisition. The calcium scoring scan was loaded in an analysis program to determine the calcium score. A trained observer identified calcifications in each coronary artery to obtain a total Agatston score [16].

Table 9-1. Patient characteristics at baseline

	Overall (n=219)	
Age (years)	62.4	(7.1)
Male sex	75.8%	
BMI (kg/m^2)	26.3	(3.6)
Systolic blood pressure (SBP) (mmHg)	146.6	(22.4)
Diastolic blood pressure (DBP) (mmHg)	82.2	(9.8)
Hypertension (SBP>140mmHg, DBP>90mmHg, medication)	69.0%	
Total cholesterol (mmol/l)	4.84	(1.16)
Total cholesterol / HDL cholesterol	3.66	(1.39)
Hypercholesterolemia (tot chol >6.5 mmol/l, history)	55.0%	
Diabetes (medication, history)	17.5%	
Current/quit smoking	97.0%	
Cholesterol lowering medication	70.7%	
Antithrombotic medication	85.1%	
Antihypertensive medication	52.7%	
Median Agatston score	276	(39-827)

Note.– continuous measures are mean with standard deviation between parentheses. Dichotomous measures are given as percentages. Median Agatston score is given with inter-quartile range between parentheses.

Coronary CT angiography acquisition and evaluation

The subjects in the screening group underwent contrast-enhanced cCTA after the calcium scoring scan acquisition. The cCTA was performed on either a 16- or a 64-detector row CT scanner. Subjects received beta-blockers in case of a heart rate above 60 bpm. Contrast medium volume and infusion rate during cCTA depended on patient weight and scan duration. Image data sets were reconstructed at several time points of the RR-interval and the most-motion free data set was selected to evaluate the left main, proximal left anterior descending and proximal left circumflex coronary artery for plaques and stenoses (segments 5, 6 and 11, respectively, according to the 15-segment tree of the AHA). Each

segment was scored for assessability on a 5-point scale (1=non-diagnostic to 5=excellent). The reason for non-assessability was also recorded. Luminal narrowing was visually determined and subdivided in 5 categories: 0-30%, 30-50%, 50-70%, 70-99% and 100%. Plaque types in each segment were recorded as soft, calcified or mixed (both soft and calcified components). Patients with a significant (>50%) left main stenosis or a significant left main equivalent stenosis (>50% stenosis of both proximal LAD and LCx coronary artery) were referred to a cardiologist.

Invasive coronary angiography (CAG)

All patients referred to a cardiologist underwent CAG unless contra-indicated. All studies were performed using digital equipment. Multiple projections were recorded for each vessel using standard orientations. Cine-fluoroscopy images were analyzed for significant left main (equivalent) stenosis by the cardiologist performing the CAG. In case a significant (equivalent) left main stenosis was detected on CAG coronary artery bypass graft (CABG) surgery was performed, if feasible.

Data analysis

Continuous variables are presented as mean with standard deviation. Categorical variables are given as percentages in each category. Calcium scores were subdivided based on the groups defined by Rumberger (0, 1-10, 11-100, 101-400, >400). Differences in cardiovascular risk factors were determined between calcium score groups with an ANOVA test for continuous data and a Kruskal-Wallis test in case of categorical variables. Univariable logistic regression was performed to determine the association between cardiovascular risk factors or calcium score groups and presence of a significant (equivalent) left main stenosis on cCTA, confirmed with CAG in the intervention group. The odds ratios were used as measures of association. All variables with a $P<0.157$ in univariable logistic regression were used for multivariable logistic regression. The prognostic ability of the model, i.e. to discriminate between patients with and without significant disease, was estimated by measuring the area under the receiver operating characteristic (ROC) curve [17].

RESULTS

231 subjects were randomized to either the intervention (n=115) or the control group (n=116) (Figure 9-1). A calcium scoring scan was successfully performed in 219 of the 231 randomized subjects (108 intervention, 111 control group). The other 12 subjects did not undergo CT imaging because of various reasons (personal reasons, sudden deteriorating physical condition or logistic reasons). In the 219 subjects who underwent

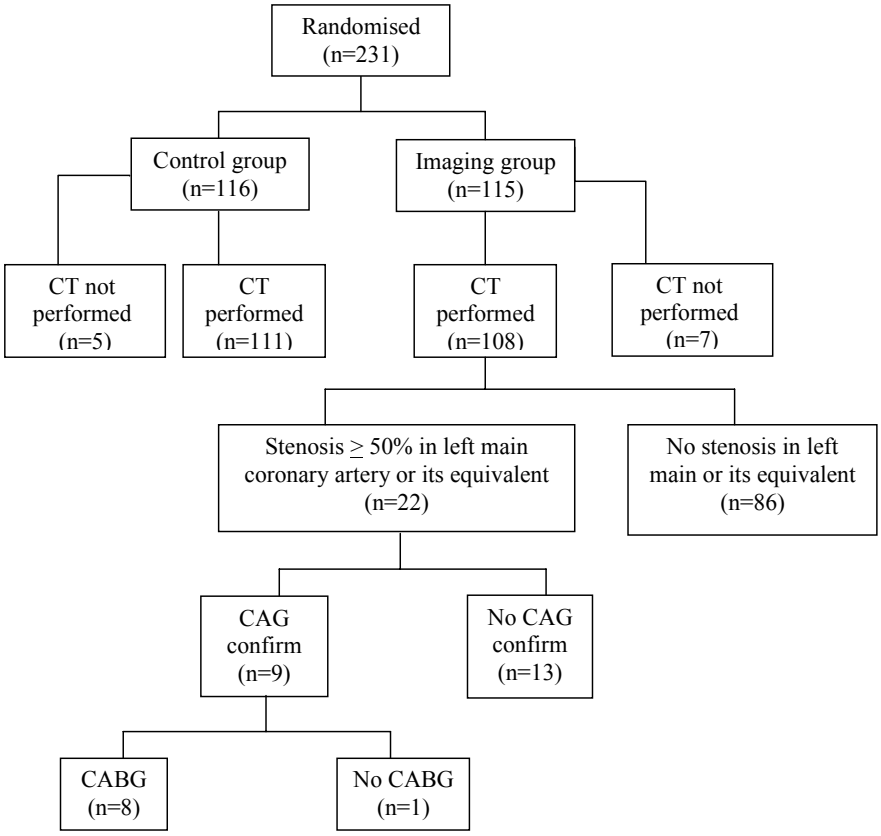

Figure 9-1. *Flow chart of the included patients in the GROUND study.*

calcium scoring mean age was 62.4 (±7.1) years and 164 patients were male (76%). Patient characteristics with regard to risk factors are shown in Table 9-1.

Calcium scores

Median Agatston score was 276 (range 0-5135). 36 subjects (16%) had an Agatston score up to 10 and 87 subjects (40%) an Agatston score above 400. In higher calcium score groups age was significantly higher (Table 9-2). No other significant relations were found.

Table 9-2. Risk factor characteristics per calcium score category

	0	>0-10	>10-100	>100-400	>400
	n=17	n=19	n=37	n=59	n=87
Age (years)*	58.6	59.3	59.9	62.6	64.7
Male sex	59%	58%	81%	76%	80%
BMI (kg/m^2)	26.0	25.0	26.7	26.6	26.4
Systolic blood pressure (SBP) (mmHg)	143.7	147.4	144.8	142.9	150.4
Diastolic blood pressure (DBP) (mmHg)	80.5	85.6	81.6	82.1	82.1
Hypertension (SBP>140, DBP>90, med)	59%	68%	62%	64%	77%
Total cholesterol (mmol/l)	4.55	4.99	4.57	5.04	4.84
Total chol / HDL chol	3.22	3.58	3.75	3.74	3.69
Hypercholesterolemia (tot chol >6.5 mmol/l, history)	35%	53%	49%	58%	61%
Diabetes (medication, history)	19%	11%	17%	14%	21%
Current/quit smoking	100%	100%	100%	94%	96%
Cholesterol lowering med	75%	60%	84%	61%	73%
Antithrombotic med	83%	93%	84%	90%	81%
Antihypertensive med	50%	40%	41%	55%	59%
Median Agatston score	0	5	39	208	985

**Note.- Only age is significantly different between calcium score groups (P<0.001 Kruskal Wallis test); all other characteristics are not significantly different.*

Significant left main (equivalent) stenosis

In the screening group 22 subjects showed a significant (equivalent) left main stenosis on cCTA (left main stenosis n=13, left main equivalent stenosis n=9). Sixteen of these 22 patients had an Agatston score above 400, five between 100 and 400. One patient had a very low Agatston score of 8. A significant left main stenosis was confirmed with invasive angiography in 9 subjects; no equivalent stenosis was confirmed. Eight of these patients underwent uncomplicated CABG surgery. Table 9-3 shows the distribution over calcium score categories of these eight patients. One patient did not undergo CABG surgery since his coronary anatomy was not suited. All other patients referred to a

cardiologist received either PCI in single significantly stenosed vessels (n=3) or maximal conservative treatment with medication.

Table 9-3. Distribution over calcium score categories of significant left main stenoses, treated with CABG

	CABG for significant left main stenosis	
Calcium score category	-	+
0	8	0
>0-10	9	1
>10-100	16	0
>100-400	31	0
>400	36	7
all	100	8

Table 9-4. Univariable logistic regression: significant left main stenosis eligible for CABG as dependent variable

	OR	95% CI	P-value
Age (years)	1.04	0.94-1.15	0.42
Male sex	$1.7x10^8$	-	1.00
BMI (kg/m^2)	1.03	0.83-1.27	0.81
Systolic blood pressure (SBP) (mmHg)	1.01	0.98-1.04	0.58
Diastolic blood pressure (DBP) (mmHg)	0.95	0.87-1.04	0.27
Hypertension (SBP>140, DBP>90, med)	1.41	0.27-7.38	0.68
Total cholesterol (mmol/l)	1.23	0.71-2.10	0.46
Total chol / HDL cholesterol ratio	1.11	0.66-1.89	0.69
Hypercholesterolemia (tot chol >6.5 mmol/l, history)	0.89	0.21-3.75	0.87
Diabetes (med, history)	6.14	1.38-27.44	0.02
Smoking (current & quit)	0.15	0.01-1.89	0.14
Agatston score (continuous)	1.00	1.00-1.00	0.07
Agatston score >400	12.44	1.47-105.21	0.02

Table 9-5. Distribution of occurrence of significant left main stenosis, eligible for CABG, according to both Agatston score (threshold 400) and diabetic status

		Number of patients	CABG for significant left main stenosis	
Agatston score <400	Diabetes -	57	1	2% (± 13%)
	Diabetes +	8	0	0% (± 0%)
Agatston score >400	Diabetes -	33	3	9% (± 29%)
	Diabetes +	10	4	40% (± 52%)

Note.- In left and middle column patient numbers are given, in right column mean percentage with standard deviation between parentheses.

Significant associations (P<0.05) between cardiovascular risk factors and significant left main stenosis eligible for surgery in the whole intervention group were found only for presence of diabetes using univariable logistic regression (Table 9-4); presence of diabetes was associated with a 6.1-fold increase (95% CI 1.4-27.4). Agatston score above 400 was also significantly associated with the presence of significant left main stenosis eligible for surgery (OR=12.4: 95% CI 1.5-105.2).

Diabetes mellitus and Agatston score above 400 were included in a multivariable logistic regression model. The ROC area of this model was 0.82 (95% CI 0.65-0.98). 40% of the patients with both an Agatston score >400 and diabetes had a significant left main stenosis, eligible for surgery (Table 9-5).

Smoking was not included in the model despite a P-value below 0.157. The reason was that there was a negative correlation between smoking and the presence of significant coronary artery disease according to the logistic regression analysis, i.e. non-smokers would have a higher risk than smokers. Thus, this was regarded as a chance finding.

DISCUSSION

The results of this study show that in this high-risk group of cardiac asymptomatic peripheral arterial disease patients coronary calcium scoring may be able to differentiate which patients are more likely to have significant coronary artery disease eligible for surgery. This ability of calcium scoring for the detection of obstructive angiographic coronary artery disease has also been found in cardiac symptomatic patients [18,19]. In a

cardiac symptomatic patient group calcium scoring may even be superior to thallium and ECG exercise tests for predicting coronary artery stenosis [20].

The role of coronary calcium scoring as a selection tool of those who need further testing for cardiac disease, such as SPECT, has been mentioned in recent reports on cardiovascular screening in cardiac asymptomatic subjects [21,22]. However, these guidelines are mainly aimed at asymptomatic subjects with cardiovascular risk factors and not yet symptomatic atherosclerosis. The subjects we studied do have symptomatic atherosclerosis and already are at a high risk, which justifies intensive medical therapy. Therefore, calcium scoring is not aimed at determining who needs intensive medical therapy but rather may have a role in selecting patients for further, more extensive tests, such as angiography, and resulting treatment. The relatively cheap and easy calcium scoring scan could possibly function as a gatekeeper for the more expensive and time-consuming further tests. Standard cardiovascular risk factors seem unable to make this subdivision between high-risk patients with a higher or lower risk. In the past thallium scintigraphy instead of calcium scoring has been suggested to be valuable for further selection in patients with PAD [23,24]. Calcium scoring would be another entirely non-invasive test which is faster, less stressful and much less expensive for the patient than thallium testing.

In case a screening endeavor is undertaken a treatable disease has to be detected. Early treatment of this disease also needs to improve patient prognosis. Studies in cardiac symptomatic patient groups studied the relation between calcium score and obstructive disease [18,19,25]. We limited our definition of significant obstructive disease to left main (equivalent) stenosis since only significant left main (equivalent) stenosis is a class I indication for treatment with CABG, even the case in absence of symptoms, in the standards set by the American Heart Association [26]. Although CABG is not without a certain morbidity and mortality risk, early treatment of a significant left main stenosis can probably prevent sudden cardiac death. However, it is unknown if a screening endeavor like undertaken in this study is changing life expectancy and if it is cost-effective since follow-up data is lacking. Especially in light of the COURAGE study, in which stable coronary heart disease patients were equally well off being treated by PCI or by optimal medical treatment, data on these issues are needed [27]. Calcium scoring as an initial test was only cost-effective in symptomatic patient groups with a significant disease prevalence below 70% [28]. Therefore, careful selection of the screening population is necessary. We chose to study cardiac asymptomatic PAD patients. In cardiac asymptomatic PAD patients the mortality risk is smaller than in PAD patients with symptoms of cardiac disease but the risk is still increased compared to subjects without PAD [5,7]. Our results suggest that CT calcium scoring may be used as a pretest to select

those patients that need to undergo morphologic tests, such as cCTA and invasive angiography.

A small percentage of the patients in our study had no to very little calcifications in their coronary arteries despite their high-risk status. Several earlier calcium scoring studies in cardiac symptomatic patients show that low calcium scores exclude the occurrence of significant findings. Janssen et al. reported that a calcium score below 11 precludes wall motion abnormalities during dobutamine stress MR and Moser et al. showed that with calcium scores below 100 SPECT is consistently negative for ischemic changes [29,30]. Other studies showed that exclusion of any calcium is highly accurate in ruling out obstructive disease [31,32]. However, in our study we did detect a significant left main stenosis due to soft plaques in one patient with an Agatston score below 10. Rubinshtein et al. even found significant coronary stenoses in 12% of patients with chest pain syndrome and a calcium score below 100 [33]. Therefore, even with a low calcium score significant disease with a treatment indication is not completely ruled out.

This study has several limitations. The sample size was relatively small. Thereby, only in the subgroup that also underwent cCTA we had information on the presence of a significant left main (equivalent) stenosis. The significant correlations we found had large confidence intervals and could have been chance findings. Thereby, the absence of significant differences in risk factors could also have been due to the small sample size.

Furthermore, we did not have any follow-up information yet. Therefore, the implications of our findings are unknown. It is uncertain if imaging findings are related to the eventual occurrence of events, such as death, and if early treatment of significant findings improves prognostics. Long-term follow-up results of the ongoing GROUND study hopefully will provide answers regarding the occurrence of events.

Despite the small sample size and the lack of follow-up, this study is one of the first efforts undertaken to screen high-risk patients for cardiac disease with both CT calcium scoring and cCTA and this study does show promising results for risk stratification in a high-risk patient group. In conclusion, calcium scores and diabetic status may help in predicting the occurrence of significant coronary artery disease, eligible for surgery, in cardiac asymptomatic PAD patients.

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Chapter 9

CHAPTER 10

GENERAL DISCUSSION

Chapter 10

Cardiac imaging with the use of computed tomography has gained widespread interest and is going through a fast development with the advent of multi-detector row CT scanners. The first focus of this thesis was the evaluation of neglected aspects of current protocols that are used for calcium scoring and contrast-enhanced CT angiography. First CT calcium scoring scan protocols were evaluated in order to find optimum settings to achieve a high reproducibility combined with a low radiation dose (**chapters 3-5**). Secondly the influence of the contrast injection protocol on contrast enhancement in cardiac CT was investigated (**chapters 6&7**). The second focus of this thesis was the application of cardiac CT in the screening of cardiac asymptomatic patients with a high risk for coronary artery disease (**chapters 8&9**).

METHODOLOGICAL EVALUATION OF CARDIAC CT

Coronary calcium scoring

Calcium scores are a measure of the extent of coronary atherosclerosis [1]. Calcium scores have also been shown to have predictive value regarding the future occurrence of cardiac morbidity and mortality [2-5]. However, several studies in the past have concluded that the standard CT scan protocol for calcium scoring with 3-mm thick sections suffers from a poor inter-scan reproducibility (mean relative difference of 15-49%) [6-9]. Numerous reasons have been given for the poor reproducibility but the magnitude of the variability through each cause of inter-scan variability was not exactly known [8-12]. In **chapter 3** in part II of this thesis the most commonly applied CT calcium scoring scan protocol was evaluated. In this chapter we show that an important reason for poor inter-scan reproducibility of the standard CT calcium scoring scan protocol is variation of scan starting position. The use of 3-mm thick sections makes calcium scoring vulnerable to partial volume effects. Due to the occurrence of partial volume effects a small variation in scan starting position can have a substantial effect on the eventual calcium score by changes in the size and density of calcifications.

The reason why these relatively thick 3-mm sections are still in use is partly historical and partly based on dose considerations. CT calcium scoring scan protocols have originally been developed for electron beam CT (EBCT). EBCT allowed ECG-synchronized scanning with a high temporal resolution long before 4-detector row CT scanners were introduced. Therefore, several large cohort studies on the prediction of cardiovascular disease used EBCT instead of MDCT for calcium scoring since only EBCT was available at the start of the study [2,4,5,13]. By the time MDCT started to be used for calcium scoring a large amount of data on the predictive ability of calcium scores was already available based on EBCT studies. Not only did the amount of calcification on EBCT correlate well with pathology findings but also did it appear to correlate with the occurrence of future

events. Logically MDCT scan protocols were copies of EBCT scan protocols to allow use of follow-up data correlated with calcium scores obtained with EBCT also with calcium scores obtained with MDCT.

The EBCT scan protocol was a compromise between optimal section thickness and scan duration since it had to be performed within one breath-hold. Thin (<3 mm) or overlapping sections were not feasible. Nowadays, with the use of MDCT for calcium scoring the use of thinner sections, which are less vulnerable to partial volume effects, is feasible. However, to yield thin images with a signal-to-noise ratio (SNR) similar to the original 3-mm sections a large increase in radiation dose to the patient is necessary. Therefore, calcium scoring scan protocols still use 3-mm sections.

In **chapter 4** we show a solution to the problem of reduced reproducibility with prospectively ECG-triggered scans. The reproducibility of calcium scores from prospectively ECG-triggered scans can be improved by using overlapping sections which can be obtained by a, in theory, relatively simple adaptation of the scanning protocol. By scanning at a thinner collimation of 16×1.5 mm a data set with thick 3-mm sections can be obtained with an increment of 1.5 mm by averaging each two consecutive 1.5-mm sections to a 3-mm section. This way reproducibility can be improved without having to increase the radiation dose to the patient. This approach has not been tried before and scanner software has not been enabled for this approach. For this reason we had to find a workaround to evaluate the effect of this simple adaptation on reproducibility. We averaged 1.5-mm sections that were reconstructed from the raw data obtained with prospective ECG-triggering to obtain 3-mm sections with a 1.5-mm increment instead of directly creating overlapping 3-mm sections from the raw data.

Such a workaround is not required if scanning is performed with retrospective ECG-gating. Raw data obtained with a retrospectively ECG-gated MDCT scan protocol for calcium scoring can be reconstructed to a data set with overlapping sections. The improved inter-scan reproducibility of this technique is in accordance with our findings [14-16]. The disadvantage of retrospective ECG-gating, however, is the markedly reduced dose efficiency of this technique: only 10 to 20% of the dose makes it into any given image. Therefore, application of a high radiation dose to the patient is necessary with retrospectively ECG-gated MDCT [17]. This is an important reason why no complete transition to retrospectively ECG-gated calcium scoring scanning has been made. A writing group of the American Heart Association in 2006 even strongly recommended the use of prospective ECG-triggering merely because of the lower radiation dose [18], despite the fact that application of retrospective ECG-gating showed an improved inter-scan reproducibility (and thus precision) over application of prospective ECG-triggering.

This implies that administering a lower dose is regarded more important than using the most reproducible technique. This general principle is summarized with the term ALARA; radiation dose should be as low as reasonably achievable [19]. In practice this means that if calcium scores are used for follow-up the most optimal reproducibility should be preferred, but in instances where a less than optimal inter-scan reproducibility suffices (e.g. risk estimation) the choice of scan protocol should be made based on dose considerations. However, if certain score thresholds are used for deciding to treat or not to treat a patient, e.g. zero vs. non-zero calcium score in chest pain triage, a precise (i.e. reproducible) score should be preferred. Otherwise, low precision will cause false-negative or false-positive results. Thus, benefit and harm for the patient should be carefully weighed dependent of the aim of using calcium scores. With the use of prospectively ECG-triggered CT data sets with overlapping images for calcium scoring such as in **chapter 4** of this thesis the advantage of a low radiation dose is combined with the advantage of an improved reproducibility. The 'benefit' of a low radiation dose is then no longer linked to the 'harm' of an imprecise calcium score.

While in **chapter 4** improving the reproducibility of the standard low dose technique was aimed for, in **chapter 5** we tried to reduce the dose of the most precise technique, retrospectively ECG-gated scanning. By doing so, the 'benefit' of the better reproducibility of this technique is no longer linked to the 'harm' of a relatively high patient radiation dose. Our goal in **chapter 5** was to define the optimal use of ECG-based tube current modulation in order to maximize radiation dose saving combined with minimal calcium score errors. The application of ECG-based tube current modulation during retrospectively ECG-gated scanning has been shown to allow a reduction in radiation dose [20,21]. Important to realize is that ECG-based tube current modulation is a prospectively applied technique in a retrospectively ECG-gated scan. After the scan has been acquired with ECG-based tube current modulation only a part of the scan will have sufficient image quality to allow calcium scoring. By observing the calcium score errors throughout the cardiac cycle by comparison to the calcium score in the most-motionless phase we found that with adaptation of the tube current modulation to the patient heart rate retrospectively ECG-gated calcium scoring scanning can theoretically be performed with maximum radiation dose saving and minimal calcium score errors. While variation of calcium scores throughout the cardiac cycle was studied by others [22,23], we were the first to include the most-motionless phase in the analysis, which is crucial if the application of tube current modulation is studied. This way we were able to show that dose modulation with maximum dose during only a single phase can be used for calcium scoring. Unfortunately, the dose reduction potential with current software is limited to

around 40%. Further optimization of the tube current modulation software is therefore warranted.

Contrast injection protocol for coronary CT angiography

Contrast-enhanced coronary CT angiography has been developed for the non-invasive evaluation of coronary artery disease. Optimum enhancement of these vessels is crucial to allow a proper evaluation. Part II.B of this thesis focused on two controversial aspects of contrast material injection: the proper choice of contrast medium concentration and the optimized enhancement not only of the left but also of the right ventricle.

Substantial controversy exists about the optimum contrast material concentration. A high contrast medium concentration performed better in studies [24,25], but the results of these studies can already be predicted from their setup. A similar volume of contrast medium is injected and thus a higher iodine load is administered with a higher contrast medium concentration. If total iodine load and iodine flux remain constant between contrast medium concentrations, two contrast medium concentrations should perform the same in theory [26,27]. In **chapter 6** we show that the two methods of increasing iodine flux, increasing the rate of contrast medium injection or increasing the contrast medium concentration, do not yield the same attenuation results despite theoretical considerations that indicate that they are equal. We found that increasing iodine flux by increasing injection rate yields higher attenuation in the aorta and left ventricle than increasing iodine flux by increasing contrast medium concentration. It is difficult to explain this finding since studies in humans on contrast medium behaviour can hardly be performed due to radiation dose restrictions. According to current models of contrast medium behaviour we should not have found a difference between two contrast medium concentrations. The explanation given in **chapter 6** is called the dead-venous-space-phenomenon; contrast medium is 'trapped' in the injection veins at the end of the contrast injection and this volume of contrast medium is not pushed forward with the initial injection rate [28]. This phenomenon is the most likely explanation of our results. The findings of this chapter illustrate that theoretic considerations are not necessarily perfect and can only be extrapolated after experimental validation.

The aim of the study in **chapter 7** was to improve the contrast injection protocol in order to obtain good contrast enhancement of both the coronaries and the left and the right ventricle. Up till now contrast medium injection protocols for cardiac CT aimed at obtaining a washout in the right ventricle since a high contrast enhancement in the right ventricle was thought to negatively influence evaluation of the right coronary artery for the presence of plaques and stenosis [29,30]. However, with washout of the enhancement of the right ventricle its function cannot be evaluated as part of a comprehensive cardiac

analysis. Thereby, enhancement of the coronary arteries and aorta in conjunction with enhancement of the pulmonary arteries is essential if a triple-rule-out scan for pulmonary embolism, aortic dissection and coronary artery disease is aimed for in patients with acute chest pain [31]. To reach a plateau in contrast enhancement a multi-phase injection protocol is designed with an initial phase with a high iodine flux to reach a threshold of contrast enhancement followed by a second phase with a lower iodine flux to create a plateau of enhancement. In **chapter 7** we show that in an injection protocol with two immediately consecutive contrast medium injection phases a decrease in iodine flux in the second phase can best be achieved by lowering contrast medium concentration instead of by lowering the contrast medium injection rate in the second phase. By maintaining the same injection rate throughout the entire injection duration an optimal throughput of contrast medium is obtained. This beneficial effect is comparable to the advantageous effect of a saline flush at the end of a contrast medium injection [32,33]. The reason why we could only now study this new contrast medium injection protocol is that technical development of contrast injectors just recently allowed the simultaneous injection of contrast medium and normal saline.

APPLICATION OF CARDIAC CT IN SCREENING

Part III of this thesis evaluates cardiac CT for its application in screening high-risk patients. The GROUND study, as described in **chapter 8** of this thesis, is one of the first efforts undertaken to study the use of cardiac CT as a screening test in a high-risk patient group. Patients with peripheral arterial disease are known to have a high risk for cardiac morbidity and mortality [34,35]. This risk may even be considered equivalent to the risk of patients with a previous myocardial infarction [36,37]. In the GROUND study cardiac asymptomatic PAD patients were included. Both CT calcium scoring and contrast-enhanced coronary CT angiography were performed in the treatment arm of the study. The baseline results of the study indicate that significant coronary artery disease is common in this patient group. The results described in **chapter 9** show that CT calcium scoring might be valuable in this patient population at a high risk for cardiac morbidity and mortality. The height of the calcium score was significantly related to the occurrence of significant left main coronary artery stenosis. These results seem promising but follow-up data is needed to determine the real value of cardiac CT, both calcium scoring and coronary angiography, for reducing the occurrence of cardiac morbidity and mortality in this high-risk patient group.

Cardiac CT is a relatively new technique, which is undergoing constant developments. The role of CT calcium scoring as a screening test is already becoming more and more accepted, especially in the intermediate risk asymptomatic population [38]. The first

potential indications of contrast-enhanced CT coronary angiography that were studied, were the existing indications of diagnostic invasive angiography: e.g. stenosis detection, stent follow-up and CABG follow-up [30,39-43]. However, research is now being done to define the indications of CT coronary angiography beyond those of invasive angiography. A focus of studies is the use of CT coronary angiography as a gatekeeper for invasive tests, such as conventional coronary angiography, in patients in whom immediate invasive examinations are not indicated but current diagnostic means are not always conclusive. For instance, several studies indicate cardiac CT is useful for the initial evaluation of patients presenting to the emergency department with atypical chest pain [44-46]. The use of cardiac CT in an cardiac asymptomatic population at high risk for cardiac disease due to an underlying conditions so far has barely been studied.

If cardiac CT were applied for screening high-risk patients, such as in the GROUND study, it is not yet known what type of scan or which combination of scans is most optimal. Should only CT calcium scoring or only contrast-enhanced CT angiography be performed or is it better to perform both? Radiation dose is substantially lower for CT calcium scoring than for contrast-enhanced coronary CT angiography [17], while coronary CT angiography can depict both plaque type and stenosis degree. A large amount of follow-up data shows the predictive ability of calcium scores [38,47], but the optimal population for screening with CT calcium scoring and/or coronary CT angiography has not been defined yet. Cardiac asymptomatic subjects at intermediate risk according to current risk scores (10-20% 10-year risk) have been suggested as a potential target population for screening with CT calcium scoring [38,48]. Subjects at low risk and those at high risk, as assessed with established risk factors, are considered less eligible. The former are less eligible because these subjects have no indication for initiation of drug treatment; the latter because there is already a treatment indication. Preventive use of medication for risk factor reduction is well accepted in high-risk subjects. It has to be kept in mind that an essential aspect of a good screening program is the availability of an effective treatment option for the early stage of disease or the pre-disease state that is found with screening. In other words, screening should only be performed if further progression of the disease can be prevented and/or life expectancy can be increased. In case of screening peripheral arterial disease patients the treatment option should be more effective in preventing events than the preventive pharmacological therapy that is already indicated.

Only determining the calcium score in a patient with peripheral vascular disease currently has no treatment implications. Already, in all treatment guidelines for PAD patients at least the use of statins and anti-platelet agents is advised since these drugs have shown their value for reducing events in high-risk patients. Finding a high calcium score in a

PAD patient will not change this guideline and is currently not an indication for more extensive pharmacological therapy. Yet, the first results of the GROUND study appear to implicate that with calcium scores a distinction can be made between cardiac asymptomatic PAD patients at higher risk for significant coronary artery disease, with a treatment indication, and those at lower risk. This distinctive ability exceeds the abilities of standard cardiovascular risk factors. CT calcium scoring could function as a gatekeeper for more extensive tests for coronary artery disease. Only those patients with a high calcium score apply for more extensive testing. One pitfall of this strategy is that a low calcium score does not necessarily exclude significant coronary artery disease. We found one patient in the GROUND study with a low calcium score and a significant left main stenosis. This phenomenon has been systematically studied recently [49]. In a study with contrast-enhanced cardiac CT in 231 patients with chest pain and a zero or low calcium score 12% of the subjects showed obstructive disease (>50% luminal narrowing) on CT. 16 of the 231 subjects (6.9%) underwent a revascularization procedure after referral based on the findings of contrast-enhanced cardiac CT. Using only CT calcium scoring or a combination of CT calcium scoring with contrast-enhanced cardiac CT in which CT calcium scoring acts as a gatekeeper will inevitably lead to a lowered sensitivity of the screening strategy. Subjects with a low calcium score and at the same time significant coronary artery disease will be missed. However, the issue at hand is to determine the best strategy, i.e. the use of a combination of imaging techniques to have the highest yield in terms of risk reduction against the lowest costs per life year gained. Every approach will have extremes in that on the one hand subjects will be missed that have the disease or condition, on the other hand some patients will be over-diagnosed.

Before the cost-effectiveness of any screening study in high-risk patients with the use of cardiac CT is analyzed, a beneficial effect of performing the screening study must have been shown. Follow-up data from randomized studies is needed to show a beneficial effect, i.e. event-reduction. In case of screening high-risk patients for significant coronary artery disease a benefit should be reported for extensive tests and resulting therapy in an asymptomatic stage. Without this data it remains, for now, unknown if treatment in an asymptomatic stage of cardiac disease will actually be beneficial. It could even be more harmful than not screening since the current treatments for significant coronary artery disease, e.g. PCI and CABG, are accompanied of a certain risk for morbidity and mortality [50]. A related example is the use of PCI in stable angina pectoris. A large study has been performed in patients with a significant stenosis in one of their coronary arteries which actually causes them to have symptoms [51]. One part of the study population received standard PCI with optimal medical treatment; the other part of the study population received optimal medical treatment and only received further invasive

treatment, such as PCI, if symptoms progressed to unstable disease. Standard PCI did not reduce the risk of death, myocardial infarction or other major cardiovascular events when added to optimal medical therapy in this study. On the other hand, standard PCI did not increase risk either.

The GROUND study is among the first studies that show promising results for the use of cardiac CT as a screening instrument in high-risk patients. However, it is not yet clear whether these results will influence patient outcome and to what extent they can be transferred to cardiac high-risk patient groups other than peripheral arterial disease patients. Cardiac CT at present is still in a phase of rapid development. Optimization of examination protocols is crucial for optimum results and containment of radiation exposure. When it comes to imaging the heart with CT we have only just started; it will take a further effort to reach the heart of the matter.

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CHAPTER 11

SUMMARY / SAMENVATTING

Chapter 11

SUMMARY

Cardiac imaging with multi-detector row CT has undergone a rapid development since the advent of 4-detector row CT scanners in 1998. The research described in this thesis dealt with the evaluation of current protocols for CT coronary calcium scoring and contrast-enhanced coronary CT angiography and of potential areas for optimization of these protocols. Furthermore, cardiac CT was studied as part of a screening protocol for cardiac disease in cardiac asymptomatic peripheral arterial disease patients at high risk for cardiac morbidity and mortality.

In **chapter 2** the technical background of cardiac CT scanning as well as contrast injection parameters were introduced to provide some basic knowledge for better comprehension of the following chapters, especially the methodological evaluation studies in part II.

Chapter 3 comprises a study on small variation of scan starting position as a source of calcium score variability in non-spiral data sets obtained with prospective ECG-triggering and reconstructed with contiguous 3-mm slices. By creating two 3-mm data sets with a 1.5-mm offset in starting position from a single 1.5-mm slice data set obtained with prospective ECG-triggering all factors influencing calcium scores other than scan starting position were kept identical. By doing so, solely the influence of scan starting position could be studied and small variation of scan starting position was shown to substantially contribute to calcium score variability in contiguous 3-mm data sets. This variability can be reduced by the reconstruction of data sets with overlapping images instead of contiguous images. Reconstruction of overlapping data sets by current scanner software is feasible if a spiral scan is acquired with retrospective ECG-gating, but not if a non-spiral scan with prospective ECG-triggering is obtained. However, retrospectively gated scanning requires a relatively high patient radiation dose to obtain adequate image quality compared to prospectively triggered scanning.

In **chapter 4** it is shown that the use of overlapping 3-mm data sets obtained with prospective ECG-triggering for calcium scoring improves reproducibility without an increase in patient radiation dose. The overlapping 3-mm data sets were obtained by a workaround (averaging of 1.5-mm data sets) since scanner software did (and does) not allow these reconstructions.

Chapter 5 deals with determining the optimal application of ECG-based tube current modulation for dose reduction during retrospectively ECG-gated calcium scoring scanning, in order to be able to combine maximum radiation dose saving with minimal errors in calcium score. By adaptation of the timing of the tube current modulation during

the RR-interval to the patient heart rate retrospectively ECG-gated calcium scoring scanning can be performed with about 38% dose saving and a median calcium score error of 0%.

Part II.B of this thesis concerns an evaluation of contrast injection for contrast-enhanced cardiac CT. In **chapter 6** a study of the effect of using moderate (300 mg Iodine / ml) instead of high (370 mg Iodine / ml) concentration contrast material under similar circumstances is described. Contrary to our expectations the use of a lower contrast material concentration yielded higher enhancement when a biphasic contrast injection protocol with a saline flush was used. This difference is most likely caused by the occurrence of the so-called dead venous space phenomenon. The dead venous space phenomenon describes 'trapping' of contrast material in the injection veins after the switch from a high injection rate to a lower or no injection rate during a contrast material injection. The contrast material, present in the injection veins at the moment injection rate is reduced, reaches the heart at a slower rate than the rate it was injected with and contributes less to enhancement. Since this volume contains more iodine if a high concentration contrast material is used than if a moderate concentration contrast material is used, lower enhancement is reached if a higher contrast medium concentration is used.

To prevent the occurrence of the dead venous space phenomenon and to improve contrast material throughput, current dual-head contrast material injectors allow simultaneous infusion of contrast material and saline. In this way, any given dilution of contrast material can be achieved. Thus, iodine flux (grams of iodine injected per second) in the second contrast material injection phase of a biphasic injection can be reduced by diluting contrast material instead of by decreasing injection rate. In **chapter 7** the applicability of this approach was tested to optimize a biphasic contrast material injection followed by a saline flush for contrast-enhanced cardiac CT. Injection of diluted contrast material instead of reducing injection rate during the second phase of the biphasic contrast material injection improved contrast material throughput and similar enhancement throughout the heart was reached with a lower iodine flux in the second contrast material injection phase. Concurrently, the homogeneity of contrast enhancement in the right ventricle was improved, which positively affects image evaluation because of fewer artifacts.

In part III cardiac CT was applied in a comprehensive screening protocol for cardiac disease in cardiac asymptomatic peripheral arterial disease (PAD) patients at high risk for cardiac morbidity and mortality. In **chapter 8** the rationale and design of the GROUND study are described. **Chapter 9** contains baseline results in the first 231 patients and an analysis of the potential role of calcium scoring in this high-risk PAD patient group. A high occurrence of severe coronary artery disease was found in this patient group. Despite

the high-risk status of this group, it appeared that calcium scores could be used to differentiate the patients most at risk for significant coronary artery disease from those at lower risk. CT calcium scoring, which is non-invasive and fast, may therefore be used as a gatekeeper for further diagnostic tests in future screening protocols.

Before large screening endeavors with cardiac CT become reality the improvement of patient outcome through this type of screening should be demonstrated. Meanwhile, cardiac CT rapidly develops and continuous improvements of protocols are necessary to obtain optimal results and to contain radiation exposure. When it comes to imaging the heart with CT we have only just started; it will take a further effort to reach the heart of the matter.

Chapter 11

SAMENVATTING

Cardiale beeldvorming met multi-detector CT heeft een snelle ontwikkeling doorgemaakt vanaf de introductie van de 4-detector CT scanners in 1998. Het onderzoek dat beschreven wordt in dit proefschrift betrof de evaluatie en verbetering van de huidige protocollen voor het scoren van kalk in de coronairarteriën met behulp van CT en voor de contrastinjectie bij niet-invasieve CT coronairangiografie. Verder werd CT van het hart bestudeerd als onderdeel van een screeningsprotocol voor coronairlijden in cardiaal asymptomatische patiënten met perifeer vaatlijden, die een hoog risico lopen op cardiale morbiditeit en mortaliteit.

In **hoofdstuk 2** werden zowel de technische achtergrond van het scannen van het hart met behulp van CT als de verschillende contrast injectie parameters besproken. Dit hoofdstuk biedt enige basiskennis om de daaropvolgende hoofdstukken beter te kunnen begrijpen, met name de hoofdstukken in deel II: de methodologische evaluatie.

Hoofdstuk 3 bevat een onderzoek naar het effect van een kleine variatie van de startpositie van de kalkscorescan op de interscan variabiliteit van de kalkscore bij het gebruik van een niet-spiraal dataset die verkregen is met prospectieve ECG-synchronisatie en gereconstrueerd met aaneensluitende 3-mm plakken. Door het creëren van twee datasets met 3-mm plakken met een verschil in startpositie van 1,5 mm uit één prospectief getriggerde niet-spiraal dataset met 1,5-mm plakken kon het effect van een verschil in startpositie op de variabiliteit van de kalkscore bepaald worden. Alle andere beïnvloedende factoren, bijvoorbeeld hart ritme, bleven constant. Een kleine verandering van de startpositie van de scan bleek substantieel bij te dragen aan de kalkscore variabiliteit die optreedt bij het gebruik van een 3-mm dataset zonder overlap tussen de plakken. Deze variabiliteit kan verminderd worden door datasets te reconstrueren met overlappende plakken in plaats van aaneensluitende plakken zonder overlap. Reconstructie van een overlappende dataset met de huidige scannersoftware is echter alleen mogelijk als een spiraalscan met retrospectieve ECG-synchronisatie is verkregen en niet als een niet-spiraalscan met prospectieve ECG-synchronisatie is gemaakt. Het grote nadeel van scannen met retrospectieve ECG-synchronisatie is de relatief hoge stralingsdosis voor de patiënt vergeleken met de stralingsdosis van een scan met prospectieve ECG-synchronisatie. Deze hoge stralingsdosis is vereist om adequate beeldkwaliteit te verkrijgen.

In **hoofdstuk 4** wordt beschreven dat het gebruik van een overlappende 3-mm dataset verkregen met prospectieve ECG-synchronisatie de reproduceerbaarheid van de kalkscore verbetert zonder dat de patiënt een hogere stralingsdosis ontvangt. De overlappende 3-mm

datasets werden via een omweg verkregen (d.m.v. het middelen van 1.5-mm datasets) aangezien de scannersoftware deze reconstructies niet toelaat.

Hoofdstuk 5 behandelt een studie waarin de optimale toepassing van modulatie van de buisstroom op basis van het ECG tijdens een kalkscorescan met retrospectieve ECG-synchronisatie wordt bestudeerd. ECG-geleide buisstroommodulatie wordt toegepast om de stralingsdosis van kalkscorescans verkregen met retrospectieve ECG-synchronisatie te verlagen. Optimale toepassing van de modulatietechniek combineert een forse verlaging van de straligsdosis met minimale fouten bij de kalkscorebepaling. Door het moment en de duur van het verlagen van de buisstroom in het RR-interval af te laten hangen van het hartritme van de patiënt kan een kalkscorescan met retrospectieve ECG-synchronisatie verkregen worden met een maximale dosisbesparing van ongeveer 38% en een mediane fout in de kalkscorebepaling van 0%.

In deel II.B van dit proefschrift wordt een evaluatie van de contrastinjectie bij cardiale CT beschreven. In **hoofdstuk 6** wwerd het verschil in aankleuring bestudeerd bij het gebruik van een gemiddelde (300 mg Jodium / ml) in plaats van een hoge (370 mg Jodium / ml) concentratie contrastmiddel onder verder gelijke omstandigheden. Tegen onze verwachtingen in leverde het gebruik van een lagere concentratie contrastmiddel een hogere aankleuring op van hart en vaten dan het gebruik van een hogere concentratie contrastmiddel bij toepassing van een bifasische contrastinjectie met een zoutflush. Dit verschil kan hoogstwaarschijnlijk verklaard worden door het optreden van het zogenaamde dode-veneuzeruimte-fenomeen. Dit fenomeen beschrijft hoe contrastmiddel, dat nog aanwezig is in het veneuze traject via welke de injectie plaatsvindt (‘injectievenen’), vlak na het beëindigen van de contrastinjectie (of bij wisselen van een hoge naar een lage injectiesnelheid) vertraagd in het hart aankomt en derhalve minder bijdraagt aan het bereiken van een piek in de aankleuring. Als een hogere concentratie contrastmiddel wordt geïnjecteerd zal relatief meer jodium in de injectievenen ‘vastzitten’ en derhalve zal minder jodium bijdragen aan het bereiken van een hoge aankleuring van hart en vaten. Dientengevolge kan bij injectie van eenzelfde hoeveelheid jodium een hogere aankleuring worden bereikt met een lagere contrastmiddelconcentratie.

Om het dode-veneuzeruimte-fenomeen te voorkomen en om contrastmiddeldoorstroming te verbeteren, kunnen de huidige dubbelkops contrastmateriaalinjectoren tegelijkertijd contrastmiddel en zout inspuiten. Op deze manier kan elke mogelijk verdunning van contrastmiddel bereikt worden. Derhalve kan de jodiumflux (het aantal grammen jodium dat geïnjecteerd wordt per seconde) verlaagd worden in de tweede fase van de bifasische contrast injectie ofwel door het verlagen van de injectiesnelheid dan wel door het verdunnen van het contrastmiddel. In **hoofdstuk 7** werd de toepasbaarheid van deze

methode getest met het doel de bifasische contrastinjectie gevolgd door een zoutflush te optimaliseren. De injectie van verdund contrastmiddel in plaats van het verlagen van de injectiesnelheid gedurende de tweede fase van de bifasische contrastinjectie verbeterde de doorstroom van contrastmiddel. Een vergelijkbare aankleuring van hart en vaten werd verkregen met een lagere jodiumflux en een kleinere hoeveelheid jodium in de tweede fase van de contrastinjectie. Tegelijkertijd verbeterde de homogeniteit van de contrastaankleuring in de rechterventrikel, wat een positieve invloed heeft op de beoordeling en bewerking van de beelden door de afwezigheid van artefacten.

In deel III van dit proefschrift is beschreven hoe cardiale CT werd toegepast in een uitgebreid protocol voor het screenen voor de aanwezigheid van ernstig coronairlijden bij cardiaal asymptomatische patiënten met perifeer vaatlijden, die een verhoogd risico hebben op cardiale morbiditeit en mortaliteit. In **hoofdstuk 8** staan de rationale en het ontwerp van de GROUND studie beschreven. **Hoofdstuk 9** bevat baseline resultaten over de eerste 231 patiënten en een analyse om de mogelijke rol van kalkscoren in deze patiëntengroep met een hoog risico te bepalen. In deze patiëntengroep kwam veel ernstig coronairlijden voor. Ondanks de hoge risicostatus van de patiënten in deze studie, leek de kalkscore in staat te differentiëren tussen de patiënten die een hogere kans hadden op ernstig coronairlijden en degenen met een lagere kans. De kalkscore-CT, een niet-invasief en snel uit te voeren beeldvormingsonderzoek, zou derhalve gebruikt kunnen worden als een poortwachter voor het ondergaan van uitgebreidere diagnostische onderzoeken in toekomstige screeningsprogramma's.

Voordat grote screeningsprogramma's met cardiale CT werkelijk geïmplementeerd kunnen worden, moet een verbetering van de prognose door het ondergaan van de screening voor de patiënt aangetoond zijn. Tot die tijd zal CT van het hart zich in een snel tempo verder ontwikkelen. Continue verbeteringen van de protocollen zullen nodig zijn om optimale resultaten te verkrijgen en om de stralingsdosis voor de patiënt te beperken. Wat betreft de cardiale beeldvorming met behulp van CT staan we nog maar aan het begin; het vereist een verdere inspanning om het hart van de materie te bereiken.

LIST OF PUBLICATIONS

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DANKWOORD

'Aim to achieve the mountain top, but don't forget to enjoy the journey.'

(Oosterse wijsheid)

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CURRICULUM VITAE

Annemarieke Rutten werd op 2 juni 1979 geboren te Leiderdorp. In 1997 behaalde zij haar VWO diploma aan het Lyceum De Grundel te Hengelo. Datzelfde jaar begon zij aan de studie geneeskunde aan de Rijksuniversiteit Groningen. In 2001 bracht ze zeven maanden door in de Verenigde Staten voor een wetenschappelijke stage in het Children's Hospital van Harvard Medical School te Boston. Uit deze stage kwam haar eerste publicatie voort en haar wetenschappelijke interesse nam verder toe. Na co-schappen in het Academisch Ziekenhuis Groningen en enkele kleinere geaffilieerde ziekenhuizen, koos ze voor een keuze co-schap op de afdeling Radiologie van het Academisch Medisch Centrum te Amsterdam. Dit was het begin van haar carrière in de radiologie. Na het cum laude behalen van haar artsenbul in augustus 2003, begon ze in oktober 2003 aan een promotie-onderzoek bij de afdeling Radiologie van het Universitair Medisch Centrum Utrecht. Het resultaat van dit promotie-onderzoek is beschreven in dit proefschrift. In april 2007 is de auteur begonnen aan haar opleiding tot radioloog in het Universitair Medisch Centrum Utrecht.